2024

Glenn T. Seaborg Symposium

Abstract Book

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Poster Abstract 1

Morgan Gee[1,*], Nika Gladkov[1,*], Todd O. Yeates[1,2,3]

[1]Department of Chemistry and Biochemistry, University of California, Los Angeles, CA, USA 90095

[2]Molecular Biology Institute, University of California, Los Angeles, Los Angeles, CA, USA 90095

[3]UCLA-DOE Institute for Genomics and Proteomics, Los Angeles, CA, USA 90095

* Equal contributions

Methods in protein design have made it possible to create large, self-assembling protein cages with diverse applications. Recent advancements include their use as cryo-EM scaffolds, ligand and protease-triggered cage disassembly, and high affinity β-2-microglobulin binding. Here, we describe two other applications of these protein cages: fluorescent protein cages as markers for cell imaging and the design of symmetry-broken protein cages.

The spatiotemporal imaging of targeted proteins is crucial in understanding the organizations and interactions of proteins in their natural cellular state. Due to current limitations in producing high-resolution images of small protein targets, we have developed a technique whereby designed fluorescent protein cages are delivered inside cells, acting as fluorescent biomarkers. By engineering symmetric protein cages with outward-facing αGFP DARPin domains, we successfully visualize the internalization and binding of GFP-tagged proteins *in vivo* with confocal microscopy.

We expand upon these existing symmetric designs by demonstrating a facile approach for creating symmetry-broken protein cages able to display single copies of outward-facing domains. We modify the subunit of an otherwise symmetric protein cage by fusing a small inward-facing domain, in which only one copy can be accommodated in the cage interior. Using biochemical methods and native mass spectrometry, we show that co-expression of the original subunit and the modified subunit, which is further fused to an outward-facing αGFP DARPin domain, leads to self-assembly of a protein cage presenting just one copy of the DARPin on its exterior.

Poster Abstract 2

Breaking Kinetic Record for Cysteine Bioconjugation with Organometallic Reagents

Evan A. Doud[1‡], James A. R. Tilden[2‡], Joseph W. Treacy[1,3‡], Elaine Y. Chao[1], Hayden R. Montgomery[1], Grace E. Kunkel[1], Nima Adhami[1], Tyler A. Kerr[1], Arnold L. Rheingold[4], Christopher G. Frost[2], K. N. Houk[1,3]*, Heather D. Maynard[1,3]*, Alexander M. Spokoyny[1,3]*

[1]*Department of Chemistry and Biochemistry, University of California, Los Angeles, Los Angeles, California 90095, United States*

[2]*Department of Chemistry, University of Bath, Claverton Down, BA2 7AY Bath, United Kingdom*

[3]*California NanoSystems Institute, University of California, Los Angeles, Los Angeles, California 90095, United States*

[4]*Department of Chemistry and Biochemistry, University of California, San Diego, La Jolla, California 92093, United States*

*Correspondence to spokoyny@chem.ucla.edu (A.M.S); maynard@chem.ucla.edu (H.D.M.); houk@chem.ucla.edu (K.N.H.)

Abstract

Through mechanistic work and rational design, we have developed the fastest organometallic abiotic cysteine (Cys) bioconjugation. As a result, the developed organometallic Au(III) bioconjugation reagents enable selective labelling of Cys moieties down to pM concentrations and allow for the rapid construction of complex heterostructures from peptides, proteins, and oligonucleotides. This work showcases how organometallic chemistry can be interfaced with biomolecules and lead to the range of reactivities that are unmatched by classical organic chemistry tools.

Funding Sources

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Poster Abstract 3

An Organometallic Strategy for Peptide Macrocyclization

Nima Adhami[a], Evan A. Doud[a], Michael, Rebello[a], Jeff Qu[a], Reanne Coutinho[a], Tyler A. Kerr[a], Jose A. Rodriguez[a,b], Alexander M. Spokoyny[a,b]

[a]Department of Chemistry and Biochemistry, University of California, Los Angeles, Los Angeles, CA 90095, USA

[b]California NanoSystems Institute, University of California, Los Angeles, Los Angeles, CA 90095, USA

Constrained peptide macrocycles are small molecule peptide hybrids that have undergone structural rigidification, resulting in a myriad of novel therapeutic properties. However, their efficient and chemoselective synthesis has proved challenging. We would like to present a robust organometallic strategy to generate complex peptide macrocycles through sulfur-aryl linkages facilitated by (MeDalPhos)Au(III)Aryl reagents. By leveraging the rapid kinetics and chemoselectivity of these Au(III) reagents towards soft nucleophiles, such as the thiol containing functional group of cysteine, we have been able to successfully generate a library of peptide tricycles, all of which bear abiotic geometries with potential therapeutic properties. Furthermore, by rigidifying the geometry of peptides around known solid-state fluorophores such as tetraphenylphenylethylene, we are able to generate constrained peptide macrocycles with unique solution-state fluorescent profiles to be used in such applications as live cell imaging.

Poster Abstract 4

Autonomous closed-loop mechanistic investigation of molecular electrochemistry via automation

Hongyuan Sheng,[1] Jingwen Sun,[1] Oliver Rodríguez,[2,3,4] Benjamin B. Hoar,[1] Weitong Zhang,[5] Danlei Xiang,[1] Tianhua Tang,[6] Avijit Hazra,[6] Daniel S. Min,[1] Abigail G. Doyle,[1] Matthew S. Sigman,[6] Cyrille Costentin,[7] Quanquan Gu,[5] Joaquín Rodríguez-López,[2,3,4] Chong Liu[1,8]

[1] Department of Chemistry and Biochemistry, University of California, Los Angeles, Los Angeles, California 90095, United States

[2] Department of Chemistry, University of Illinois at Urbana−Champaign, Urbana, Illinois 61801, United States

[3] Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana−Champaign, Urbana, Illinois 61801, United States

[4] Joint Center for Energy Storage Research (JCESR), Argonne National Laboratory, Lemont, Illinois 60439, United States

[5] Department of Computer Science, University of California Los Angeles, Los Angeles, California 90095, United States

[6] Department of Chemistry, University of Utah, Salt Lake City, Utah 84112, United States

[7] Université Grenoble Alpes, DCM, CNRS, 38000 Grenoble, France

[8] California NanoSystems Institute, University of California, Los Angeles, Los Angeles, California 90095, United States

Abstract

Electrochemical research often requires stringent combinations of experimental parameters that are demanding to manually locate. Recent advances in automated instrumentation and machine-learning algorithms unlock the possibility for accelerated studies of electrochemical fundamentals via high-throughput, online decision-making. Here we report an autonomous electrochemical platform that implements an adaptive, closed-loop workflow for mechanistic investigation of molecular electrochemistry. As a proof-of-concept, this platform autonomously identifies and investigates an *EC* mechanism, an interfacial electron transfer (*E* step) followed by a solution reaction (*C* step), for cobalt tetraphenylporphyrin exposed to a library of organohalide

electrophiles. The generally applicable workflow accurately discerns the *EC* mechanism's presence amid negative controls and outliers, adaptively designs desired experimental conditions, and quantitatively extracts kinetic information of the *C* step spanning over 7 orders of magnitude, from which mechanistic insights into oxidative addition pathways are gained. This work opens opportunities for autonomous mechanistic discoveries in self-driving electrochemistry laboratories without manual intervention.

Funding sources

Funding for this work was provided by the National Science Foundation (NSF) (CHE-2140762 and CHE-2247426 to C.L. and Q.G.; CHE-2102266 to A.G.D.; CHE-2002158 (Center for Synthetic Organic Electrochemistry) to M.S.S.), the Joint Center for Energy Storage Research (JCESR), an Energy Innovation Hub funded by the U.S. Department of Energy, Office of Science, Basic Energy Sciences (to J.R.L.), and partially the Agence Nationale de la Recherche (Labex ARCANE, CBH-EUR-GS, ANR-17-EURE-0003 to C.C.).

Poster Abstract 5

Authors: Ajmera, P., Chaturvedi, S. S., Vargas, S., Alexandrova, A.N.
Affiliation and Funding: UCLA Department of Chemistry and Biochemistry | NIH, NSF
Title: Electric Fields in Enzymatic Catalysis
Abstract: Electrostatic preorganization is a pivotal concept in the discussion of enzyme catalysis. In recent years, electric fields have become a good descriptor to gauge this preorganization experienced by the enzyme's active site. We contend that the electric field vector at a single point might not capture the entirety of the electrostatic landscape necessary for a reaction. Our findings suggest that a dynamic approach, encompassing the entire heterogeneous three-dimensional electric field and its topology, offers a more comprehensive assessment of an enzyme's electrostatic preorganization and its influence on catalytic activity. We introduce an adaptable, open-source Python framework for such analyses, applicable across various classes of enzymatic reactions. In a notable application, we demonstrate that a machine learning model, trained on three-dimensional electric field topologies can precisely predict heme enzyme functions. This implies that enzymes adjust their three-dimensional electric fields to suit specific catalytic tasks. Further, we illustrate that the directed evolution of protoglobin for a non-native cyclopropanation reaction modulates the enzyme's inherent electric field, optimizing it for the new reaction. Our research highlights the intricate ways in which natural and evolved enzymes tailor the electric fields at their active sites for optimized catalysis.

Poster Abstract 6

Abstract for Seaborg Symposium 2024

Misaki Nagae

Title: A Readily Scalable, Clinically Demonstrated, Antibiofouling Zwitterionic Surface Treatment for Implantable Medical Devices (published on Advanced Materials)

Authors: Brian McVerry, Alexandra Polasko, Ethan Rao, Reihaneh Haghniaz, Dayong Chen, Na He, Pia Ramos, Joel Hayashi, Paige Curson, Chueh-Yu Wu, Praveen Bandaru, Mackenzie Anderson, Brandon Bui, Aref Sayegh, Misaki Nagae, Shaily Mahendra, Dino Di Carlo, Evgeniy Kreydin, Ali Khademhosseini, Amir Sheikhi,* and Richard B. Kaner*

Abstract:
Unlike growth on tissue, microbes can grow freely on implantable devices with minimal immune system intervention and often form resilient biofilms that continuously pump out pathogenic cells. The efficacy of antibiotics used to treat infection is declining due to increased rates of pathogenic resistance. A simple, one-step zwitterionic surface modification is developed to significantly reduce protein and microbial adhesion to synthetic materials and demonstrate the successful modification of several clinically relevant materials, including recalcitrant materials such as elastomeric polydimethylsiloxane. The treated surfaces exhibit robust adhesion resistance against proteins and microorgan- isms in both static and flow conditions. Furthermore, the surface treatment prevents the adhesion of mammalian fibroblast cells while displaying no cyto- toxicity. To demonstrate the clinical efficacy of the novel technology in the real- world, a surface-treated, commercial silicone foley catheter is developed that is cleared for use by the U.S. Food and Drug Administration (K192034). 16 long- term catheterized patients received surface-treated catheters and completed a Patient Global Impression of Improvement (PGI-I) questionnaire. 10 out of 16 patients described their urinary tract condition post implantation as “much better” or “very much better” and 72% (n = 13) of patients desire to continue using the surface-treated catheter over conventional latex or silicone catheters

Affiliations:
B. McVerry, E. Rao, N. He, P. Curson, M. Anderson, Misaki Nagae, R. B. Kaner
Department of Chemistry and Biochemistry
University of California
Los Angeles, CA 90095, USA
E-mail: kaner@chem.ucla.edu

B. McVerry, E. Rao, B. Bui, R. B. Kaner
Silq Technologies, Corp.
Los Angeles, CA 90025, USA

A. Polasko, P. Ramos, S. Mahendra
Department of Civil and Environmental Engineering University of California

Los Angeles, CA 90095, USA

R. Haghniaz, J. Hayashi, P. Bandaru, A. Khademhosseini Center for Minimally Invasive Therapeutics (C-MIT) University of California, Los Angeles
Los Angeles, CA 90095, USA

R. Haghniaz, J. Hayashi, P. Bandaru, A. Khademhosseini, R. B. Kaner California NanoSystems Institute (CNSI)
University of California, Los Angeles
Los Angeles, CA 90095, USA

D. Chen, R. B. Kaner
Department of Materials Science and Engineering University of California
Los Angeles, CA 90095, USA

C.-Y. Wu, D. D. Carlo
Department of Bioengineering
University of California, Los Angeles
Los Angeles, CA 90095, USA

A. Sayegh, E. Kreydin
Department of Urology
Keck School of Medicine of University of Southern California Los Angeles, CA 90033, USA

A. Sayegh, E. Kreydin
Rancho Research Institute
Rancho Los Amigos National Rehabilitation Center
Downey, CA 90242, USA

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Poster Abstract 7

3D-Printed Carbon Scaffold for Long-lasting and High-energy-density Lithium Metal Secondary Batteries

Joanne Hui, Yuto Katsuyama, Richard B. Kaner

The advancement of compact and efficient energy storage has fueled progress in portable consumer electronics such as phones and laptops. However, the current focus has shifted towards curbing carbon emissions in the transportation sector by promoting electric vehicles (EVs) as an eco-friendly alternative to traditional internal combustion engines. Critical to this shift are lithium-ion batteries (LIBs), valued for their lightweight design and high capacity. In 2022, EV sales surpassed 10 million units, projected to increase by 35% in 2023, reaching a total of 14 million units.

Nevertheless, a significant barrier to widespread EV adoption persists: range anxiety, the fear of running out of charge before reaching a destination. One potential solution involves enhancing the energy density of LIBs using lithium metal, which boasts an impressive capacity of 3860 mAh g^{-1}, dwarfing the conventional graphite anode's capacity of 372 mAh g^{-1}. However, this solution encounters durability issues due to dendrite growth and electrode thickness fluctuations, leading to short circuits and loss of electrical contact within the cell.

A promising approach involves using a 3D carbon scaffold to control dendrite growth and maintain stable electrode thickness. This scaffold's success relies on its ability to confine Li metal deposition inside the scaffold and maintain structural strength. In this study, we developed strong 3D-printed carbon scaffolds using an affordable stereolithography-type home 3D printer (~$200) and simple carbonization. This research has demonstrated that the 3D carbon scaffold outperforms bare Li metal anodes, with lower overpotential and stable cycling. This improvement is set to enhance lithium metal anode performance, boosting battery safety and lifespan.

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Poster Abstract 8

Tunable Coacervates Derived from Functionalized Poly(Dehydroalanine)

Casey A. Morrison[1]; Thatcher Lee[3]; **Ethan P. Chan**[1]; Timothy J. Deming[1,2*]
[1]Department of Chemistry and Biochemistry, UCLA; [2]Department of Bioengineering, UCLA
[3]Department of Chemistry, Smith College

Long-chain dehydroalanine polymers ($\mathbf{A^{DH}}$) were previously synthesized by researchers in the Deming group and found to adopt an uncommon "hybrid coil" conformation. The unsaturated side chains of $\mathbf{A^{DH}}$ feature high electrophilic reactivity, allowing for functionalization via Michael addition with mercaptoamido amino acids to produce a variety of functionalities and promote coacervate formation ideal for polynucleotide and protein delivery. Here, we report the successful synthesis of multiple mercaptoamido amino acid functionalized $\mathbf{A^{DH}}$ polymers capable of coacervate formation under desired conditions. Successful formation of coacervates was observed with MetSH, LeuSH, and ValSH derivatives of $\mathbf{A^{DH}}$, while precipitate formation was observed with AlaSH and ProSH derivatives. MetSH derivative $\mathbf{A^{DH}}$ exhibited excellent reversibility under different temperature and redox conditions, while all resultant polymers showcased highly tunable properties under physiologically-relevant pH and temperature ranges. GPC and NMR data showed near-quantitative post-polymerization functionalization, supporting the pursued synthetic strategy. The reversibility of MetSH-derivative $\mathbf{A^{DH}}$ yields high potential for triggered release of therapeutics under physiological conditions, and high tunability via choice of amino acid showcases potential for future use in a number of applications. Further studies on mercaptoamido-peptide incorporation may provide further contextualization of stimuli-responsive properties.

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Poster Abstract 9

Designer bioorthogonal host–guest pairs for cell-surface labeling

Prairie Hammer, Ellen M. Sletten
Department of Chemistry & Biochemistry, UCLA

Abstract: The study and manipulation of biomolecules in their natural environments is a key goal in the field of chemical biology. One approach to this goal is the chemical reporter strategy, which relies on bioorthogonal chemical reactions to visualize, alter, and discover complex biological processes. While these reactions are often efficient, their kinetics do not translate well to complex biological systems. The Sletten lab has shifted focus onto an alternative approach, using noncovalent, host–guest complexation to evade the kinetic limitations of bioorthogonal chemistry. Inspired by an established macrocyclic host, we have redesigned the host to selectively bind perfluoroaromatic guests of interest. Our host–guest pairs are the first ever to be designed for use in the chemical reporter strategy, making them especially bioorthogonal and selective in the cellular environment. The work described herein demonstrates the design principles necessary for bioorthogonal complexation, and showcases the ability of host–guest chemistry to surpass traditional bioorthogonal chemistry for certain biological applications.

Poster Abstract 10

2024 Seaborg Conference—Abstract submission:

Shortwave Infrared Fluorescent Star Polymers as Water-Soluble Optical Imaging Probes

Emily B. Mobley[1,2], Ellen M. Sletten[1,3]

[1] *Department of Chemistry and Biochemistry, University of California, Los Angeles, Los Angeles, CA 90095, United States*

[2] *emilybrimobley@chem.ucla.edu*

[3] *sletten@chem.ucla.edu*

Optical imaging utilizing fluorophores as contrast agents has revolutionized the way we study biological processes in cells and transparent organisms, facilitating the advancement of biomedicine. Although optical imaging has many advantages such as low cost, fast speed, high resolution, and safe/non-toxic nature, there have been challenges effectively translating these advantages to humans. This is because imaging more complex organisms suffers from significant background autofluorescence of endogenous chromophores, light scattering and limited tissue penetration. Taking advantage of the red-shifted wavelengths of the shortwave infrared (SWIR, 1000-2000 nm), we are able to achieve substantial penetration of light through tissue with decreased scattering. *Unfortunately, the vast majority of small molecule organic SWIR probes are extremely hydrophobic, displaying poor water solubility and non-emissive aggregation* in vivo, *which limits their photophysical properties, bioavailability, and most importantly, clinical applications.* This research seeks to merge biocompatible poly(2-oxazoline)s with SWIR fluorophores, resulting in well-defined SWIR-emissive star polymers that will overcome these limitations and enable faster, more accurate imaging of disease. These contrast agents will be modular, require no additives, and can be targeted to disease-associated epitopes, thereby facilitating new diagnostic procedures, or helping surgeons selectively identify and remove diseased tissues.

Poster Abstract 11

Macromolecular Crowding as an Intracellular Stimulus for Responsive Polyoxazoline Nanomaterials

Paige S. Kotowitz,[1] Daniel A. Estabrook,[1] John O. Chapman,[1] Shuo-Ting Yen,[2] Helen H. Lin,[1] Ethan T. Ng,[1] Linglan Zhu,[1] Heidi L. van de Wouw,[1] Otger Campàs[2,3], Ellen M. Sletten[1]*

[1] *Department of Chemistry and Biochemistry, University of California, Los Angeles, 619 Charles E Young Dr E, Los Angeles, California 9009, United States*

[2] *Department of Mechanical Engineering, University of California, Santa Barbara, California 93106, United States*

[3] *Cluster of Excellence Physics of Life, TU Dresden, Dresden 01062, Germany*

**e-mail: sletten@chem.ucla.edu*

Soft nanomaterials have been extensively studied as "smart" therapeutic carriers due to high biocompatibility and tailorable response to various stimuli. A promising polymer scaffold for smart materials is poly(oxazoline)s due to their thermoresponsive, water-soluble, and peptidomimetic nature.[1–4] Thanks to amphiphilic character, poly(oxazoline)s can form various nanoscale conformations, such as self-assembled micelles or oil-in-water emulsions.[1,5,6] As thermoresponsive materials, poly(oxazoline)s undergo an entropically-driven phase separation at elevated temperatures due to polymer dehydration and subsequent collapse and aggregation into a polymer rich phase.[7] Inspired by parallels to entropically-driven protein folding, the Sletten Group recently identified that the crowded intracellular environment (macromolecular crowding) can serve as an endogenous stimulus for typically thermoresponsive poly(oxazoline)-stabilized nanoemulsions by reducing the lower critical solution temperature (LCST) to physiological temperature.[8] Macromolecular crowding as an intracellular stimulus is a new concept, and thus little is known mechanistically of the interactions between the nanomaterial and the intracellular environment that drives the response. Various polymer compositions and architectures will be discussed to elucidate the role of the polymer in the crowding mechanism and practical applications of a novel class of stimuli-responsive materials that capitalizes on the intracellular environment. Studies include polymer backbone modifications, and evaluating physical interactions between the polymer and protein crowders, thus enhancing the understanding of macromolecular crowding-induced responses. Additional work aims to evaluate the versatility of macromolecular crowding as an intracellular stimulus and develop predictable metrics for vast applications of this novel behavior.

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Poster Abstract 12

Enhancing photostability and brightness of fluorous soluble fluorophores for biological imaging via counterion exchange

Helen H. Lin,[1] Irene Lim,[1] Ellen M. Sletten[1*]

[1] *Department of Chemistry and Biochemistry, University of California, Los Angeles, 607 Charles E Young Dr E, Los Angeles, CA, USA.*

Perfluorocarbons are chemically and biologically inert molecules, making them ideal platforms to deliver diagnostic and therapeutic agents. However, there are significant challenges to making fluorous soluble molecules, specifically fluorous soluble fluorophores. These obstacles include decreased brightness and photostability of the fluorophore, rendering them less compatible for biological imaging. To overcome these limitations, we performed a counterion exchange to decrease aggregation of fluorous cyanine dyes (F_{86}Cy5) by replacing the chloride counterion with larger and more fluorous counterions. This approach also has the added benefit of avoiding tedious synthetic modifications to the dye scaffold. Photophysical characterization of the exchanged dyes displayed up to a 5-fold increase in overall brightness of F_{86}Cy5 fluorophores paired with the larger counterions. However, the most significant progress has been made in overcoming the poor photostability of the F_{86}Cy5 dyes. After exchanging the chloride counterion with a tetrakis[3,5-bis(trifluoromethyl)phenyl] boron ($BArF^-$) counterion on F_{86}Cy5, we saw a 54-fold reduction in photobleaching rates. Further investigation of counterion effects towards photostability revealed F_{86}Cy5 associated with $BArF^-$ generates less reactive singlet oxygen and reduces the ground state reactivivty of the fluorophore's polymethine chain. Additionally, we observed similar brightness and photostability trends with fluorous rhodamine dyes, showcasing the versatility of counterion exchange. We believe the increased strength of ion pairs in the fluorous phase renders counterion effects particularly impactful for fluorous fluorophores.[1] The ultra-facile approach of counterion modifications show tremendous promise towards expanding the utility and tunability of fluorous fluorophores for current and new imaging assays and platforms.

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- NIGMS
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Poster Abstract 13

Seaborg Symposium

Poster Title: Uniform Trehalose Nanogels for Glucagon Stabilization

First Author: Ellie Puente
Affiliation: University of California Los Angeles Department of Chemistry and Biochemistry
Funding sources: National Institutes of Health (NIH R01DK127908).

Abstract: Glucagon is a peptide hormone that acts via receptor-mediated signaling predominantly in liver to raise glucose levels by hepatic glycogen breakdown or conversion of noncarbohydrate, 3 carbon precursors to glucose by gluconeogenesis. Glucagon is administered to reverse severe hypoglycemia, a clinical complication associated with type 1 diabetes However, due to low stability and solubility at neutral pH, there are limitations in the current formulations of glucagon. Trehalose methacrylate-based nanoparticles were utilized as the stabilizing and solubilizing moiety in the system reported herein. Glucagon was site-selectively modified to contain a cysteine at amino acid number 24 to covalently attach to the methacrylate-based polymer containing pyridyl disulfide side chains. PEG2000 dithiol was employed as the crosslinker to form uniform nanoparticles. Glucagon nanogels were monitored in phosphate-buffered saline (PBS) pH 7.4 at various temperatures to determine its long-term stability in solution. Glucagon nanogels were stable up to at least 5 months by size uniformity when stored at -20 °C and 4 °C, up to 5 days at 25 °C and less than 12 hours at 37 °C. When glucagon stability was studied by either HPLC or thioflavin T assays, the glucagon was intact for at least 5 months at -20 °C and 4 °C within the nanoparticles at -20 °C and 4 °C and up to 2 days at 25 °C. Additionally, the glucagon nanogels were studied for toxicity and efficacy using various assays in vitro. The findings indicate that the nanogels were nontoxic to fibroblast cells and nonhemolytic to red blood cells The glucagon in the nanogels were as active as glucagon. These results demonstrate the utility of trehalose nanogels towards a glucagon formulation with improved stability and solubility in aqueous solutions, particularly useful for storage at cold temperatures.

Poster Abstract 14

Integrating cryoEM and cryoET to localize the elusive capping enzyme of a dsRNA virus

Nicolas Coral*[1,2,3] , Yao He*[1,2], Po-Yu Sung[4], Polly Roy[4], and Z. Hong Zhou[1,2]

1. Department of Microbiology, Immunology & Molecular Genetics, University of California Los Angeles, Los Angeles, CA 90095, USA.
2. California NanoSystems Institute, University of California Los Angeles, Los Angeles, CA 90095, USA.
3. Molecular Biology Institute, University of California Los Angeles, Los Angeles, CA 90095, USA.
4. Department of Pathogen Molecular Biology, London School of Hygiene and Tropical Medicine, WC1E 7HT London, United Kingdom

Bluetongue virus (BTV), a major threat to livestock, is a multilayered, nonturreted member of the *Reoviridae*, a family of segmented dsRNA viruses characterized by endogenous RNA transcription. Many eukaryotic viruses have evolved unique strategies of adding a methylguanosine "cap" to nascent mRNA, which stabilizes the transcript and prevents its detection and degradation by the host. Thus, viral RNA capping machinery may be a promising antiviral drug target. Using single-particle cryoEM, our group recently reported the asymmetric reconstruction of the BTV vertex and solved an *in situ* structure of the RNA-dependent RNA polymerase (RdRp) VP1. Curiously, the density for the capping enzyme VP4 was not observed using this subparticle reconstruction method. To determine the location of VP4, we are using cryoET to image recombinantly expressed BTV core-like particles (BTV CLP) that lack RNA genome and encapsidate VP4 and/or VP1. Our preliminary subtomogram averaging (STA) of 170 VP4 particles inside BTV CLP suggests VP4 is located at the 2-fold axes adjacent to the BTV vertices, which has been proposed for the closely related rotavirus capping enzyme and may explain why subparticle reconstruction of the BTV vertex with C5 symmetry has not elucidated the location of VP4.

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Poster Abstract 15

Solution-Processable Semiconductors for Next-Generation Optoelectronics: From Bulk, Metal Halide Perovksites to Nanocrystal, Metal Chalcogenides

Eugenia S. Vasileiadou,[1,2] Tasnim Ahmed, [1] Belle Coffey, [1] Elijah Cook, [1] Caleb Pike, [1] Victoria Rubio,[1] Mercouri G. Kanatzidis,[2] Alexander M. Spokoyny [1] and Justin R. Caram[1]

[1] Department of Chemistry and Biochemistry, University of California, Los Angeles, Los Angeles, California 90095, United States

[2] Department of Chemistry, Northwestern University, Evanston, Illinois 60208, United States

Optoelectronic devices are key in establishing clean energy-efficient optical sources. Herein, we report the synthesis, characterization and stability studies of several novel families of hybrid metal halide perovskites. Firstly, the structure-stability-property relationships of the two most representative families of 2D halide perovskites for photovoltaics: Ruddlesden-Popper and Dion-Jacobson were investigated by tailoring the structure type through the organic cation.[1] Next, we report the series of perovskites with bifunctional cations of allylammonium (AA) containing an alkene group: $(AA)_2(CH_3NH_3)_{n-1}Pb_nI_{3n+1}$ (n = 1-3) and of iodopropylammonium (IdPA) containing iodine: $(IdPA)_2(CH_3NH_3)_{n-1}Pb_nI_{3n+1}$ (n = 1-3) that exhibit trap-state photoluminescence.[2] Further engineering the organic layers with the symmetric triamine luminophore T = 1,3,5-tris-(4-aminophenyl)benzene leads to hybrid lead halides with unprecedented 3D structural motifs and exceptional environmental stability.[3] Lastly, we focus on tailoring the inorganic components of the perovskite structure.[4-6] Through increasing the electronegativity from X=I to X=Br in the family $(C_mH_{2m+1}NH_3)_2(CH_3NH_3)Pb_2X_7$ (m = 6–8), the carrier lifetime and extrinsic stability was observed to increase.

In parallel, we report developments of non-standard, metal chalcogenide nanocrystal semiconductors. Initially, we are preparing CdSe nanocrystals with carborane functional surface ligands where we are working to tune the surface dipoles of the carboranes and investigate the resultant changes in nanocrystal dynamics. Also, we are mapping out the growth mechanism of HgTe nanocrystals to derive design principles for new infrared-emitting semiconductors. Altogether, our work has elevated the current synthetic output and structure-property relationships of solution-processable semiconductors, thus advancing the rational design of next-generation optoelectronics.

Funding:
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[1] Vasileiadou, E. S., et. al., *J. Am. Chem. Soc.* **2021,** *143* (6), 2523-2536. [2] Vasileiadou, E. S., et. al., *J. Am. Chem. Soc.* **2022,** *144* (14), 6390-6409. [3] Vasileiadou, E. S., et. al; *Chem. Mater.* **2023**, *35, 14,* 5267—5280. [4] Vasileiadou, E. S., et. al., *Chem. Mater.* **2021,** *33* (13), 5085-5107. [5] Vasileiadou, E. S., et. al; *J. Am. Chem. Soc.***2023**, *145 (29),* 15997-16014. [6] Vasileiadou, E. S.; Kanatzidis, M. G., *Israel Journal of Chemistry* **2021,** *61* (11-12), 782-817.

Poster Abstract 16

In-Situ Tools to Study the Growth of Semiconducting Nanocrystals in Real Time

Caleb Pike

Justin Caram Group

Semiconducting Nanocrystals are a promising class of materials that have found remarkable applications in solar energy, photodetection, displays, and lighting due to their tunable photonic properties and synthesis compared to other semiconducting materials. Recent innovations in their synthesis has resulted in an explosion of extremely interesting new materials, including 1D nanorods, 2D nanoplatelets (NPLs), polycrystalline materials, and "magic sized clusters", stable crystals made of only a few atoms.

However, while the syntheses of these materials are easy to execute, the actual mechanisms that guide their formation are poorly understood. Their synthesis usually involves the dissolution of toxic organometallic precursors into a high boiling solvent, and heating to 250-300C, which allows for some combination of precursor dissolution, monomer formation, nucleation, and crystal growth to occur, eventually producing the various forms of nanocrystals. Traditional forms of mechanistic analysis, such as taking aliquots or isolating intermediates, are invalidated due to the extreme temperatures and toxic reagents, which results in a large lack of understanding in the field and a large portion of the work being achieved through tedious trial and error studies.

In this poster, we will present the success we have found with several different in-situ techniques that allow for real-time analysis of the reaction as it is happening, which can be combed for clues into the mechanism. We have successfully utilized in-situ UV-Vis and Near IR spectroscopy via a fiber optic dip probe to measure the absorption spectra of 2D semiconducting nanoplatelets as they are being synthesized, which has provided unprecedented insight into how these crystals grow. We have also utilized measurement of the temperature and heating to create a rudimentary form of differential scanning calorimetry, which has given us thermodynamic insight into the reaction's progression. Utilizing the data collected, we hope to propose a rock-solid model of the crystal growth, which would be an invaluable tool in the field.

Poster Abstract 17

Nathan C. Incandela
UCLA Research Advisors: Kendall N. Houk, Stuart J. Conway

The emergence of high-level QM theory and high-efficiency computations over the last century has enabled chemists to effectively explore the free energy surfaces of organic reactions. This has not only provided insight into reaction mechanisms and regio- and chemoselectivity, but has also described novel modes of reactivity such as ambimodal transition state. This has been described in [6 + 4] cycloaddition reactions, where the intrinsic reaction coordinate reaches an entropic intermediate and bifurcates to allow for two unique products from a single transition state. Here, we explore (3,3)- and (5,5)-sigmatropic rearrangements in 10 electron systems, with scaffolds such as barbaralane and semibullvalene that enable low-energy sigmatropic shifts. Using DFT and Molecular Dynamics, we have succeeding in tuning the electronics of these systems and have discovered the first ambimodal transition state outside of cycloadditions. Furthermore, we describe the presence of energy minima structures with closed-shell, bis-homoaromatic electron configurations, which serve as intermediates in two-step (5,5)-sigmatropic rearrangements rather than transition state structures in their 6 electron counterparts. In addition, we have explored different types of bridgehead linkers to explore how different lengths in the central scaffold impart reactivity to the system.

Poster Abstract 18

sCIP-ing Towards Streamlined Isobaric Multiplexing

Nikolas R. Burton‡†, Daniel A. Polasky`, Flowreen Shikwana‡†, Samuel Ofori†, Tianyang Yan‡†, Daniel J. Geiszler^, Felipe da Veiga Leprevost`, Alexey I. Nesvizhskii`^, and Keriann M. Backus‡†§‖⊥#

† Department of Biological Chemistry, David Geffen School of Medicine, UCLA, Los Angeles, California 90095, United States
‡ Department of Chemistry and Biochemistry, UCLA, Los Angeles, CA, 90095, United States
§ Molecular Biology Institute, UCLA, Los Angeles, California 90095, United States
‖ DOE Institute for Genomics and Proteomics, UCLA, Los Angeles, California 90095, United States
⊥ Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research, UCLA, Los Angeles, California 90095, United States
Jonsson Comprehensive Cancer Center, UCLA, Los Angeles, California 90095, United States
^ Department of Computational Medicine and Bioinformatics, University of Michigan, Ann Arbor, Michigan 48109, United States
`Department of Pathology, University of Michigan, Ann Arbor, Michigan 48109, United States

Abstract

The human proteome harbors thousands of potentially druggable cysteine residues. Consequently, pinpointing the optimal covalent molecule for each cysteine residue represents an exciting means to close the druggability gap, namely the ~96% of human proteins not yet targeted by an FDA approved drug. While mass spectrometry-based chemoproteomic platforms have made significant inroads into this challenge, achieving comprehensive cysteine-SAR necessitates technical innovation in two key areas: (1) streamlined sample preparation workflows and (2) high throughput data acquisition. To achieve this goal, we have developed the silane-based Cleavable Linkers for Isotopically labeled Proteomics (sCIP) method. sCIP streamlines sample preparation with unparalleled early-stage isobaric labeling and sample pooling, allowing for high coverage and increased sample throughput via customized low cost 6-plex sample multiplexing. The sCIP method is distinguished by its unprecedented click-assembled isobaric tags, in which the reporter group is encoded in the sCIP capture reagent and balancer in the pan cysteine-reactive probe. Expanding upon this work we coupled our sCIP method with commercially available tandem mass tag (TMT) reagents in a method we call sCIP-TMT. sCIP-TMT pairs a custom click-compatible sCIP capture reagent that is readily functionalized in high yield with commercially available TMT tags. Synthesis and benchmarking of a 10-plex set of sCIP-TMT reveals a 1.5-fold decrease in sample preparation time together with high coverage and high accuracy quantification. Distinguished by its compatibility with established enrichment and quantification protocols, we expect sCIP-TMT will readily translate to a wide range of chemoproteomic applications.

Funding Sources

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Training Program (D.J.G.), U24CA271037, GM094231 (A.I.N.), and National Institute of General Medical Sciences T32 GM067555-11 (N.R.B.).

Poster Abstract 19

Title: Function and Regulation of Fhod3 *in vitro* and in Cardiomyocytes

Authors: Angela Koeberlein[1], Dylan Valencia[1], Austin Nakano[2,3,4,5*], Margot Quinlan[1,2*]

Abstract

Building and maintaining cardiac sarcomeres requires a high degree of regulation; small changes in sarcomere structures can disrupt sarcomere function and cause heart diseases. Fhod3 (Formin Homology 2 Domain Containing Protein 3) is a protein that is required for sarcomere formation. Fhod3 assembles actin, and actin thin filaments comprise a key structure in cardiac sarcomeres. Recently, several disease-causing Fhod3 mutations were found outside of the domains known to directly drive actin assembly. Other proteins in the same family as Fhod3 are known to be self-regulated by an intramolecular interaction, and we hypothesize that these Fhod3 mutations are causing disease by altering this autoinhibitory interaction. In this study, I will use fluorescence-based actin assembly experiments to study how mutations in Fhod3 regulatory domains affect its biochemical activity. Then, I will study the effects of these Fhod3 mutations on cardiac sarcomeres in cardiomyocytes. To study this, I will degrade native Fhod3 in cardiomyocytes and then reintroduce mutant Fhod3 using Adenoviral infection. Using these rescue experiments, I will quantify changes in actin structures within the sarcomeres to determine how Fhod3 mutations could be causing disease. Overall, this study will help determine the effects of Fhod3 function and regulation on sarcomere assembly.

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Affiliations

[1]Department of Chemistry and Biochemistry, University of California, Los Angeles, CA 90095, USA. [2]Molecular Biology Institute, University of California, Los Angeles, CA 90095, USA. [3]Department of Molecular, Cell, and Developmental Biology, University of California Los Angeles, Los Angeles, CA 90095, USA. [4]Department of Medicine, Division of Cardiology, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA 90095, USA. [5]Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research, University of California Los Angeles, Los Angeles, CA 90095, USA.

Poster Abstract 20

Proteomic Insights on Actin Mesh Regulation in Drosophila Oogenesis

Merin Rixen, Joseph Loo, Margot Quinlan

Actin filaments form networks that play pivotal roles in many cellular processes, including cell polarity establishment. During egg development, oogenesis, an actin network called the actin mesh assists in establishing oocyte polarity. Polarity establishment is a critical event that determines the major body axes of the egg and ensures the development of healthy offspring. This process is highly conserved, and analogous actin mesh networks have been observed in various species, including fruit fly (*Drosophila melanogaster*), worm, mouse, and human oocytes. The *Drosophila* actin mesh fills the oocyte during mid-oogenesis but disappears at the onset of late oogenesis. Studies have shown that the timely removal of the mesh is integral for the proper establishment of germline polarity. However, little is understood about the mesh and the mechanism behind its removal. This research aims to identify candidate proteins that regulate actin mesh removal and investigate their functions in relation to mesh disappearance. I will use bottom-up mass spectrometry to measure protein levels and abundance changes in the *Drosophila* oocyte between mid and late egg development stages. This technique will allow me to identify the proteins that reflect statistically relevant abundance changes between the stages of mesh maintenance and disappearance. I will complement my mass spectrometry analysis by using fly knockdown lines to determine what role these proteins have on actin mesh disassembly. Identifying the proteins that regulate actin mesh removal, and determining their roles, will advance our comprehension of the mechanisms and machinery that direct actin mesh regulation. Thereby, promoting our understanding of the developmental defects that arise from improper egg maturation across multiple species. Furthermore, the relevant results from this research may be extended to other systems of organized actin assembly that govern important cellular processes.

Poster Abstract 21

Using Native Mass Spectrometry Approaches to Characterize Amyloidogenic Protein Oligomers Linked to Neurodegenerative Diseases

Eileen J. Olivares,[1] Carter Lantz,[1,2] Rachel R. Ogorzalek Loo, [1] Joseph A. Loo[1]

[1] Department of Chemistry and Biochemistry, University of California Los Angeles, Los Angeles, CA, USA

[2] Department of Chemistry, Texas A&M University, College Station, TX 77843 (current affiliation)

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Over 50 neurodegenerative and systemic diseases are linked to the misfolding and aggregation of proteins (e.g., amyloid beta and Tau for Alzheimer's Disease and α-synuclein for Parkinson's Disease). These aggregates are comprised of protein fibers that form extracellularly and/or intracellularly in affected regions. A dominating hypothesis believes that oligomers and protofibrils are precursors to fibers and are the toxic species involved in disease initiation and progression. Oligomers are small and unique, making them great targets for designing therapeutics. Opportunities exist for native mass spectrometry (nMS) to provide fundamental information of oligomer molecular weights (MW) and aggregation interfaces. Determining the size and interface for these heterogeneous species would advance our understanding of their role in neurodegenerative diseases (NDs).

Electrospray ionization (ESI) is a soft ionization technique that allows molecule analysis in near-physiological conditions, allowing for the mass determination of intact proteins and mass, structural and binding information for protein-protein and protein-ligand complexes, as well as revealing protein dynamics in native ESI mass spectrometry (nESI-MS) studies. Although nMS shows potential for revealing oligomer structure, the aggregates are dynamic and populate different states and conformations, generating overlapping MS charge state distributions that are difficult to deconvolute.

Advanced MS technology has allowed us to reveal key oligomeric information. nESI-MS studies using the ThermoFisher Scientific Q Exactive UHMR orbitrap and Waters quadrupole time-of-flight (Synapt G2-Si) instruments allowed for MW determination of amyloid beta, Tau, and α-synuclein. Native top-down ESI-MS studies on the UHMR provided insight into oligomeric interfaces of α-synuclein and amyloid beta.

nMS measurements using current technology have allowed us to deduce the sizes and interfaces of amyloidogenic protein oligomers linked to NDs. Soon, we will use single ion charge detection technology to analyze oligomers.

Poster Abstract 22

Authors: Luca McDermott Catena, Zach Walters, Jiaming Ding, Jason V. Chari, Neil K. Garg

All authors are UCLA affiliated.

Research is funded by the NIH (pre-doctoral fellowship for L.M.C. and NSF grant for the lab)

Abstract: Due to their remarkable structures, synthetic chemists have been interested in the preparation of highly symmetrical molecules. A subset of these are the Platonic hydrocarbons, including prismane, cubane, and dodecahedrane. This presentation will detail a new approach toward dodecahedrane, with an emphasis on symmetry-based disconnections and strategies.

Poster Abstract 23

Authors: Dominick C. Witkowski, Andrew V. Kelleghan, Ana S. Bulger, Daniel W. Turner, and Neil K. Garg

Affiliations: University of California, Los Angeles

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Title: Exploring the reactivity and utility of strained cyclic cumulenes (65 characters)

Abstract: Since the 1950s, transient strained intermediates, such as arynes, have evolved from scientific curiosities to valuable synthetic building blocks in complex molecule synthesis. The considerable ring strain (30–50 kilocalories per mole) that characterizes these transient intermediates imparts high reactivity in many reactions, including cycloadditions, nucleophilic trappings, and metal-catalyzed reactions, often generating structurally complex products. Whereas arynes have seen significant reaction development, reactions of related strained cyclic intermediates, such as 1,2,3-cyclohexatriene and its derivatives, are relatively less developed. This poster will discuss the in-situ generation and trapping of strained cyclic cumulenes, as well as their utility in the synthesis of complex scaffolds. (804 characters)

Poster Abstract 24

Authors: Arismel Tena-Meza[*], Christina Rivera[*], and Neil K. Garg[*]
[*]University of California, Los Angeles

Title: Exploring the Reactivity of Strained Cyclic Allenes with Bicyclo[1.1.0]butanes

Abstract: Cyclic strained intermediates, such as arynes and cyclic alkynes, have become versatile building blocks in the synthesis of complex polycyclic scaffolds. One such class of cyclic strained intermediates are cyclic allenes, which bear two adjacent double bonds confined within a small cyclic ring. These species have seen recent interest due to their ability to undergo strain-driven reactions. Recent efforts by our lab are underway to explore a new mode of reactivity using a strain-strain-driven approach. This presentation will describe the reactivity of strained cyclic allenes with bicyclo[1.1.0]butanes, ultimately demonstrating an unconventional approach for the synthesis of complex molecular scaffolds.

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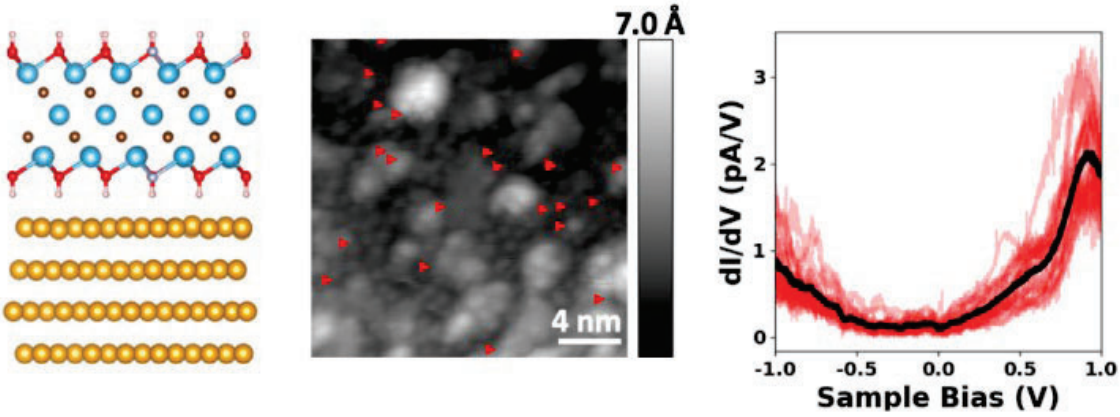
Poster Abstract 25

Atomic-Scale Exploration of Functional Ti_3C_2 MXene

Katherine White,[1,2] Yi Zhi Chu,[3] Gilad Gani,[1,2] Stefano Ippolito,[4] Kristopher Barr,[1,2] John C. Thomas,[5] Alexander Weber-Bargioni,[5] Kah-Chun Lau,[3] Yury Gogotsi,[4] & Paul S Weiss[1,2,6,7]

[1]Department of Chemistry and Biochemistry, University of California, Los Angeles, Los Angeles, California 90095, United States
[2]California NanoSystems Institute, University of California, Los Angeles, Los Angeles, California 90095, United States
[3]Department of Physics and Astronomy, California State University Northridge, Northridge, CA 91330, United States
[4]A. J. Drexel Nanomaterials Institute, Department of Materials Science and Engineering, Drexel University, 3141 Chestnut St,
Philadelphia, Pennsylvania 19104, USA
[5]Molecular Foundry, Lawrence Berkeley National Laboratory, Berkeley, CA 94720, United States
[6]Department of Bioengineering, University of California, Los Angeles, Los Angeles, California 90095, United States
[7]Department of Materials Science and Engineering, University of California, Los Angeles, Los Angeles, California 90095, United States



MXenes, a new family of 2D materials, have shown function across range of applications and in particular, are promising candidates for hydrogen storage. We are examining how terminal groups interact with and modify the chemistry and electronic structure of the surface as well as what happens when these terminal groups undergo selective chemical reactions towards the goal of hydrogen storage. To date, little information is known about defects, adsorption sites, and other structures responsible for the interactions with hydrogen and other materials. We are using spectroscopic imaging with atomic resolution and closely coupled theory to determine the electronic, chemical, and physical properties of these sites in and on $Ti_3C_2T_x$. Terminal functional groups as well as the small TiO_2 clusters that form upon oxidation are resolved and are being characterized.

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Poster Abstract 26

Title: Amphiphilic Conjugated Polyelectrolytes: Design and Optimization of Solution Conditions for Self-Assembly into Rod-like Micelles

Xinyu Liu*[1], Alexander F. Simafranca[1], Julia Chang[1], Benjamin J. Schwartz[1], Yves Rubin[1], Sarah H. Tolbert[1,2]

* Presenter

[1] Department of Chemistry and Biochemistry, University of California, Los Angeles, Los Angeles, CA 90095-1569, USA

[2] Department of Materials Science and Engineering, University of California, Los Angeles, Los Angeles, CA 90095-1595, USA

Conjugated polyelectrolytes (CPEs), incorporating conjugated backbones and charged sidechains, exhibit distinctive electronic properties, tunable optical features, solution processibility, low cost, and biocompatibility, facilitating diverse applications such as biosensing, bioimaging, and drug delivery. In this study, we have designed and synthesized a series of CPEs with poly(cyclopentadithiophene-*alt*-thiophene) (PCT, **1 - 3**) and poly(cyclopentadithiophene-*alt*-fluorene) (PCF, **4,5**) backbones that self-assemble into rod-like micelles in aqueous solutions. The self-assembly of the polymers enhances the alignment of their conjugated backbones, potentially reducing defects in conduction pathways and improving conductivity compared to polymers with a random coil conformation. Here, we specifically employ solution based small-angle X-ray scattering (solution SAXS) to characterize the shapes of polymer micelles and analyzed conformational changes that occur under varying conditions. Our findings suggest that PCT variants with differently charged sidechains all form cylindrical micelles, with the micelle size and shape modulated by electrostatic interactions between charged sidechains that are cationic (**1**), anionic (**2**), or zwitterionic (**3**) and their local solvent environment. To further minimize the torsion angle between neighboring monomeric units, we turn to PCF based systems. The inclusion of additional charged sidechains on the fluorene unit, along with its extended conjugation, results in straighter and more rigid micelles (**4**). However, due to the high charge density within one monomeric unit, a single strand of PCF with doubly cationic sidechains (**5**) is capable of dissolving into water without forming micelles and exhibits an increased critical micelle concentration (CMC). The single-stranded polymer adopts a random coil shape, potentially hindering its conductivity, but self-assembly of these single strands can be induced by changing solvent conditions. Utilizing UV-visible absorption spectroscopy, we elucidated the influence of solvents, concentration, and ionic strength on the self-assembly of PCFs. Consequently, by adjusting solution conditions, we can tailor the optical and electronic properties of these CPEs, offering versatility in their applications in biology, chemistry, and materials science.

Poster Abstract 27

Saarang Kashyap

De novo Identification of Flagellar Microtubule Doublet Proteins in Trichomonas *vaginalis* Using cryo-EM

Trichomonas vaginalis (*Tv*), the flagellated extracellular protist and causative agent of the sexually transmitted infection, Trichomoniasis, is implicated in many perinatal complications, male and female UTIs, and increased rates of HIV transmission. The *Tv* flagella, composed of outer microtubule doublets (OMDs) forming a ring around a central pair of microtubules, produces a unique "run and tumble"-like motility that facilitates locomotion and host cell adherence. Currently, the lack of a high-resolution structure for the Tv OMDs presents a gap in our understanding of integral proteins for flagellar assembly and their potential applications in drug development. To address this, we utilized cryo-electron microscopy (cryo-EM) to image the OMDs of *Tv* flagella. Using single particle analysis, we successfully resolved a high resolution 3.65 Å (.37 nanometer) reconstruction of the OMDs. We identified ~29 distinct internal and external proteins by fitting atomic models from our mass spectrometry data into our reconstruction. We designated two previously uncharacterized proteins, TvMIP35 and TvMIP40, at the inner and outer junction where the α and β tubule converge to form the doublet. Based on homologous comparison with sea urchin and bovine sperm microtubule proteins, we suspect these two unidentified proteins are involved in assembly of the B-tubule and stabilizing of the microtubule seam, supporting Tv's flagellar beating. This work elucidates the structures which contribute to the stability of the OMDs and the OMDs' connection with other flagellar proteins. More broadly, this research unveils novel protein densities that provides a molecular basis for targeted therapies against Tv.