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Abstract Book

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UNDERGRADUATE ABSTRACTS

#1: Carborane RAFT Agents as Tunable and Functional Molecular Probes for Polymer Materials

Omar M. Ebrahim,[1] Ramya S. Pathuri,[1] Marco S. Messina,[*,1] Christian T. Graefe,[3] Paul Chong,[1] Nicholas A. Bernier,[1] Harrison A. Mills,[1] Arnold L. Rheingold,[4] Renee R. Frontiera,[*,3] Heather D. Maynard,[*,1,2] and Alexander M. Spokoyny[*,1,2]

Functional handles appended to polymer chain ends are important tools often used as spectroscopic probes for determining polymer structure, affinity labels, and as reactive handles for the conjugation of functional payloads. An easily tunable molecular handle able to carry out multiple functions simultaneously would be of significant use at the polymer, materials, and biology interface. Here, we report the development of carborane-containing chain transfer agents (CTAs, commonly referred to as RAFT agents) which are used in reversible addition-fragmentation chain transfer (RAFT) polymerization. These carborane RAFT agents establish control over polymerization processes leading to monodisperse (Đ = 1.03-1.15) polymers made from N-isopropylacrylamide, styrene, 4-chlorostyrene, and methyl acrylate monomers. The tunable nature of the carborane-based scaffold appended on the polymer chain end serves as a general 1H NMR spectroscopic handle, which can be used to elucidate polymer molecular weight via end-group analysis. Isothermal titration calorimetry (ITC) measurements show that synthesized carborane terminated polymers exhibit strong binding to β-cyclodextrin with an affinity (Ka) of 9.37x104 M-1, thereby demonstrating its potential use as an affinity label. Additionally, we show that the free B-H vertices on the carborane RAFT agents exhibit a Raman vibrational signal at ~2550 cm-1, a Raman-silent region for a biological milieu, indicating its potential utility as an innate Raman active probe. The reported carborane RAFT agents bolster the expanding toolbox of molecular probes and serve as tunable platforms for incorporating additional and complementary handles for tailoring chain-end functionality and facilitating polymer analysis.

[1] Department of Chemistry and Biochemistry, University of California, Los Angeles, 607 Charles E. Young Drive East, Los Angeles, [2] California NanoSystems Institute, University of California;[3] Department of Chemistry, University of Minnesota, Minneapolis, Minnesota, 55455, [4] Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, California, 92093.

#2: Modeling 2-Dimensional Molecular Aggregates as Transition Dipole Moments

Danielle Koppel[1], Arundhati P. Deshmukh[1], Chern Chuang[2] and Justin R. Caram[1]*

In nature, incredibly efficient light-harvesting processes are utilized by plants and photosynthetic bacteria. These capabilities are attributed to the optical and transport properties of self-assembled molecular aggregates. These systems are highly ordered with large absorption cross-sections and exciton migration. Modeling and recreating artificial mimics of these systems provides an intriguing opportunity to fundamentally understand energy transfer and utilize some of these astounding properties for applications such as photochemical antennas. Photophysical observables are governed by the nanoscale stacking of monomers within the aggregate. Without structural characterization, the correlation between these two is challenging to elucidate. A successful model describes these systems as arrays of transition dipole moments that couple through long-range dipole-dipole interactions. The interaction energies geometrically relate to an adjustable parameter, slip, which controls whether the aggregate blue-shifts (H-aggregates) or red-shifts (J-aggregates) relative to the monomer. Through our calculations of these differing morphological arrangements, the density of states and absorption spectra reveal an interesting relationship between the bright state and band-edge as a function of slip. Our results set the stage for modeling exciton transport and designing new aggregate structures with tunable photophysics.

[1]Department of Chemistry and Biochemistry, University of California, Los Angeles, 607 Charles E. Young Dr. East, Los Angeles, California-90095, United States. [2]Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, Ontario M5S 3H6, Canada. *UCLA Advisor

GRADUATE STUDENT ABSTRACTS

#3 - Arynes and Cyclic Alkynes as Synthetic Building Blocks for Stereodefined Quaternary Centers

Sarah M. Anthony, Elias Picazo, Maude Giroud, Adam Simon, Margeaux A. Miller, K. N. Houk, and Neil K. Garg*

Despite traditionally being avoided due to their high electrophilicity, arynes have recently gained popularity as useful synthetic building blocks. Arynes can now be used in a host of transformations typically yielding racemic products. In this presentation, we describe a new aryne methodology that allows for the preparation of ketones bearing alpha quaternary stereocenters. Specifically, arynes generated *in situ* are trapped with stereodefined enamines to give enantioenriched products upon workup. Our reaction design, optimization studies, and trapping results will be presented. In addition to providing access to adducts bearing stereodefined quaternary centers, this methodology demonstrates that highly reactive arynes and related intermediates can serve as building blocks to access enantioenriched products.

These studies were supported by the National Institutes of Health, the Eugene V. Cota–Robles Fellowship, the Christopher S. Foote Graduate Fellowship and Swiss National Science Foundation.

#4 - Nickel-Catalyzed Suzuki–Miyaura Couplings of Aliphatic Amides

Timothy B. Boit, Nicholas A. Weires, Junyong Kim, and Neil K. Garg*

The Suzuki–Miyaura coupling has become one of the most important and prevalent methods for the construction of carbon–carbon bonds. Although palladium catalysis has historically dominated the field, the use of nickel catalysis has become increasingly widespread due to its unique ability to cleave carbon–heteroatom bonds that are unreactive toward other transition metals. This presentation will focus on the development of the nickel-catalyzed Suzuki–Miyaura coupling of aliphatic amides derived from aliphatic carboxylic acids, which proceeds by an uncommon cleavage of the amide C–N bond following *N*-Boc activation. The reaction allows for the coupling of heterocyclic substrates, avoids the use of pyrophorics, and provides access to a range of (hetero)aryl–(hetero)alkyl ketones in synthetically useful yields. These studies reinforce the notion that amides, despite classically being considered inert substrates, can in fact be harnessed as synthons for use in C–C bond forming reactions through cleavage of the amide C–N bond using non-precious metal catalysis.

This work was supported by the UCLA Gold Shield Alumnae, the University of California, Los Angeles, and the National Institutes of Health. T.B.B. and K. J. Y. acknowledge the University of California, Los Angeles and N.A.W. acknowledges the National Science Foundation and the Foote Family for fellowship support. These studies were also supported by shared instrumentation grants from the National Science Foundation and the National Center for Research Resources.

#5 - Structural Studies of a Functional Amyloid Necessary for Long-Term Memory Formation in *Drosophila*

Jeannette Bowler[1,2], Michael Sawaya[1,2], David Boyer[1,2], Duilio Cascio[1,2], David Eisenberg[1,2]

Amyloid protein aggregation is typically associated with neurodegenerative diseases such as Alzheimer's and Parkinson's diseases. However, not all amyloid proteins are pathogenic in their aggregated state. The neuronal cytoplasmic polyadenylation element binding (CPEB) protein has been shown to form "functional" amyloid aggregates in several model organisms. CPEB is a regulator of synaptic mRNA translation, and CPEB aggregation has been shown to be an important step in the formation of long-term memory. Our work is focused on the *Drosophila* CPEB homolog, termed Orb2A. The first 9 N-terminal amino acid residues of Orb2A are necessary for its aggregation, and this segment has been suggested to form the amyloid fiber core. Intriguingly, a single point mutation of the phenylalanine residue in the 5th position to tyrosine (F5Y) decreases Orb2A aggregation and prevents long-term memory formation in *Drosophila*. To understand the structural basis for Orb2A aggregation, we characterized this critical 9-residue segment of Orb2A, which we call M9I-WT. Using micro-electron diffraction, we determined the crystal structure of M9I-WT at a resolution of 1.0 Å. The segment forms an array of parallel in-register β-sheets, which are held together tightly by inter-strand aromatic and hydrophobic side chain interactions. By computation, we compared the structural properties of M9I-WT with M9I-F5Y, and observed that while both are capable of forming amyloid-like fibrils, their morphology and stability differs significantly. Our model provides an explanation for the decreased aggregation observed for the F5Y mutant, and offers a hypothesis for how the addition of a single atom (the tyrosyl oxygen) can affect memory. Ultimately we aim to understand the differences between functional and pathological amyloids, and thus further our understanding of amyloid disease mechanisms, and improve therapeutic strategies.

[1]*Molecular Biology Institute, University of California, Los Angeles,* [2]*Howard Hughes Medical Institute*

#6 - Design of a Novel One-Component Icosahedral Protein Cage and Application of Designed Protein Cages for Enzyme Display

Kevin Cannon[1,2], Christian Morgan[3], Scott McConnell[1,2], Robert T. Clubb[1,2,4], and Todd O. Yeates[1,2,4]

Exploiting the natural symmetry of supramolecular protein assemblies found in biology has led to many recent successes in engineering novel self-assembling protein structures of types yet unknown in the natural world. Designing symmetric protein cages with a wide range of properties has been of particular interest for their potential to be applied in the fields of medicine, energy, imaging and more. Using a genetically-encoded alpha-helical protein fusion approach which holds two natural oligomeric protein components in a specific orientation without requiring any heavy computational interface design nor extensive mutagenesis of the native protein sequences, we have designed and characterized a one-component icosahedral protein cage that self-assembles from 60 identical subunits. In addition to rigidly fusing dimeric and pentameric protein components with an alpha-helical linker, to further prevent any unwanted lower-symmetry assemblies from forming, a flexibly linked trimeric coiled-coil has also been incorporated to create a double fusion protein which contains all three rotational symmetry elements (C2, C3, and C5) present in icosahedral symmetry. Structural characterization of this cage is being carried out by single-particle Cryo-Electron Microscopy. One emerging application of designed protein cages is in enzyme display for improving pathway flux of sequentially acting enzymes. In a separate project, we have engineered a cellulolytically active protein cage by covalently linking multiple cellulase enzymes to the exterior of a designed cage via the sortase enzyme SrtA. These cages can be applied in engineering more efficient microbes for the production of ethanol and other biocommodities.

[1]*UCLA-DOE Institute for Genomics and Proteomics, Los Angeles, CA;* [2]*UCLA Department of Chemistry and Biochemistry, Los Angeles, CA;* [3]*UCLA Department of Ecology and Evolutionary Biology, Los Angeles, CA;* [4]*UCLA Molecular Biology Institute, Los Angeles, CA*
Funding: This work is supported by award E-FC02-2ER63421 from the BER program of the DOE Office of Science.

#7 - Nucleic-Acid-Functionalized Field-Effect Transistors for Biomolecule Detection

Kevin M Cheung,[1,2] Nako Nakatsuka,[1,2] Kyung-Ae Yang,[3] John M Abendroth,[1,2] Chuanzhen Zhao,[1,2] Paul S Weiss,[1,2] Milan Stojanović,[3,4] and Anne M Andrews[1,2,5]

We have designed and developed ultrathin-film field-effect transistors (FETs) coupled to rationally designed and chemically synthesized oligonucleotide sequences with molecular recognition capabilities, termed aptamers, for the specific detection of a diverse range of biologically important small-molecule targets (*e.g.*, neurotransmitters, amino acids, sugars, lipids). Upon target capture, aptamers undergo conformational changes that redistribute charge densities on FET surfaces resulting in measurable changes in conductance. We demonstrate the detection of biomolecules in full ionic strength biological fluids, with high specificity and selectivity, over a wide dynamic range of concentrations with unprecedented detection limits. Using this platform, we are developing sensors for the direct detection of the amino acid phenylalanine for potential point-of-care use for patients with phenylketonuria, a common genetic disorder. Three phenylalanine-specific DNA sequences were investigated to determine sensor responses contingent on different primary base sequences, secondary structures, and target affinities. In parallel, we have extended this FET biosensor platform for the detection and discrimination of single-nucleotide polymorphisms. The development of biosensors with high selectivity and sensitivity in full ionic strength biological fluids presents opportunities for fundamental studies in biological signaling, as well as in precision medicine.

1. California NanoSystems Institute, 2. Chemistry and Biochemistry, University of California, Los Angeles, 3. Division of Experimental Therapeutics, Department of Medicine, Columbia University, New York, New York, 4. Biomedical Engineering and Systems Biology, Columbia University, New York, 5. Department of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience and Human Behavior, and Hatos Center for Neuropharmacology, University of California, Los Angeles

This research was supported by the Cal-Brain Neurotechnology Program, the National Institute on Drug Abuse (DA045550), Nantworks, and Hewlett Packard.

#8 - Near-infrared J-aggregates from cyanine dyes

Arundhati P. Deshmukh[1], Danielle Koppel[1], Chern Chuang[2] and Justin R. Caram[1]*

Cyanine dye derived J-aggregates were first discovered in the 1930s and have been subject to extensive study due to their narrow linewidths and long-range exciton migration. Similar to protein self-assemblies, cyanine dyes can aggregate into double-walled nanotubes, nanosheets and other morphologies, each having a distinct absorption spectrum. However, most of the cyanine dye aggregates absorb in the visible region with very few examples in the near infrared (NIR, 700-1100 nm) and short-wave infrared (SWIR, 1100-2000 nm). Aggregates in NIR/SWIR would be advantageous for diverse applications like biomedical imaging and telecommunications where lower scattering and background allows deeper penetration through tissue and atmosphere respectively. We present the J-aggregates of two cyanine dyes with optical transitions above 1000 nm with extremely narrow linewidths (~450 cm^{-1} / ~56 meV). Temperature dependent absorption spectroscopy shows that the linewidths follow surprisingly different trends for the two aggregates revealing a distinct band structure arising from their 2-dimensional geometric arrangement. Using cryo-electron microscopy, atomic force microscopy and dynamic light scattering we can correlate the aggregate structure with optical properties. Computational modelling provides further support for a molecular brick-like arrangement within the aggregates and explains the distinct temperature dependence as a function of molecular packing. These aggregates are exciting avenues for further investigations of the aggregate lineshape and exciton migration in near-infrared.

*[1]Department of Chemistry and Biochemistry, University of California, Los Angeles, 607 Charles E. Young Dr. East, Los Angeles, California-90095, United States. [2]Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, Ontario M5S 3H6, Canada. *UCLA Advisor.*

#9 - Incoherent Upconversion using SWIR Triplets in Polyacenes

Hannah C. Friedman and Justin R. Caram

We studied upconversion in TIPS-pentacene for applications in Shortwave infrared (SWIR, 1 - 2 μm) sensing. SWIR light has a wealth of applications in deep-tissue imaging, biometric identification, satellite telemetry, and pedestrian imaging for self-driving cars. However, current SWIR photodetectors remain prohibitively expensive for commercial or industrial applications. We propose using incoherent upconversion (IU) materials to overcome this limitation. In IU, two SWIR triplet excitons annihilate to form a singlet exciton above the bandgap of silicon, allowing for an inexpensive addition to the ubiquitous silicon photodetectors. Here, we report the first evidence of non-geminate triplet-triplet annihilation in a solution of TIPS-pentacene from PbS nanocrystals. We firmly establish experimentally the energy of T_1 state in TIPS-pentacene via bracketing with known tunable triplet band gaps of quantum dots. By characterizing the upconversion process and the triplet energy level, we facilitate mechanistic understanding for materials design for efficient IU in the SWIR.

#10 - Sub-ångström CryoEM structure of a prion protofibril

Marcus Gallagher-Jones[1a], **Calina Glynn**[1a], David R. Boyer[2], Michael W. Martynowycz[3], Evelyn Hernandez[1], Jennifer Miao[1], Chih-Te Zee[1], Irina V. Novikova[5], Lukasz Goldschmidt[2], Heather T. McFarlane[2], Gustavo F. Helguera[4], James E. Evans[5], Michael R. Sawaya[2], Duilio Cascio[2], David Eisenberg[2], Tamir Gonen[3] and Jose A. Rodriguez[1]

The cryo electron microscopy (CryoEM) method, micro electron diffraction (MicroED), has been proven successful in revealing atomic resolution structures of amyloid assemblies from protein nanocrystals. MicroED now extends the reach of CryoEM in to the sub-angstrom realm with the 0.75Å structure of a wild-type segment from the β2α2 loop of the bank vole prion protein. Its ultrahigh resolution maps inform hydrogen positions that differ from idealized geometry. Hydrogen bond networks in the structure present a motif we call a 'polar clasp', which offers insights into prion stability and may be predictive of long-lasting and potentially infectious amyloid assemblies.

[1] Department of Chemistry and Biochemistry, UCLA-DOE Institute for Genomics and Proteomics, University of California Los Angeles, Los Angeles, CA 90095, USA.

[2] Department of Biological Chemistry and Department of Chemistry and Biochemistry, University of California Los Angeles, Howard Hughes Medical Institute, UCLA-DOE Institute for Genomics and Proteomics, Los Angeles, CA 90095, USA.

[3] Janelia Research Campus, Howard Hughes Medical Institute, 19700 Helix Drive, Ashburn, VA 20147, USA.

[4] Laboratory of Pharmaceutical Biotechnology, Institute of Biology and Experimental Medicine, Buenos Aires, AR.

[5] Environmental Molecular Sciences Laboratory, Pacific Northwest National Laboratory, Richland, WA 99354.

[a] Authors contributed equally to this work.

Presenting and corresponding authors underlined

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#11. Genome-mined Diels-Alderase catalyzes the formation of the cis-octahydrodecalins of varicidin A and B

Dan Tan,[1,2†] **Cooper S. Jamieson**,[3†] Masao Ohashi,[2] Yiu-Sun Hung,[2] Man-Cheng Tang,[2*] K. N. Houk,[2,3*] Yi Tang[2,3*]

Pericyclases are an emerging family of diverse enzymes catalyzing pericyclic reactions. A class of lipocalin-like enzymes in fungi has been characterized as Diels-Alderases (DAases) catalyzing decalin formation through intramolecular Diels-Alder (IMDA) reactions between electron-rich dienes and electron-deficient dienophiles. Using this class of enzyme as a beacon for genome mining, we discovered a biosynthetic gene cluster from *Penicillium variable* and identified that it encodes for the biosynthesis varicidin A (**1**), a new antifungal natural product containing a *cis*-octahydrodecalin core. Biochemical analysis reveals a carboxylative deactivation strategy used in varicidin biosynthesis to suppress the spontaneous IMDA reaction of an early acyclic intermediate that favors *trans*-decalin formation. Starting from a relatively unreactive combination of an electron-deficient diene and an electron-deficient dienophile, the DAse PvhB catalyzes an IMDA to form the *cis*-decalin that is important for the antifungal activities of **1.**

[1] School of Life Science and Technology, Xi'an Jiaotong University, Xi'an, 710049, P. R. China; [2] Departments of Chemical and Biomolecular Engineering, [3] Chemistry and Biochemistry, University of California, Los Angeles, California 90095, United States.
[†]These authors contributed equally.
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#12 -The CryoEM Method MicroED as a Powerful Tool for Small Molecule Structure Determination

Christopher G. Jones[1], Michael W. Martynowycz[2], Johan Hattne[2], Tyler Fulton[3], Brian M. Stoltz[3], Jose A. Rodriguez[1], **Hosea M. Nelson**[1], Tamir Gonen[2]

Over the past 50 years, NMR and other spectroscopic techniques have been the primary method for identifying small molecules. While these techniques rely on inference of connectivity, unambiguous determination of a small molecule's structure requires X-ray diffraction. In practice, however, X-ray crystallography is rarely applied in routine organic chemistry due to the inherently difficult crystal growing process. Even after a substance has been crystallized, there is no guarantee that the particular crystal form will be amenable to X-ray diffraction. Here, we demonstrate the use of the cryo-electron microscopy (CryoEM) method micro-electron diffraction (MicroED) for routine, unambiguous structural determination of small organic molecules. Using commercially available compounds from a bottle, it is possible to generate molecular structures with sub- Å resolution in as little as 30 minutes. Furthermore, a single nanocrystal, equating to femtograms of material, was shown to often be sufficient for complete structural elucidation. From seemingly amorphous powders with no formal recrystallization, we were able to obtain structures of 10 different compounds which included natural products, pharmaceuticals, and the large macrocyclic peptide thiostrepton. Among these compounds, two were recovered directly from flash columns with no additional preparation. Not only did MicroED sufficiently identify homogenous samples, two common pharmaceuticals, acetaminophen and ibuprofen, were identified from crushed tablets containing an abundance of binders, fillers, and other impurities. Upon mixing four distinct small molecules, MicroED was used to rapidly examine and identify each compound within minutes through verification of unit cell parameters. The ease in which rapid, high-resolution structures can be obtained through MicroED will no doubt have profound implications for the field of organic chemistry and pharmaceutical research as this technology continues to expand.

[1]Department of Chemistry and Biochemistry, University of California, Los Angeles; [2]Howard Hughes Medical Institute, Departments of Biological Chemistry and Physiology, University of California, Los Angeles:[3]The Warren and Katharine Schlinger Laboratory of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena.
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#13 - Mass Spectrometry Analysis of Tau Protein and its Interaction with the Aggregation Inhibiting Compound CLR01

Carter Lantz[1], Michael Nshanian[1], Piriya Wongkongkathep[1], Gal Bitan[2], Joseph A. Loo[1,3]

Over the last century, many diseases have been characterized by protein aggregates in brain neurons. One such disease known as Alzheimer's disease has been linked to plaques of amyloid beta and neurofibrary tangles of tau. Recent analysis has found tau to be the toxic species in Alzheimer's disease. Although tau has been researched extensively, the mechanism of aggregation is unknown. Hyperphosphorylation has been shown to increase aggregation of tau. This study aims to pinpoint phosphorylation sites on tau and determine how phosphorylation affects tau structure. Electron capture dissociation (ECD) with Fourier transform-ion cyclotron resonance mass spectrometry (FT-ICR MS) will be utilized to pinpoint phosphorylation sites, and ion mobility-mass spectrometry (IM-MS) will be used to determine the structural implications of phosphorylation. Analysis of how phosphorylation affects tau structure may provide insight into the mechanism of tau protein aggregation in Alzheimer's disease patients.
A cure for protein aggregation diseases remains a mystery. There are a few compounds that have been shown to decrease the rate of amyloid protein aggregation. One of these compounds known as CLR01 interacts with proteins by electrostatically binding to lysine and arginine residues. This project aims to determine the interaction of CLR01 and tau. Using mass spectrometry techniques such as ECD with FT-ICR MS, the location of CLR01 binding will be pinpointed, and using IM-MS, the structural implications of CLR01 binding will be shown. This analysis may provide insight into how CLR01 interacts with tau and inhibits aggregation of tau in brain neurons. Analysis of tau and its interaction with aggregation inhibiting compounds may provide new insight into Alzheimer's disease and give rise to new therapies and cures for Alzheimer's disease patients.

[1]Department of Chemistry and Biochemistry, [2]Department of Neurology, David Geffen School of Medicine, [3]Department of Biological Chemistry University of California-Los Angeles, Los Angeles, CA 90095

#14 - The Structure and Mechanism of an Essential Glycosyltransferase, TagA

Michele D. Kattke, Jason E. Gosschalk, **Orlando E. Martinez**, Garima Kumar, Robert T. Gale, Duilio Cascio, Michael R. Sawaya, Martin Philips, Eric D. Brown, and Robert T. Clubb

Wall teichoic acids (WTA) are abundant glycopolymers embedded in the Gram-positive bacterial cell wall that have numerous essential functions, including cell morphogenesis and division, host-pathogen interactions, and antibiotic resistance. WTA biosynthetic enzymes are promising anti-microbial drug targets, as abrogation of WTA display in Gram-positive bacteria severely decreases virulence and restores β-lactam sensitivity. The first committed step in the WTA pathway, catalyzed by TagA, synthesizes a conserved linkage unit and can be inactivated to produce viable, WTA-devoid cells. Here, we present the high-resolution crystal structure and propose a unique catalytic mechanism of the TagA glycosyltransferase (GT). Crystal structures of a soluble *Thermoanaerobacter italicus* apo-TagA construct ($TagA^{\Delta C}$) at 1.9 Å resolution and UDP-bound $TagA^{\Delta C}$ at 3.1 Å resolution reveal a novel GT fold, termed GT-E. Cellular fractionation studies of TagA indicate that full-length TagA peripherally associates with the membrane as a monomer, whereas soluble $TagA^{\Delta C}$ adopts a dimeric state. These results suggest a unique molecular mechanism in which membrane association activates TagA by triggering a dimer to monomer quaternary structural change that facilitates lipid-α substrate recognition and formation of a catalytically competent active site. These findings will facilitate further study of the WTA biosynthetic pathway in Gram-positive organisms, guide rational drug design of anti-microbial compounds to combat antibiotic-resistance, and promote glycobiology study within the WecB/TagA/CpsF GT-E superfamily.

#15 - Structural and Mechanistic Insight Into How Pathogenic Bacteria Assemble Adhesive Surface Pili Via Isopeptide Bonds

Scott McConnell[1], Rachel McAllister[1], Chris Sue[1], John Muroski[1], Brendan R. Amer[1], Hung Ton-That[2] and Robert T. Clubb[1].

Infections caused by antibiotic-resistant bacterial pathogens are a significant threat to public health. Many species of Gram-positive bacteria display pili (hair-like filaments that protrude from the cell wall) to form biofilms and to adhere to host tissues and cells. These pili are constructed on the cell surface by sortase pilin polymerases, which concatenate pilin subunits via isopeptide bonds.

The SpaA-pilus in *Corynebacterium diphtheriae* is archetypal and provides mechanistic insight applicable to all Gram-positive pilus systems. The substrate of the isopeptide crosslinking reaction is a nucleophilic lysine ε-amine group positioned within the N-terminal domain of a pilin protomer (^{N}SpaA). This reaction is highly specific, preferentially crosslinking a single "pilin lysine" out of a sea of nucleophiles. To understand the origins of this specificity, and to visualize the first atomic resolution structure of the isopeptide linkage between pilins, we are using NMR to study the structure and dynamics of the ^{N}SpaA-isopeptide crosslinked species. Significant structural rearrangements accompany the crosslinking event, which may help stabilize the linkage and explain the impressive tensile strength of pilus structures.

In addition to providing important understandings about pilus-mediated virulence, this unique crosslinking reaction could be developed into a useful tool for synthetic biology applications. As such, we have developed the pilin transpeptidase SrtA into a robust bioconjugation tool, capable of selectively modifying proteins with labeled peptides via isopeptide linkages at high yield. Importantly, this bioconjugation approach installs peptides (or proteins) irreversibly and orthogonally to other established sortase-conjugation techniques. Additional insights obtained from future study of the pilus biogenesis mechanism will be leveraged to further improve our bioconjugation tool.

[1]*UCLA Department of Chemistry and Biochemistry* [2]*Division of Oral Biology and Medicine, School of Dentistry,UCLA*

#16 – Boron Cluster Pharmacophores: Development of Next Generation Histone Deacetylase (HDAC) Inhibitors

Harrison A. Mills, Jessica K. Logan, Kierstyn P. Anderson, Rafal M. Dziedzic, Prof. Alexander M. Spokoyny*

Carbon-based molecules have persisted as dominant building blocks for the assembly of complex molecular architectures. Importantly, the classical toolbox of 2D aromatic building blocks presents inherent topological limitations, sometimes referred to as the "molecular flatland". Our group has been interested in expanding the available toolbox by going beyond classical 2D aromatic building blocks. We and others have recently developed efficient synthetic methodology allowing for the incorporation of 3D boron cluster building blocks into the framework of complex organic molecules. Most recently, we have studied the potential of boron cluster-containing HDAC inhibitors. Our results to date have shown that this inhibitor presents comparable binding to HDAC, relative to the recently reported adamantane-containing HDAC inhibitor, Martinostat, but with decreased cell-toxicity. However, over 10 isoforms of HDAC proteins are expressed in humans that are differentially involved in cancer, drug addiction, and neurodegenerative diseases. Therefore, isoform specificity is a critical aspect to consider when designing these drug molecules. By incorporating these 3D boron clusters, unprecedented isoform specificity could be achieved due to the increasing number of vertex-selective functionalization methods available for these molecules. With these vertex-selective methods, we could then rationally introduce B-C, B-N, B-O, B-B, and/or C-C functionality to fine-tune the protein-drug interaction in order to generate isoform specificity and modify lipophilicity. Thus far, our results have indicated the promise of introducing boron clusters with enhanced tunability as surrogates for lipophilic groups in complex molecular architectures without adversely affecting intermolecular interactions.

We would like to thank the UCLA Summer Research Program, UCLA Departmental Scholars Program and UCLA Startup funds for supporting our research.

#17 - Massively parallel design of de novo amyloid aggregation inhibitors

Kevin A. Murray[1], Paul Seidler[2], Gregory Rosenberg[2], Carolyn Hu[2], Nicole Wheatly[2], Eric Jones[2], Michael Sawaya[2], Sriram Kosuri[2], David S. Eisenberg[1,2,3]

The presence of amyloid fibrils is a common pathological hallmark of many neurodegenerative diseases, including Alzheimer's disease (AD) and Parkinson's disease (PD), and multiple systemic amyloid diseases. A potential therapeutic route for treatment of these diseases is through inhibition of amyloid fibril growth and propagation. Recently, atomic-resolution structures have been determined for tau and alpha-synuclein fibrils, the amyloids associated with AD and PD, respectively. In order to block the growth of these fibrils, we aimed to design molecules that cap the growing end of the fibril structures. Utilizing recent advances in de novo protein design, a library of ~40,000 39-50 residue 'mini-proteins' was created, with sequences optimized for binding to the fibril ends. Using a FRET-based HEK293 biosensor cell assay, we have developed and optimized a high-throughput screen for determining mini-protein designs that inhibit intracellular tau and alpha-synuclein aggregation. Integrating technologies in oligonucleotide synthesis and next-generation sequencing, we are able to test several orders of magnitude more designed sequences than in previous investigations of anti-amyloid peptides or proteins. Results from the screen will be used to evaluate and iteratively improve the computational model. Top hits from the screen will be selected for further biophysical and in vivo characterization.

1Molecular Biology Interdepartmental Program, UCLA; 2Dept. of Chemistry and Biochemistry, UCLA; 3Howard Hughes Medical Institute

#18 - The role of p-coumaric acid as a Coenzyme Q ring precursor in *Saccharomyces cerevisiae*

Anish Nag[1], Michelle C. Bradley[1], Ohyun Kwon[1], Gilles J. Basset[2], and **Catherine F. Clarke**[1]

Coenzyme Q (ubiquinone or Q) is a redox active lipid molecule, with a fully substituted benzoquinone ring and a polyisoprenoid tail, containing up to ten isoprene units. Q is an essential component of the mitochondrial respiratory electron transport chain (1). Q deficiency has been directly as well as indirectly linked to a number of neurological, muscular, and cardiovascular disorders in humans that range from encephalomyopathy and cerebellar ataxia, to Parkinson's disease (2). Q_{10} is used as a dietary supplement, albeit its efficiency is limited due to its hydrophobic nature, and therefore, ongoing biotechnological efforts aim at improving Q biosynthesis (3). The exact biosynthetic pathway in eukaryotes has still not been completely characterized. Traditionally, 4-hydroxybenzoic acid (4-HB) serves as the ring precursor for Q biosynthesis in eukaryotes (4). In addition to 4-HB, recent reports have revealed additional phenolic compounds, such as resveratrol, p-coumaric acid, and kaempferol to be novel compounds that can act as Q ring precursors and enhance Q content in mammalian cells (5, 6). It has been hypothesized that these phenolic compounds may be converted to 4-HB in living systems. *S. cerevisiae* uses tyrosine as precursor for 4-HB biosynthesis, and recent studies indicate that its metabolism to 4-hydroxybenzaldehyde is an essential step in its use in Q biosynthesis (7, 8). P-coumaric acid, which was shown to be utilized as a Q ring precursor in yeast, could be a potential intermediate in the biosynthesis of 4-HB from tyrosine, through a possible beta-oxidative pathway. However, it is also possible that the role of p-coumaric acid might be independent of tyrosine, and there may exist multiple pathways of 4-HB biosynthesis. To identify the metabolic steps responsible for the use of p-coumaric acid in the biosynthesis of Q in yeast, a number of candidate genes with hypothesized roles in conversion of p-coumaric acid to Q were knocked out (9), and the corresponding yeast null mutants were grown in presence of [$^{13}C_6$-ring]-p-coumaric acid. Subsequent high performance liquid chromatography tandem mass spectrometry allows us to analyze [$^{13}C_6$-ring]-Q_6 levels. This approach should provide further insight into the uptake and conversion of p-coumaric acid into Q. Current results suggest that the corresponding uptake of p-coumaric acid and its utilization as a Q ring precursor is heavily dependent on the growth medium and culture conditions.

[1] Department of Chemistry and Biochemistry, University of California, Los Angeles, CA, USA;[2] Department of Plant, Molecular and Cell Biology, University of Florida, Gainesville, FL, USA

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#19 - SPOP Regulates the Nuclear Pore Protein NupJ

Joseph Ong and Jorge Z. Torres

Cell processes like growth and division are tightly regulated. One such mechanism of regulation is ubiquitination. Ubiquitination can change a protein's localization or activity, or it can mark the protein for degradation by the ubiquitin proteasome system. The final step of ubiquitination, transferring ubiquitin to the target protein, is mediated by E3 ligases and their substrate adaptors, proteins that allow E3 ligases to be selective in choosing their targets. Understanding the targets of E3 ligases and substrate adaptors, then, is crucial to understanding cell regulation and disease mechanisms linked to misregulation of protein levels and activity. SPOP is a Cul3 E3 ubiquitin ligase substrate adaptor whose targets, such as c-Myc, PD-L1, and ERG, are crucial for cell cycle progression and cancer proliferation. Through a mass spectrometry screen, we identified SPOP as a potential regulator of NupJ, a nuclear pore protein. Nuclear pore proteins play canonical roles in transport across the nuclear envelope and emerging roles in nuclear envelope morphology and cell division. SPOP and NupJ both co-localize at the nuclear envelope via immunofluorescence microscopy, and co-immunoprecipitation experiments demonstrate that SPOP and NupJ bind to each other in vitro and from cell lysates. Similar to overexpression of NupJ, siRNA against SPOP leads to an increase in the number of nuclear envelope defects. Moreover, overexpressed NupJ leads to defects in cell division. Our results suggest that SPOP regulates NupJ activity and perhaps NupJ protein stability.

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#20 - Uncovered Allosteric Pathway Resolves the Ambiguous Mechanism of Phenylalanine Hydroxylase

David J. Reilley,[†] Konstantin Popov,[‡] Nikolay V. Dokholyan,[¶,‡] and Anastassia N. Alexandrova[*,†,§]

Phenylalanine hydroxylase (PAH) is an iron enzyme catalyzing the oxidation of L-Phe to L-Tyr during phenylalanine catabolism. Dysfunction of PAH leads to the debilitating condition phenylketonuria (PKU), which prompted research into the structure and function of PAH over the last 50 years. Despite intensive study, there is no consensus on the mechanism of wild type PAH and how it varies with PKU-inducing mutations, Arg158Gln and Glu280Lys. We studied the structures involved in two proposed mechanisms for the wild type and mutants using extensive mixed quantum-classical molecular dynamics simulations. Simulations reveal a previously unobserved allosteric pathway involving the mutation sites, suggesting how they can affect the catalytic performance of PAH. Dynamic coupling of the mutation sites to the active site results in structural changes consistent with just one of the two previously proposed mechanisms of PAH, discriminating against the other. The allosterically-enabled effect on PAH structure agrees with the experimentally observed differences in activity between the wild type and mutants.

† Department of Chemistry and Biochemistry, University of California; ‡ Department of Biochemistry and Biophysics, University of North Carolina at Chapel Hill; ¶ Department of Pharmacology, Department of Biochemistry & Molecular Biology, Penn State University College of Medicine; § California NanoSystems Institute.

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#21 - Fragment Based Phasing for Electron Diffraction of Protein Crystals

Logan Richards, Claudia Millán, Calina Glynn, Jennifer Miao, Paul Sieminski, Isabel Uson, and Jose Rodriguez

Crystallographic structure determination depends on use of an existing solution to the phase problem. Computational solutions to the phase problem include the use of existing structures as probes for molecular replacement, or the use of direct methods when atomic resolution data is available. Molecular replacement has been broadly successful for structure determination by X-Ray crystallography, but fails where appropriate probes are unavailable. Molecular replacement is a key method for structure phase determination in the cryoEM method, MicroED. If probes for molecular replacement are unavailable and the resolution of MicroED data is not sufficient to enforce atomicity (1.2Å or better) for ab initio methods, no other phasing options remain. To broaden phasing solutions for MicroED, particularly for data that is 2.0-1.2Å in resolution, we demonstrate the utility of fragment-based molecular replacement. This approach obviates the need for a single accurate probe and allows the use of large fragment libraries for phasing. We implement fragment-based molecular replacement using the ARCIMBOLDO suite of programs and show that ARCIMBOLDO-SHREDDER can facilitate the determination of the structure of Proteinase K from 1.6Å MicroED data. We further demonstrate the utility of this approach for the determination of amyloidogenic peptide structures that are difficult to achieve by traditional molecular replacement at resolutions too poor for direct methods. This approach offers new hope for those MicroED structures with resolution between 2.0 and 1.2Å that may otherwise remain unsolved.

#22 - Perfluorocarbon Nanoemulsions Enhance Kinetics in Hybrid Biological Inorganic CO_2-Reducing System for Increased Output

Roselyn M. Rodrigues, , Xun Guan, Jesus A. Iñiguez, Scarlett Huang, Daniel A. Estabrook, John Chapman, Ellen M. Sletten, Chong Liu*

Hybrid systems combining CO_2-fixing microorganisms with electrochemical water-splitting have achieved high energy efficiencies while converting CO_2 into commodity chemicals. However, current systems face a limitation to achieving high throughput. The reducing equivalents of H_2 gas are poorly soluble in the aqueous system which potentially limits the overall output. We added perfluorocarbon nanoemulsions to a hybrid system to improve the delivery of the reducing equivalents to the microbes. In four days our system achieved average titers of 5.9 ± 1.1 $g_{acetate}L^{-1}$ at a current density of about 2 mA/cm^2 (n = 4), one of the highest titer values reported for similar systems. Additionally, we report an increase in Faradaic efficiency (*F. E.*) of over 58%. We believe that an observed increase in the kinetic transfer of reducing equivalents to the microbes, of over 250%, is the main contributor to this increase in *F. E.* and overall throughput of the system. A local increase in the H_2 gas concentration at the microbe interface was also detected and is believed to have also played a role in the overall enhancement of the system. We believe that the perfluorocarbon nanoemulsions also have potential to be used in other microbial electrosynthetic systems where gas solubility and transfer kinetics are limiting, perhaps for N_2 reduction to NH_3, to enhance the overall throughput of the system.

#23 - Exploring post-translationally modified and mutated amyloid-β segments by micro electron diffraction

Rebeccah Warmack, Chih-Te Zee, David Boyer, Logan Richards, Duilio Cascio, Michael Sawaya, Tamir Gonen, David Eisenberg, **Steven Clarke**

Amyloid proteins form elongated, unbranched fibers that influence the pathogenicity of various neurodegenerative diseases. The design of therapeutics for amyloid is complicated by the fact that many amyloid protein sequences are able to form structurally distinct polymorphs. This underscores the need for characterization of prominent polymorphs en route to pharmacophore development. These efforts are limited by the recalcitrance of amyloid segments longer than 11 residues to crystallization, particularly those bearing post-translational modification (PTMs). Here we make progress in the structural characterization of two 15-residue amyloidogenic peptides containing an isomerized aspartate and an early-onset familial mutation. Both of these synthetic peptides, derived from Amyloid-β, show accelerated amyloid fibril formation. X-ray diffraction of aligned fibrils shows cross-β diffraction with interstrand and intersheet distances of 4.8 Å and 10 Å, respectively, confirming their amyloid nature. To inform the atomic basis for structural polymorphism induced by post-translational modification of these amyloid forming peptides, we have grown crystals of the Amyloid-β segments by sonic agitation. A structure of the segment containing isomerized aspartate has been solved by direct methods at 1.1 Å resolution, revealing two distinct protofilament interfaces, one which may be a target for novel, specific inhibitors. These results underscore the need for atomic detail to enlighten the effects of post-translational modifications on amyloid fibrils and demonstrate the need for emerging cryoEM technologies to reveal the atomic basis for amyloid polymorphism.

#24 - Large-area ultrathin metal-oxide semiconductor nanoribbon arrays and aptamer field-effect transistor biosensors fabricated by chemical lift-off lithography

Chuanzhen Zhao[1,2], Xiaobin Xu[1,2], Wenfei Liu[1,2], Kevin M. Cheung[1,2], Nako Nakatsuka[1,2], Sang-Hoon Bae[1,3], Qing Yang[1,2], Jason N. Belling[1,2], You Seung Rim[1,3,4], Yang Yang[1,3], Milan Stojanovic[5], Anne M. Andrews[1,6], and Paul S. Weiss[1,2,3]

One-dimensional nanostructure-based field-effect transistors (FETs), such as nanoribbon and nanowire FETs, are of great importance to the development of highly sensitive chemical and biological sensors because of their high surface-to-volume ratios. Challenges remain within conventional nanofabrication techniques, such as high cost and low throughput, which hinder the widespread application of these nanoelectronics and biosensors. In this work, we demonstrated a high-throughput nanolithographic method to fabricate ultrathin (~3 nm) In_2O_3 nanoribbon arrays, and constructed nanoribbon-based FETs on the wafer scale, using a sol-gel process followed by chemical lift-off lithography, a subtractive soft lithographic technique developed by our groups. Nanoribbon arrays of 200-nm width and 400-nm pitch were fabricated, and then used as a channel material for FETs, which have current on/off ratios of over 10^7 and a peak mobility of ~13.7 cm^2/Vs. Field-effect transistors with ultrathin In_2O_3 channels were explored as highly selective neurotransmitter sensors, where the channel was functionalized with oligonucleotide stem-loop receptors, aptamers, which were selected for the adaptive recognition of neurotransmitter targets. Upon binding neurotransmitters, such as serotonin, aptamers with negatively charged backbones are hypothesized to change the electric potential of the semiconducting channel through their conformational changes. Nanoribbon-based serotonin-specific aptamer FETs had high sensitivities, down to 10^{-15} M, and excellent selectivity. The functionality of these biosensors was extended to full ionic strength biological fluids, such as undiluted artificial cerebrospinal fluid. Ultrathin In_2O_3 nanoribbon transistor biosensors, fabricated by straightforward top-down fabrication processes, are of great interest for nanoelectronics and next-generation ultrasensitive biosensor platforms.

(1) California NanoSystems Institute; (2) Department of Chemistry & Biochemistry; (3) Department of Materials Science and Engineering, UCLA; (4) School of Intelligent Mechatronics Engineering, Sejong University, Seoul 05006, Republic of Korea; (5) Division of Experimental Therapeutics, Department of Medicine, Department of Biomedical Engineering, Columbia University, New York, New York (6) Department of Psychiatry and Biobehavioral Health, Semel Institute for Neuroscience and Human Behavior, and Hatos Center for Neuropharmacology, UCLA. *This work was supported by National Science Foundation (grant no. CMMI-1636136) and the National Institute on Drug Abuse (grant no. DA045550).*

Postdoctoral Researcher Abstracts

#25 - Atomic structures of a single chain antibody that binds and inhibits seeding by tau oligomers

Romany Abskharon[1,2*], Paul Seidler[1,2*], Michael R. Sawaya[1,2], Duilio Cascio[1,2], Stephan Philipp[3], Charles G. Glabe[3], David S. Eisenberg[1,2**]

Alzheimer disease (AD) is the only disease among the 10 leading causes of death that cannot be cured, prevented, or even slowed. Amyloid plaques and tau neurofibrillary tangles are the pathological hallmarks of AD, and levels of tau aggregation are tightly linked to cognitive decline. Several lines of evidence suggest that toxic tau oligomers play a pivotal role in the spread of tau pathology, and passive immunization using antibodies that neutralize tau oligomers offers promise in the battle to delay, and potentially even prevent onset of AD.

Here we report a monoclonal antibody (M204) that binds tau oligomers of the full-length tau (Tau 40) and also the four-repeat domain of tau (Tau k18). M204 binds the aggregation-prone segments VQIINK and SVQIV in tau, and inhibits cell-to-cell seeding by tau oligomers, confirming the powerful role of theses sequences in promoting tau oligomerization. To minimize the size of the antibody, we sought to produce M204 as a single-chain variable-fragment (scFv). In this work, we established a system to express and purify a completely functional single chain antibody fragment in *Escherichia coli*. The scFv-M204 was found to purify in three different conformations: monomer, dimer and trimer when expressed in the bacterial periplasm. The dimeric and trimeric conformations bind tau oligomers better than the monomeric form of scFv-M204, and importantly also inhibit tau aggregation *in vitro* and in HEK293 biosensor cells seeded by brain homogenates from human patients with tauopathies including AD and Chronic Traumatic Encephalopathy (CTE). The crystal structures of the monomer, dimer and trimer were determined revealing differences that could contribute to the increased binding and inhibition that we observed by higher order structures of scFv-M204. We anticipate that these structures will lead to the design a second generation of scFv-M204 antibodies with greater potency and tau binding. Furthermore we speculate that by binding toxic oligomers, which are hypothesized to be early seeding-competent species that are formed by tau, our scFv-M204 antibody may have potential as an early-stage diagnostic for AD and other tauopathies, in addition to holding promise as a prospective therapeutic.

1 Departments of Chemistry and Biochemistry and Biological Chemistry, UCLA-DOE Institute, UCLA, Los Angeles, California 90095, USA.

2 Howard Hughes Medical Institute, UCLA, Los Angeles, California 90095, USA.

3 Department of Molecular Biology and Biochemistry, University of California, Irvine, California 92697.

***To whom correspondence should be addressed: Howard Hughes Medical Inst., Los Angeles, CA 90095-1570. E-mail: david@mbi.ucla.edu.*

**Both authors contributed equally to this work.*

#26 - Decay Associated Fourier Spectroscopy: Detecting Luminescence from Visible to Shortwave Infrared

Timothy L. Atallah, Anthony V. Sica, Ashley J. Shin, Justin R. Caram

Acquiring time-resolved images and spectra from fluorescent molecules simultaneously across the visible, near- and shortwave-infrared (SWIR, 1-2 μm) introduces methods for understanding biological systems that include determining local oxygen concentrations, deep tissue imaging and uncovering enzyme mechanisms. We have developed decay associated Fourier spectroscopy (DAFS) to do just that: obtain picosecond time-resolved photoluminescence spectra from the SWIR to UV with photon counting. We leverage interferometric balanced detection, superconducting nanowire single photon detectors and Si single photon avalanche photodiodes to achieve this. We show preliminary results for semiconductor thin films and dye molecules. Future applications include imaging oxygen concentrations using singlet oxygen photoluminescence to reveal mechanisms of radical oxygen formation/elimination, deep tissue imaging using SWIR emitting dyes (due to less Rayleigh scattering) and studying biochemical processes using resonance energy transfer between dyes. With DAFS we overcome many limitations of Si detectors leading to exciting new prospects in biophysics research.

#27 - The genome inside a multipartite RNA virus is essentially disordered

Christopher Beren, William Gelbart

We report the first asymmetric reconstruction of the single-stranded (ss) RNA content in one of the three otherwise-identical virions of a multipartite RNA virus, brome mosaic virus (BMV). We exploit a sample consisting exclusively of particles with the same RNA content — specifically, RNAs 3 and 4 — assembled *in planta* by agrobacterium-mediated transient expression. We find that the interior of the particle is nearly empty with most of the RNA genome situated at the capsid shell. But this density is flexible and disordered, demonstrating that the RNA is associated with an ensemble of secondary/tertiary structures that interact with the capsid protein. Our results illustrate a fundamental difference between the ssRNA organization in the multipartite BMV viral capsid and the monopartite bacteriophages MS2 and Qβ, for which a dominant RNA conformation is found inside the assembled viral capsids, with RNA density conserved even at the center of the particle. This can be understood in the context of the viral life-cycle, as BMV must package separately each of several different RNA molecules and has been shown to replicate and package them in isolated, membrane-bound, cytoplasmic complexes, while the bacteriophages exploit sequence-specific “packaging signals” throughout the viral RNA to package their monopartite genomes.

#28 - Androgen receptor degraders and signaling axis inhibitors targeting castration-resistant prostate cancer

N. G. R. Dayan Elshan[1], Jiabin An[2], Matthew B. Rettig[2,3] and Michael E. Jung[1]

Prostate cancer (PCa) is the second leading cause of cancer-related mortality in men in the United States. Androgen deprivation therapy (ADT) through surgical or chemical castration is the mainstay of therapy for patients with metastatic PCa. The androgen receptor (AR) plays a central role in the progression of this disease. The AR has three distinct regions in its structure; a *N*-terminal transactivation domain (TAD), a DNA binding domain (DBD), and a ligand binding domain (LBD). ADT and all current AR antagonists function by directly or indirectly targeting the AR–LBD which inhibits PCa progression. Patients eventually develop resistance to these current therapies, leading to the lethal form of PCa termed metastatic castration-resistant prostate cancer (mCRPC). Primary resistance mechanisms involve but are not limited to 1) LBD mutations and 2) the evolution of constitutively active AR splice variants that lack a functional LBD. Given that the primary resistance mechanisms are centered upon the AR–LBD, there is an unmet need to develop therapies that target the other functional domains on the AR. Here, we show the targeting of CRPC through a novel class of AR inhibitors that target the AR–TAD and also enhance the degradation of AR protein. These compounds have shown excellent *in vitro* and *in vivo* characteristics in inhibiting AR-driven CRPC tumor growth. Given the promising ability to inhibit the AR signaling axis even in the presence of constitutively active AR splice variants, these compounds are currently being further-developed as potential therapeutics for the treatment of CRPC.

1. Department of Chemistry and Biochemistry, UCLA, Los Angeles, CA, United States.
2. Division of Hematology/Oncology, VA Greater Los Angeles Healthcare System West LA, Los Angeles, CA, United States.
3. Departments of Medicine and Urology, David Geffen School of Medicine, UCLA, Los Angeles, CA, United States.

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#29 - Lattice Nanoripples in Protein Crystals Detected by Scanning Electron Nanodiffraction

1[1] Marcus Gallagher-Jones, [2] Colin Ophus, [2] Karen C. Bustillo, [1] Calina Glynn, [1] Chih-Te Zee, [2,3] Ouliana Panova, [2,3] Andrew M. Minor and [1] Jose A. Rodriguez.

Macromolecular crystals are assumed to be monolithic assemblies of identical molecules. In reality, such crystals exhibit a complex structure on the micro and nanoscale. Deviations from a perfect lattice can impact the ability of crystals to grow large, and limit diffracting power, complicating the process of data reduction. This impairs atomic-scale structural studies of the underlying molecules. Large crystals are assumed to form from the coalescence of nano to micro-scale crystalline subdomains - an assumption that remains unproven by direct observation. To improve our knowledge of macromolecular crystal complexity, we have employed a new electron microscopy technique, 4D-STEM to create spatial maps of diffraction from nanoscale regions of cryogenically cooled macromolecular micro-crystals. Within these crystals, fewer than 2500 molecules can produce meaningful diffraction to atomic resolution. Using unsupervised clustering in combination with large scale lattice simulations we are able to assign orientation parameters to nm-sized regions of a single crystal. Our analysis reveals a continuous, rather than discrete, ripple-like reorientation of the crystal lattice.

1 Department of Chemistry and Biochemistry, University of California Los Angeles, CA, USA
2 National Center for Electron Microscopy, Molecular Foundry, Lawrence Berkeley National Laboratory, CA, USA
3 Department of Materials Science and Engineering, University of California Berkeley, CA, USA

#30 - Structural basis of reversible amyloid associated with membraneless organelles

Michael Hughes, David Eisenberg

Subcellular membraneless assemblies are a reinvigorated area of study in biology, with spirited scientific discussions on the forces between the low-complexity protein domains within these assemblies. To illuminate these forces, we determined the atomic structures of five segments from protein low-complexity domains associated with membraneless assemblies. Their common structural feature is the stacking of segments into kinked β sheets that pair into protofilaments. Unlike steric zippers of amyloid fibrils, the kinked sheets interact weakly through polar atoms and aromatic side chains. By computationally threading the human proteome on our kinked structures, we identified hundreds of low-complexity segments potentially capable of forming such interactions. These segments are found in proteins as diverse as RNA binders, nuclear pore proteins, and keratins, which are known to form networks and localize to membraneless assemblies.

#31 - A Boron Cluster-Based Approach to Nucleophilic Borylation

Mu, X.†; Axtell, J. C.†; Bernier, N. A.†; Spokoyny, A. M.*†‡

The creation of complex organic substrates through the intermediacy of species containing boron-carbon bonds has emerged as one of the most powerful tools in synthetic chemistry over the past several decades. Most of the methods for B–C bond formation rely on reagents where a boron center formally behaves as an electron-poor Lewis acid. Recently, several classes of isolable compounds in which boron exhibits electron-rich and nucleophilic characteristics have been discovered. Despite these efforts, the synthetic utility of these nucleophilic boron reagents has been limited given the multistep protocols needed for their synthesis as well as their poor stability to air and moisture. Furthermore, sterically encumbering, high molecular weight ligand scaffolds are often needed to stabilize these highly reactive nucleophilic boron centers, severely limiting their practicality for use in borylation procedures.

In this presentation, we will showcase recent work from our laboratory focused on addressing these challenges. Specifically, we employ a conceptually different approach toward stabilizing nucleophilic sources of boron via three-dimensional electron delocalization instead of steric protection. We discovered that the reaction of air-stable, 6-membered hexaborate clusters with benzyl and alkyl halides as well as pseudohalides under mild conditions affords compounds featuring B–C bonds. Importantly, unlike the dodecaborate (B12-based) cluster system, which is well known to resist degradation even under exceedingly harsh conditions, electrochemical studies of these clusters reveal an irreversible one-electron oxidation, indicating degradative cage rupture. Our results have proved that this redox instability can be harnessed to conveniently prepare benzyl and alkyl pinacol boron ester derivatives by controlled cage degradation in good yields.

The nucleophilic character of the boron clusters also facilitates the construction of B-heteroatom bonds through treatment with main-group electrophiles (e.g., RSeCl, R2PCl and B-chloro-catecholborane), generating the corresponding compounds in high yields.

Preliminary mechanistic studies have been carried out to explore the substitution step. First, a radical clock, (bromomethyl)cyclopropane, was tested as an electrophile. The direct B–C bond formation without any observed ring opening byproduct indicates that the observed substitutions likely do not proceed through radical pathways. In addition, the reaction between the hexaborate cluster and a chiral alkyl halide resulted in the inversion of stereocenter of the electrophile, further suggesting the substitution step follows an SN2 pattern.

We are currently developing this chemistry further in the context of late-stage functionalization of complex molecules. We envision subsequent transfer and/or addition chemistry using these reagents to be a highly valuable addition to the chemist's synthetic arsenal.

†Department of Chemistry and Biochemistry, University of California, Los Angeles, 607 Charles E. Young Drive East, Los Angeles, California 90095-1569, United States; ‡California NanoSystems Institute, University of California, Los Angeles, 570 Westwood Plaza, Los Angeles, California 90095-1569, United States

#32 - Development of a structure-based panel of tau inhibitors for probing structural strains in neurodegenerative disease

Paul Seidler1, David Boyer1, Kevin Murray1, Jose Rodriguez1, Michael Sawaya1, Duilio Cascio1, Tamir Gonen1, David Eisenberg1

Aggregation of tau into neurofibrillary tangles is the histological hallmark of some 24 different dementias referred to as tauopathies, the most prevalent of which is Alzheimer's disease (AD). In total, our structural studies of tau, determined using the cryoEM method micro-electron diffraction have revealed a total 5 different aggregation surfaces, 3 deriving from a segment with sequence VQIINK, and 2 from a segment with sequence VQIVYK. Using these structures, we developed a panel of peptide-based inhibitors that targets each of the different aggregation surfaces of tau, and show that these inhibitors block the ability of full length tau fibrils to template seeded aggregation, a process that is thought to be responsible for driving the spread of tau pathology in neurodegenerative disease. Here, we go on to show that this panel of structure-based inhibitors of tau blocks seeding by patient-derived tau fibrils that were extracted from autopsied brain tissue of patients with AD, and another tauopathy called progressive supranuclear palsy (PSP). Surprisingly our studies suggest that these inhibitors have potential to discriminate different polymorphic aggregates of tau that are found in the brains of individual tauopathy patients. In summary, these inhibitors show promise as prospective therapeutics and potential imaging agents.

1Howard Hughes Medical Institute, UCLA-DOE Institute, Departments of Biological Chemistry and Chemistry and Biochemistry, Los Angeles, CA 90095

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#33 - Mimicking Thiol Gold Nanoparticles (AuNP) with Atomically-Precise Organometallic Equivalents

Julia M. Stauber[1], Elaine A. Qian[1,2,3], Petr Král[4,5,6], Heather D. Maynard[1,3], Alexander M. Spokoyny[1,3]*

There is significant interest in the ability to build atomically precise nanocluster molecules with complex three-dimensional structures resembling the intricate molecular architectures found in natural systems. We have developed a platform to access a class of robust, well-defined, three-dimensional hybrid nanomolecules with high tunability using an air-stable, organometallic gold(III) dodecaborate cluster. This cluster serves as a template for further diversification with a wide array of thiol-containing substrates including alkanes, arenes, alcohols, amines, peptides, and sugar molecules. The conjugation reactions proceed rapidly with high chemoselectivity to produce a library of nanocluster assemblies that exhibit high structural stability under biologically relevant conditions due to their full covalency. Glycosylated nanomolecules displayed increased binding affinity to target proteins when compared with the free sugar molecules, showcasing how this strategy allows for the generation of precise multivalency for molecular recognition.

Institutions:

1. Chemistry and Biochemistry, University of California, Los Angeles, Los Angeles, CA, United States

2. Bioengineering, University of California, Los Angeles, Los Angeles, CA, United States

3. California NanoSystems Institute, University of California, Los Angeles, Los Angeles, CA, United States

4. Department of Chemistry, University of Illinois at Chicago, Chicago, Illinois 60607, United States

5. Department of Physics, University of Illinois at Chicago, Chicago, Illinois 60607, United States

6. Department of Biopharmaceutical Sciences, University of Illinois at Chicago, Chicago, Illinois 60612, United States

#34 - CryoEM Structure of Telomerase with Telomeric DNA

Yaqiang Wang,[1] Jiansen Jiang,[2,3,4] Lukas Susac,[1] Henry Chan,[1] Ritwika Basu,[1] Z. Hong Zhou,[2,3] and Juli Feigon[1]

Telomerase is an RNA–protein complex (RNP) that extends telomeric DNA at the 3' ends of chromosomes using its telomerase reverse transcriptase (TERT) and integral template-containing telomerase RNA (TER). Its activity is a critical determinant of human health, affecting aging, cancer, and stem cell renewal. Lack of atomic models of telomerase, particularly one with DNA bound, has limited our mechanistic understanding of telomeric DNA repeat synthesis. We report the 4.8 Å resolution cryoelectron microscopy structure of active Tetrahymena telomerase bound to telomeric DNA. The catalytic core is an intricately interlocked structure of TERT and TER, including a previously structurally uncharacterized TERT domain that interacts with the TEN domain to physically enclose TER and regulate activity. This complete structure of a telomerase catalytic core and its interactions with telomeric DNA from the template to telomere-interacting p50–TEB complex provides unanticipated insights into telomerase assembly and catalytic cycle and a new paradigm for a reverse transcriptase RNP.

[1]Department of Chemistry and Biochemistry, University of California, Los Angeles, Los Angeles, CA 90095, USA
[2]Department of Microbiology, Immunology and Molecular Genetics, University of California, Los Angeles, Los Angeles, CA 90095, USA
[3]California NanoSystems Institute, University of California, Los Angeles, Los Angeles, CA 90095, USA
[4]Present address: Biochemistry and Biophysics Center, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD 20892, USA

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