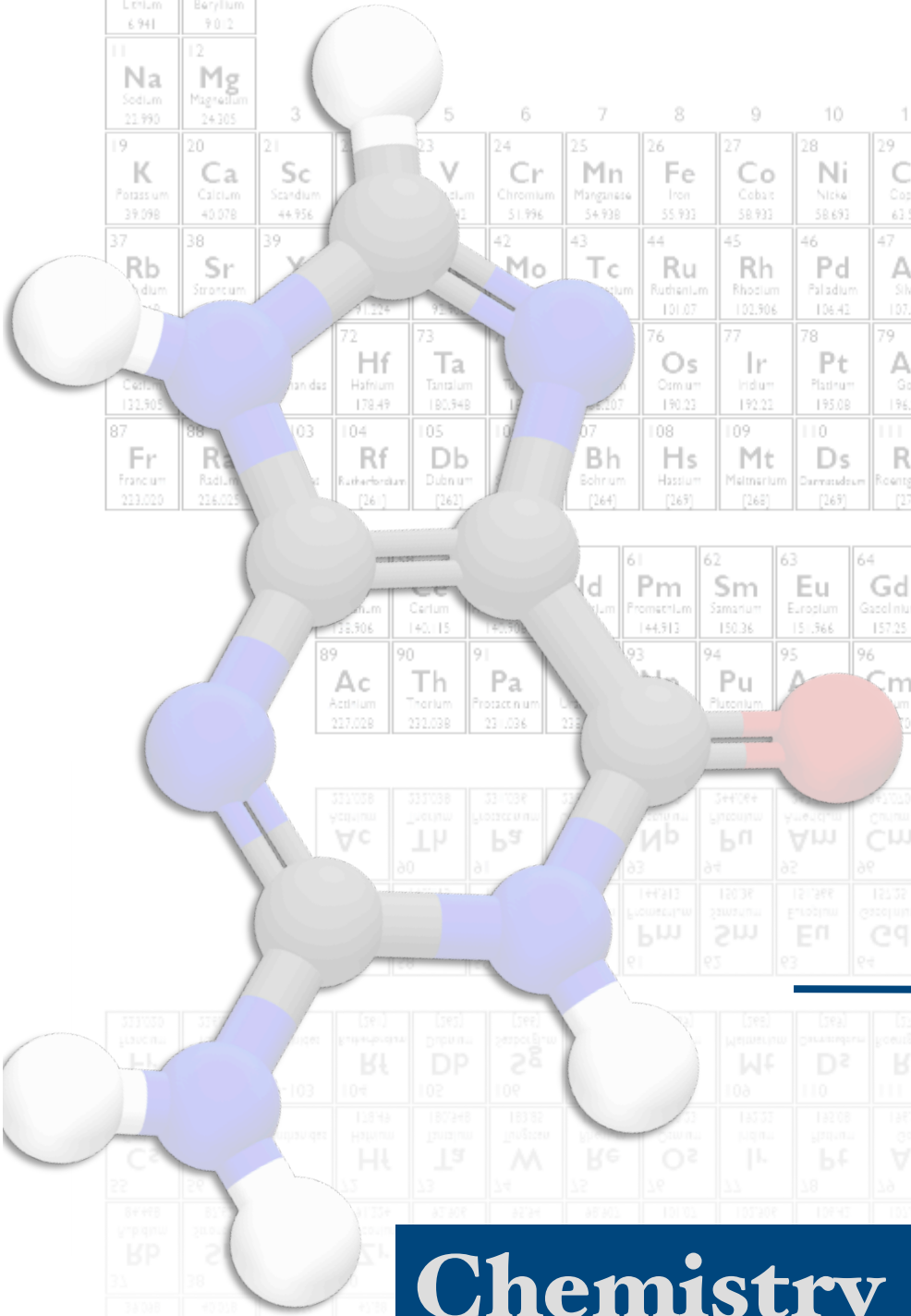


Yale

Chemistry Symposium

Friday, August 26, 2016
Sterling Chemistry Laboratory

Presentation Schedule

Morning Session

Keynote Lecture

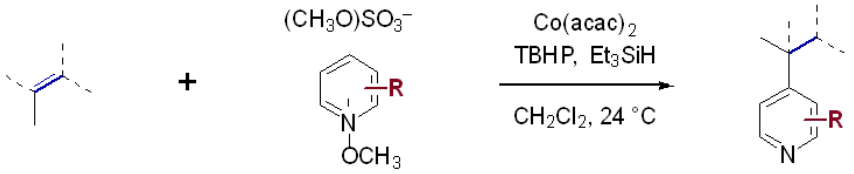
Afternoon Session

Xiaoshen Ma (Herzon Group)

Intermolecular Hydropyridylation of Unactivated Alkenes via Hydrogen Atom Transfer

Applications of transition metal hydrides as hydrogen atom donors to alkenes have been intensively studied. Mukaiyama, Carreira, Boger, Baran, Shenvi, our group, and others recently reported a range of useful alkene hydrogenation and hydrofunctionalization reactions mediated by cobalt-, manganese-, and iron-based catalysts.

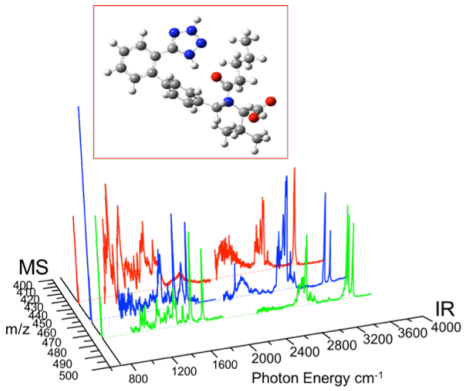
Unactivated alkenes are inexpensive starting materials for synthesis. Hydroarylation - the direct or formal addition of arene C–H bonds across an alkene p-bond - is a useful method to functionalize alkenes. Most reported hydroarylation protocols are initiated by metal-mediated cleavage of an aryl C–H bond. In many instances isomeric mixtures of products are formed, and the scope of the alkene is limited. We have developed a mechanistically-distinct hydropyridylation reaction that proceeds by hydrogen atom transfer (HAT) to alkenes. The reaction occurs under mild conditions, is compatible with 1–4 carbogenic substituents on the alkene, and leverages the selectivity of HAT to achieve regiocontrol.



Olga Gorlova (Johnson Group)

Adding the optical dimension to mass spectrometry: A powerful new platform for ultrasensitive spectrochemical analysis of metabolites

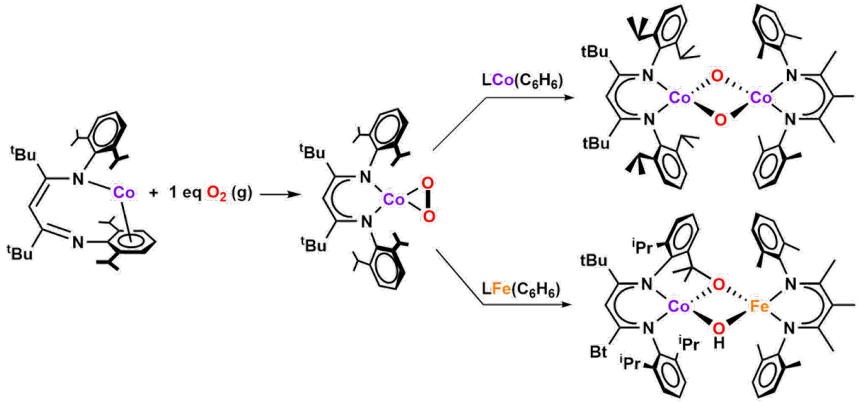
We describe a new type of chemical analysis based on a hybrid technology that combines traditional aspects of high performance mass spectrometry with recent innovations in chemical physics. This involves incorporation of cryogenically cooled ion traps to prepare mass selected ions for interrogation by laser spectroscopy. Optical spectra are recorded by photoevaporation of weakly attached rare gas atoms or molecules, which affords the acquisition of linear infrared spectra that are readily compared to calculated spectra of candidate structures at o K. This capability has been widely used to study reaction intermediates in the catalytic activation of small molecules, but here we discuss how it can be used to characterize structural isomers created in the metabolic decomposition of drug molecules. The characterization of these metabolites is one of the major obstacles in the development of new drug candidates because their characterization by traditional analysis (NMR, MS/MS) requires large scale workup of raw material. We are therefore developing a mass-spec based alternative strategy to provide structural information on microscopic amounts of material with minimal purification. In a collaborative effort with the Miller and Crawford groups, we present the first successful results on the popular heart medication Diovan, along with on-going work where we isolate genetically encoded biosynthesized small molecules.



Daniel Edward DeRosha (Holland Group)

A side-on cobalt dioxygen complex and its conversion to homobimetallic and heterobimetallic products

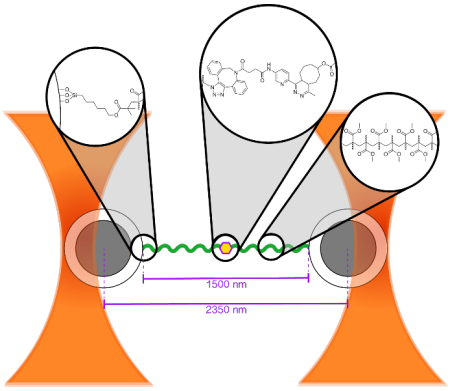
Transition metal complexes of dioxygen (O_2) are important in the oxidation of biological and synthetic systems. Reaction of O_2 with the diketiminate supported cobalt(I) complex $L^{tBu}Co$ (L^{tBu} = 2,2,6,6-tetramethyl-3,5-bis(2,4,6-triisopropylphenylimido)hept-4-yl) gives a rare example of a side-on dioxygen complex of cobalt. Characterization by X-ray diffraction, spectroscopy, and DFT calculations is most consistent with the assignment of the O_2 ligand in $L^{tBu}Co(O_2)$ as peroxo (O_2^{2-}). Although unreactive toward weak C-H bonds, the cobalt dioxygen complex reacts with N-H bonds in aryl hydrazines to abstract hydrogen atoms. Treatment of $L^{tBu}Co(O_2)$ with low-valent iron and cobalt diketiminate complexes gives new bimetallic products that exhibit enhanced reactivity toward C-H bonds. While intramolecular C-H activation occurs at ambient temperature in the case of the Fe/Co heterobimetallic complex, the Co/Co homobimetallic complex affords a stable bis(□-oxo) species that undergoes intramolecular C-H activation only at elevated temperature. Mechanistic and computational studies are employed to investigate why the heterobimetallic species is more reactive.



Jake Black (Ganim Group)

Development of a Universal Optical Tweezers Platform for Single Molecule Spectroscopies in

With the goal of expanding single molecule spectroscopies to better study the intricacies of chemical catalysis, we have developed the first widely applicable optical tweezers platform for use in organic solvents. Optical tweezers measurements have focused on biophysical applications in aqueous solution due to the availability of bead substrates and coupling chemistries. Our approach utilizes PS@SiO_2 core-shell microspheres coated with "click" functional poly(methyl methacrylate) polymers to form tethers immobilizing single molecules in organic solvents. We establish stable trapping of PS@SiO_2 in organic solvents. Next, single tethers are formed on-the-fly using orthogonal inverse electron-demand Diels-Alder and strain-promoted azide-alkyne cycloaddition "click" reagents. We demonstrate single molecule force extension studies on poly(methyl methacrylate) polymers in a variety of different solvents, including nonpolar, polar aprotic, and polar protic solvents. This platform opens the doors for high resolution force investigation in the 5 to 80 picoNewton regime and immobilization for new single molecule spectroscopies on any molecule functionalized with "click" compatible organic moieties in nearly any solvent.

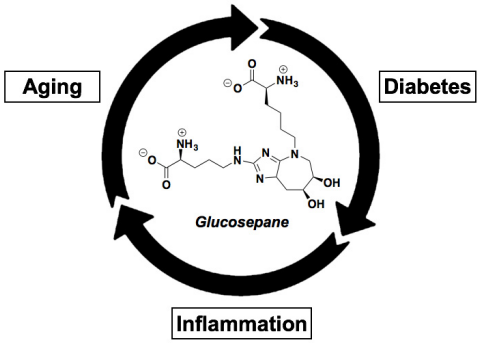


Matthew Streeter (Spiegel Group)

From Synthesis to Pathology: Identifying Glucosepane's Role in Diabetes and Aging

Glucosepane, a non-enzymatic protein crosslink, is formed from the slow reaction of glucose with the nucleophilic residues lysine and arginine, resulting in protein damage. This product has been observed in human tissue samples, with significantly more glucosepane formed in diabetics and the elderly. Moreover, increased glucosepane levels have been strongly correlated with various diabetic complications, including diabetic neuropathy, nephropathy, and retinopathy. This correlative evidence has led researchers to speculate about the potential mechanistic underpinnings of glucosepane in disease. However, concrete experimentation to test these hypotheses has been notably absent.

In an effort to facilitate further studies on glucosepane, our lab has leveraged our synthetic capabilities towards a bottom-up approach, where we aim to gain access to synthetic glucosepane constructs that can then be used to test long-held hypotheses in the field. Having published the first total synthesis of glucosepane last year, we are currently working to incorporate the molecule into more physiologically relevant systems and developing tools, such as antibodies, to better probe glucosepane's effects on human health and biology.



Alanna Schepartz (Keynote Speaker)

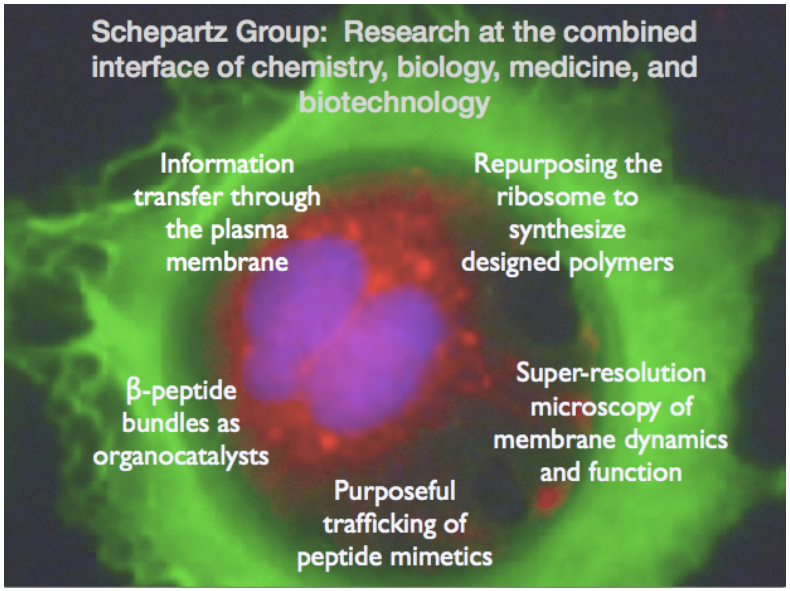
Biography

Alanna Schepartz, Ph.D. is the Milton Harris '29 Ph.D. Professor of Chemistry and Professor of Molecular, Cellular, and Developmental Biology at Yale University.

Professor Schepartz was born on January 9, 1962 in New York City. After receiving a B.S. degree in Chemistry from the State University of New York-Albany in 1982, Alanna carried out graduate work at Columbia University under the supervision of Ronald Breslow. Following postdoctoral work with Peter Dervan at the California Institute of Technology, she joined the faculty at Yale University in July of 1988. She was promoted to Associate Professor in 1992, to Full Professor with tenure in 1995, and was named the Milton Harris, '29 Ph.D. Professor of Chemistry in 2000. From 2002-2007, she held a Howard Hughes Medical Institute Professorship. From 2011-2014, she served as the inaugural Director of the Yale Chemical Biology Institute.

Alanna Schepartz is known for the creative application of chemical synthesis and principles to understand and control biological recognition and function. Her research has contributed to and shaped thinking in multiple areas, including the molecular mechanisms of protein-DNA recognition and transcriptional activation; protein design and engineering and their application to synthetic biology; and the mechanisms by which chemical information is trafficked across biological compartments. She is also widely recognized for her design of β-peptide bundles, the first and only example of a protein-like architecture that lacks even a single α-amino acid.

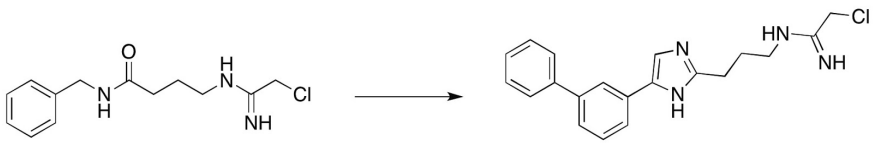
Alanna Schepartz has received a number of awards for her work, including a David and Lucile Packard Foundation Fellowship (1990), a N.S.F. Presidential Young Investigator Award (1991), a Camille and Henry Dreyfus Teacher-Scholar Award (1993), an Alfred P. Sloan Research Fellowship (1994), an A.C.S. Arthur C. Cope Scholar Award (1995), the A.C.S. Eli Lilly Award in Biological Chemistry (1997), the Dylan Hixon '88 Award for Teaching Excellence in the Natural Sciences (1999), the Agnes Fay Morgan Research Award (2002), the Frank H. Westheimer Prize Medal (2008), the ACS Chemical Biology Prize & Prize Lecture (2010), for which she was the inaugural recipient, the Alexander M. Cruickshank Prize (2010), the Ronald Breslow Award for Achievement in Biomimetic Chemistry (2012), and the Wheland Medal (2015). In 2010, Schepartz was elected as a Fellow of both the American Academy of Arts & Sciences and the American Chemical Society. Since 2005, she has served the chemical biology community as an Associate Editor of the *Journal of the American Chemical Society*. In 2014, she was elected to the National Academy of Sciences.



Haya Jamali (Ellman Group)

Substrate Activity Screening Toward the Discovery of Protein Arginine Deiminase (PAD) Inhibitors

Protein Arginine Deiminases (PADs) catalyze the post-translational modification of charged arginine residues to neutral citrulline residues. Due to the net loss of charge, this post-translational modification has the potential to modulate transcription as well as a host of protein-protein interactions. Biologically relevant substrates of this family of enzymes include the tumor suppressor protein p53, histone tails H3 and H4, and cytosolic proteins keratin and myelin basic protein. Due to their pervasive expression in a number of tissues, dysregulation of PADs has been implicated in various disease states, such as the autoimmune disorders Rheumatoid Arthritis and Multiple Sclerosis. PAD3, one isozyme in the family, has been implicated in the neurodegenerative response to spinal cord injury. In this work, Substrate Activity Screening has been applied for the discovery of the first PAD3-selectived inhibitors reported in the literature. Multiple classes of small-molecule inhibitors were screened, identified, and optimized for potency and selectivity. The best inhibitors are over 10-fold selective for PAD3 over other isozymes and have been shown to be active in a cellular assay.



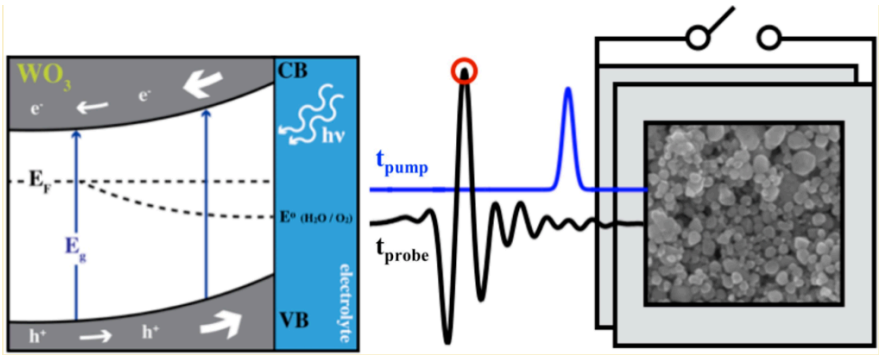
PAD inhibitor library hit

Optimized, cell-active PAD3 inhibitor

Kevin Regan (Schuttenmaer Group)

Size-Dependent Ultrafast Charge Carrier Dynamics of WO_3 for Photoelectrochemical Cells

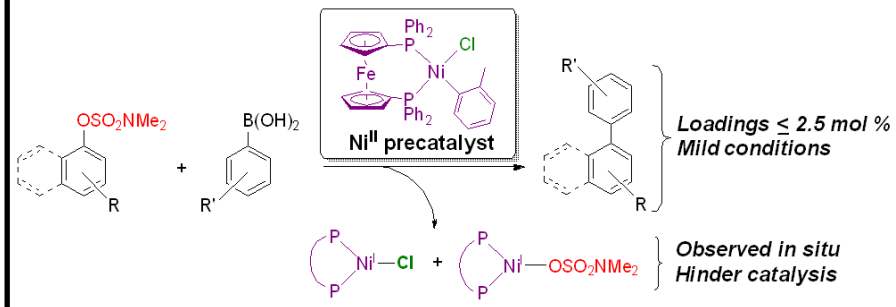
Time-resolved terahertz (THz) spectroscopy and open-circuit photovoltage measurements were employed to examine the size-dependent charge carrier dynamics of tungsten(VI) oxide (WO_3) particles for their use as the photoanode in photoelectrochemical cells. Specifically, films of commercially available WO_3 nanoparticles (NPs) and granular particles (GPs) with diameters of 77 ± 34 and 390 ± 260 nm, respectively, were examined in air and while immersed in 0.1 M Na_2SO_4 electrolyte (pH = 2). Examination of the frequency-dependent transient photoconductivity at short and long time scales indicates the presence of both photoinduced high net transport charge carriers at early times and in some cases low net transport charge carriers at later times. The high net transport charge carriers dominate the photoconductivity signal for ~100 ps after photoexcitation. Depletion of the short-lived high net transport carriers due to trapping leads to the detection of longer- lived low net transport photoinduced charge carriers that likely contribute to surface chemistry.



Megan Mohadjer Beromi (Hazari Group)

Mechanistic Study of an Improved Nickel Precatalyst for Suzuki-Miyaura Reaction of Aryl Sulfamates: Understanding the Role of Ni(I) Species

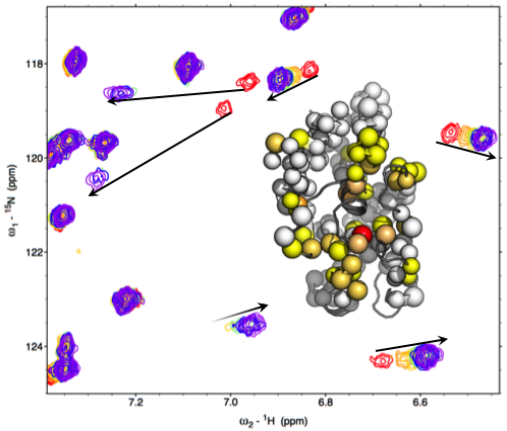
Nickel precatalysts are potentially a more sustainable alternative to traditional palladium precatalysts for the Suzuki-Miyaura coupling reaction. Currently, there is significant interest in Suzuki-Miyaura coupling reactions involving readily accessible phenolic derivatives such as aryl sulfamates, as the sulfamate moiety can act as a directing group for the prefunctionalization of the aromatic backbone of the electrophile prior to cross-coupling. By testing complexes in the Ni(0), (I), and (II) oxidation states, we report a precatalyst, (dppf)Ni(*o*-tolyl)(Cl) (dppf = 1,1'-bis(diphenylphosphino)ferrocene), for Suzuki-Miyaura coupling reactions involving aryl sulfamates and boronic acids, which operates at significantly lower catalyst loading and at milder reaction conditions than other reported systems. Mechanistic studies on precatalyst activation and the speciation of nickel during catalysis reveal that Ni(I) species are formed in the catalytic reaction via two different pathways. In both cases, the formation of Ni(I) is detrimental to catalysis, which is proposed to proceed via a Ni(0)/Ni(II) cycle. Our mechanistic investigation provides guidelines for designing even more active nickel catalysts.



Victor Beaumont (Loria Group)

Functional Implications of the Loop Dynamics of Vaccinia H1-Related Protein Tyrosine Phosphatase

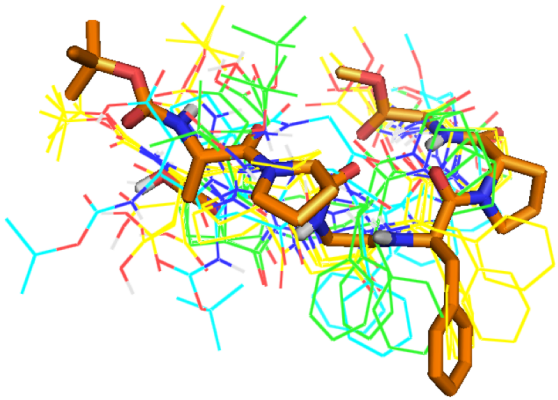
Vaccinia H1-related (VHR) protein tyrosine phosphatase (PTP) is involved in cell cycle regulation. Disruptions in the activity of VHR lead to certain cancers, but drugs targeting VHR and other similar PTPs have yet to advance past the early stages of clinical trials. Further understanding of the mechanism and conformational dynamics may identify novel mechanisms in PTP activity that can be exploited for the development of alternate therapeutics. Previous work in the lab established a correlation between the rate of phosphotyrosine cleavage and the rate of closure in YopH and PTP1b, PTPs that are structurally similar to VHR. Although the crystal structures of YopH and PTP1b show clear conformational differences in the open and closed forms, VHR lacks this duality in conformations in its crystal structures. This suggests that either VHR functions in a rigid form contrary to the other PTPs or the crystal structures do not show the expected relevant conformations. Our recent work focuses on the NMR backbone assignments of VHR to ultimately determine the dynamics of the acid loop. Suspected exchange broadening and NMR relaxation dispersion studies give preliminary



Nadia Abascal (Miller Group)

NMR and X-Ray Crystallography-Based Structural Investigations of Peptide Catalysts

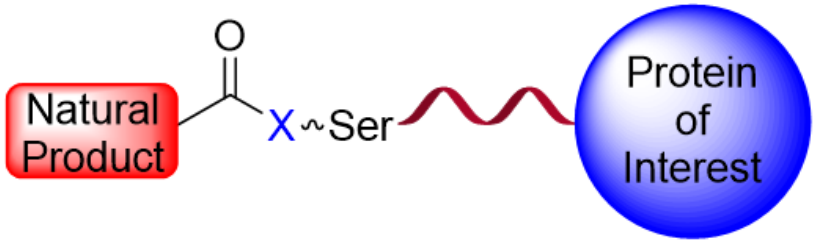
While investigations of protein structure have steadily become more and more refined over the years, similar investigations in the realm of peptide structure have been less numerous. This poster will present studies of peptide-based catalyst structures in the context of oxidation-competent tetra-, penta-, and hexamers. Employing both X-ray crystallography and two-dimensional NMR spectroscopy, we have improved our understanding of the conformational preferences of the catalysts, and their possible connections to the selectivity the catalysts induce in bromination, Baeyer-Villiger, and epoxidation reactions. This poster will discuss structure-function trends in two classes of catalytic peptides, which contain N-terminal dimethylaminoalanine (Dmaa) or aspartic acid as essential catalytic residues, respectively.



Yick Chong Lam (Crawford Group)

Natural Products - Protein Conjugation Through Biosynthetic Engineering

The rise of multidrug resistance in pathogenic bacteria and cancers demands strategies for designing new classes of antimicrobial and anticancer agents. Inspired by the pharmacological Trojan horse mechanism of sideromycins, conjugates between iron-binding siderophores and antibacterials, we have focused on engineering the biosynthetic pathway for the siderophore yersiniabactin in pathogenic Escherichia coli and Yersinia pestis to make yersiniabactin - protein conjugates. Biosynthetic engineering of this pathway allows access to a variety of labile conjugates between yersiniabactin and targeted proteins of interest. We demonstrate the biosynthesis of a transient yersiniabactin - protein conjugate and are currently stabilizing the linkage chemistry for antimicrobial applications. Our approach will enable us to establish the foundational methodologies for engineering other natural product - protein conjugates for functional activity studies.



Speaker Biographies

Xiaoshen Ma (Herzon Group)- Xiaoshen was born and raised in Beijing, China. He attended Peking University for undergrad where he studied copper-carbene chemistry in Prof. Jianbo Wang's group. Upon graduation, he decided to join Prof. Seth Herzon's lab at Yale University. He has been majorly studying cobalt-mediated hydrogenation and hydrofunctionalization of carbon—carbon multiple bonds via hydrogen atom transfer.

Olga Gorlova (Johnson Group)- Olga received an accelerated B.A./M.S. in X-ray crystallography from Rutgers University in New Jersey. Before beginning her degree in chemistry she tried her hand at various research projects at St. Luke's Hospital in New York City as well as other departments at Rutgers. She joined Yale in 2012 and is now in her 5th year with the Johnson Lab where she is pioneering new applications for structural mass spectrometry in the analysis of biologically synthesized small molecules. Her work has been widely recognized by her election to serve as the co-chair of two 2016 Gordon Research Seminars (Molecular and Ionic Clusters and Molecular Interactions and Dynamics). She was also selected as the physical chemistry keynote speaker at the 2016 Pathways to Science Summer Scholars series sponsored by the Yale Chemistry Department. She is an enthusiastic pianist and practitioner of Acro-Yoga.

Daniel Edward DeRosha (Holland Group)- Dan grew up in the rural Midwestern paradise of Elk Rapids, Michigan. As an undergraduate at Carleton College, Dan conducted research in the lab of Professor Matt Whited, synthesizing new bis(phosphine) dihydrosilyl pincer ligands, and was the recipient of the James Finholt Prize in Inorganic Chemistry. As a fourth year graduate student in the Holland lab, Dan studies the reactivity of cobalt diketiminate complexes with O_2, CO_2, and diazoalkanes. Outside of the glovebox, Dan enjoys running, cycling, and singing tenor in the Yale Citations, the Graduate School's co-ed a cappella group.

Jake Black (Ganim Group)- Jake grew up in Littleton, Colorado on the edge of the great Rocky Mountains. Opting to leave this virtual paradise and explore the rest of the country, Jake attended Villanova University just outside Philadelphia, PA. While there he discovered his passion for chemistry and conducted research under the tutelage of Professor Kevin P. C. Minbiole, synthesizing antibacterial amphiphiles. At Yale, Jake joined the lab of Professor Ziad Ganim and now works on the development of new optical tweezers methods for performing single molecule infrared spectroscopy on transition metal catalysts. While not pondering the mysteries of the natural world, Jake enjoys the great outdoors, drinking beer, regretting not going to the gym, not regretting playing video games, pseudointellectual philosophical discussion, and buying new books to really fill out his bookshelf.

Speaker Biographies (continued)

Matthew Streeter (Spiegel Group)- Matt Streeter completed his undergraduate studies in Chestertown, MD, where he attended Washington College. There he double-majored in Chemistry and Behavioral Neuroscience, gaining research experience in both fields. Now a 4th year graduate student in the Spiegel lab, Matt has continued pursuing interdisciplinary research, working on the chemical synthesis and biological characterization of a class of non-enzymatic protein modifications called advanced glycation endproducts (AGEs). Outside of lab, Matt enjoys hiking, playing IM soccer, and participating in science-related outreach.

Haya Jamali (Ellman Group)- Haya grew up in the small town of Richland, Washington, which is best identified by the fact that it is 4 hours away from Seattle. As an undergraduate, she attended Whitman College, where she performed research on the design and synthesis of small molecule inhibitors of the proteasome. Haya is now a fifth-year graduate student in the Ellman lab, and enjoys working at Yale's West Campus in vibrant West Haven. When the weather is good, Haya enjoys taking photographs of mountains and reluctantly climbing them.

Kevin Regan (Schuttenmaer Group)- Kevin Regan is originally from Manchester, NH. He graduated from Bates College in Lewiston, ME with a B.S. in Chemistry. Currently, he is a rising fourth year graduate student in Charles Schmuttenmaer's Lab. His interest is in spectroscopy, mainly studying the ultrafast photoinduced charge dynamics in various metal oxides for their use in photoelectrochemical cells using time-resolved THz spectroscopy.

Megan Mohadjer Beromi (Hazari Group)- Megan is a third year graduate student in the Hazari lab. Originally from Mount Airy, Maryland, she attained her Bachelor of Science from the University of the Sciences in Philadelphia, majoring in chemistry with a minor in mathematics. At the University of the Sciences, she researched the transition metal catalyzed degradation of pyrolytic lignin into useful phenolics, and now works on understanding the mechanism of nickel catalysts in the cross-coupling of phenolic derivatives.

Speaker Biographies (continued)

Victor Beaumont (Loria Group)- Victor Beaumont graduated from the State University of New York at Buffalo University in 2013 with a Bachelor's Degree in Science in Chemistry and Medicinal Chemistry. His undergraduate research under Dr. Thomas Szyperski focused on methods development of NMR experiments for the structure determination of large macromolecules. Victor came to Yale University in the fall of 2013 as part of the biophysical chemistry discipline in the department of chemistry as a trainee of the NIH Biophysical Training Grant. He joined the laboratory of Dr. Patrick Loria in 2014 where he works on protein dynamics of protein tyrosine phosphatases (PTPs) using NMR spectroscopy. He recently presented his research on *Vaccinia-H1*-Related PTP at the 2016 Experimental NMR Conference (ENC) and Gordon Research Conference on Molecular Structure Elucidation.

Nadia Abascal (Miller Group)- Nadia Abascal has recently completed her fifth year of graduate study in the Miller Group and plans to defend her Ph.D. in December 2016. While her current research deals mainly with the structural characterization of Miller Group peptide catalysts using techniques based in two-dimensional NMR, her post-doctoral research, in Prof. Lynne Regan's group, will take her into the realm of molecular biophysics and biochemistry. Aside from "chemist," Nadia also describes herself as a proud daughter of Maryland, Barnard College, and Michelle Abascal—all-around sassy lady and world-renowned mom. In her spare time, she likes to lift heavy things and put them back down, quickly. Nadia has enjoyed working under the impeccable guidance of Prof. Scott Miller and with all of her fun, friendly, and startlingly sharp colleagues in the Miller Group. Moreover, she would be truly delighted to answer any questions about her research, Maryland, Barnard, or her mom, among many other potential topics of conversation. She also extends a hearty welcome to Yale!

Yick Chong Lam (Crawford Group)- Yick Chong Lam was raised in Rochester, NY and attended the University of Rochester, from which he graduated with a B.S. Degree in Chemistry. Throughout his undergraduate career, he conducted research in the laboratory of Rudi Fasan, developing methods that exploit unnatural amino acid mutagenesis towards synthesizing cyclic peptides. Immediately before matriculating at Yale, he worked in the laboratory of Gary Brudvig, synthesizing corrole derivatives capable of electron transfer reactions for dye-sensitized photoelectrochemical cells. In the Crawford Lab, Yick is harnessing the modularity of select metabolic pathways to engineer new bioactive macromolecules.

Acknowledgments

The second year graduate students would like to thank everyone who made this symposium possible, including Yale University's Chemistry Department for their support and generosity, the outstanding student speakers for highlighting the department's research diversity, and to Professor Alanna Schepartz for graciously agreeing to deliver this year's keynote lecture. Finally, we'd like to welcome Yale Chemistry's newest graduate student class!