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Meeting Proceedings, 2017 Cornell University Baker — Symposium *Quo Vadis: The Boundless Trajectories of Chemical Biology*

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Cornell University's Baker Lectures are the oldest continuous lecture series presented by a Chemistry Department at an American university. Established in 1923 and endowed by the banker and philanthropist George Fisher Baker, these lectures have historically provided opportunities for prominent chemists to spend mini-sabbaticals at Cornell's Ithaca campus. In fact, 21 Nobel Prizes have been awarded to Baker Lecturers, and in most cases the Baker Lecture preceded the Nobel Prize. Notable among Baker lectures is the series presented in 1939 by Linus Pauling, the product of which was his seminal book *The Nature of the Chemical Bond*, published by the Cornell University Press.¹

In recent years, the Baker Lectures have adopted a different format, wherein several luminaries are welcomed to Ithaca to present seminars in a one-day symposium on a specific theme. The focus of the symposium rotates through the different subfields of chemistry, with chemical biology occurring only once every six or seven years. On April 8, 2017, five outstanding chemical biologists traveled to Cornell's campus to present keynote lectures in a symposium titled "*Quo Vadis: The Boundless Trajectories of Chemical Biology*." The invited speakers included Christopher J. Chang (University of California Berkeley), Jon Clardy (Harvard Medical School), Laura L. Kiessling (University of Wisconsin—Madison/Massachusetts Institute of Technology), Alanna Schepartz (Yale University), and David A. Tirrell (California Institute of Technology), see Figure 1.

In a first, this year we were enabled to extend invitations beyond the Cornell community to several local institutions due to generous sponsorship from *ACS Central Science*, *ACS Chemical Biology*, and *Biochemistry* that supplemented funds from the Baker Endowment. Thus, we were pleased to welcome attendees from several schools from upstate New York,

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Notes

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including the Hobart and Williams Smith Colleges, SUNY Albany, SUNY Binghamton, SUNY Buffalo, SUNY College of Environmental Science and Forestry, SUNY Cortland, Syracuse University, University of Rochester, and Wells College.

Set in Cornell's historic Baker 200 lecture hall, the attendees were treated to a day of outstanding lectures that collectively illuminated us all on *quo vadis*, or "where are you going," in chemical biology. Collectively, the talks touched on many diverse groups of biological molecules, from ions and reactive oxygen species to secondary metabolites, lipids, carbohydrates, and proteins: how and where they are being made, what they are doing, and how we can monitor and manipulate them.

Jon Clardy (Harvard Medical School) kicked off the day with a seminar titled "Molecular View of Multilateral Symbioses." He began by describing how we as humans share one important characteristic with ants, termites, and beetles: we all practice agriculture, a specialized form of symbiosis. Fungi are the crops that these insects culture, and the collective encompassing the insects, commensal and pathogenic fungi, and bacteria represents a rich ecosystem to mine for new chemotypes.² A major focus of the seminar was the varying genetic contexts in which secondary metabolite biosynthetic clusters reside, and that chemical diversity within metabolite families is facilitated by the evolutionary transfer of their biosynthetic genes from a bacterial plasmid to the chromosome.³

These elusive compounds have been termed cryptic metabolites, which Professor Clardy suggested are so-named to "remove any sense of guilt about not finding them." As an example of these themes, he described his group's recent work to elucidate the identity and biosynthesis of 9-methoxyrebecca-mycin, an analog of the antitumor agent rebeccamycin.⁴ This "bacterial Game of Thrones," he described, with "names you can't pronounce trying to take each other over," can provide outstanding starting points for therapeutic agents to treat emerging infectious disease. Such therapeutic agents represent a major unmet need, he argued, as invasive fungal diseases collectively cause greater mortality worldwide than either tuberculosis or malaria.⁵

Laura Kiessling (University of Wisconsin–Madison/Massachusetts Institute of Technology) followed by presenting a seminar titled "Mining Microbial Carbohydrates for Health and Disease." She began by describing how a 50- μ m-thick layer of mucus within the lumen of our gut separates the epithelial barrier from the gut microbiota, a complex mixture of bacteria, fungi, and phages that is responsible for so many aspects of physiology and disease. Within this mucus layer are molecular sensors that help us control which bacterial species can colonize, and a major part of this sensing comes from the unique and varied carbohydrate coats on bacterial surfaces.⁶ While the complement of mammalian glycans is limited to a few dozen monosaccharide building blocks, she informed us that the chemical space of bacterial glycans is enormous, resulting from more than 700 known monosaccharides, which can be recognized by nearly 100 lectins, or carbohydrate-binding proteins.

Professor Kiessling focused on one such lectin, called intelectin-1, which appears to keep both commensal and pathogenic bacteria at bay. This remarkable sensor was originally

thought to recognize the minor furanose form of galactose, but exhaustive studies with glycan arrays and structural studies revealed that evolution had permitted intelectin-1 to recognize a variety of acyclic 1,2-diols derived from bacterial glycans while not recognizing 1,2-diols in mammalian glycan structures.⁷ She proposed that the molecular recognition of 1,2-diols within intelectin-1 and many other X-type lectins occurs *via* aromatic residues in an “aromatic box” on the basis of ¹H NMR binding studies.⁸ Biological studies of specific bacterial targets of intelectin-1, as well as functional consequences to gut physiology due to its absence, are currently underway.

Christopher Chang (University of California, Berkeley) contributed to the afternoon session with a talk titled “Transition Metal Signaling in the Brain and Beyond.” Professor Chang began with a chronicled panorama of his lab’s science, highlighting technological challenges underlying the measurements of the microenvironment and tissue-specific dynamic pools of metal ions. A plethora of both redox- and nonredox-active metal ions modulate, for instance, brain anatomy, activity, and function.⁹ One of the fundamental difficulties in developing fluorescent small-molecule reporters with specificity for unique ions in live cells includes getting the right affinity such that the probe is functionally adaptable to both binding and release events, without being influenced by environmental variables, such as endogenous small-molecule ligands, redox, and pH fluctuations.

Several notable recent developments of reactivity-based metal-ion reporters and related discoveries were then highlighted. Beyond the brain, the talk extended to metal homeostasis in the gut. The audience was also shown how bioluminescence imaging of mobile copper in live mice with copper-caged luciferin-1 revealed the mechanistic nuances of hepatic copper deficiency during progression of a diet-induced nonalcoholic fatty liver disease, such as expression changes in the major copper exporter proteins.¹⁰ Another example highlighted the role of copper in cyclic-AMP-dependent lipolysis through selective copper-targeted modulation of the enzymatic activity of the phosphodiesterase isoform PDE3B.¹¹ Drawing functional connections between metal-ion homeostasis and redox biology, the presentation also spotlighted an inaugural methionine–oxaziridine-coupling-based approach to profile methionine residues.¹²

Alanna Schepartz (Yale University) followed with a seminar titled “Watching Organelles for (Almost) Forever at Super-Resolution,” which featured a clever solution to a major problem in live-cell imaging: photobleaching of fluorophores in the context of super-resolution imaging. To acquire long movies, one would need to limit photobleaching, and this goal was accomplished by using a fluorophore that spends far more than 99% of its time in the off state. But high resolution requires high photon counts. The enabling insight was to append the switchable fluorophore to a lipid rather than a protein, because there are approximately 100 times more lipids than proteins in a given membrane area.¹³ The balance between high density and a superlow on fraction enabled superlong time-lapse movies to visualize organelle dynamics within live cells.

The labeling method capitalizes upon silicon rhodamine fluorophores, which exhibit pH- and environment-dependent reversible switching between fluorescent and nonfluorescent states.^{14–16} Using the inverse electron-demand Diels–Alder cycloaddition^{17–19} between

tetrazine–fluorophores and trans-cyclooctene (TCO) lipid or small-molecule probes that localize to specific organelle membranes,²⁰ Professor Schepartz and her collaborators at Yale, which included Joerg Bewersdorf, Derek Toomre, and James Rothman, were able to generate movies of up to 30 min, with 2 s temporal resolution and sub-50 nm spatial resolution, of the dynamics of various organelles using these lipid-based targeting probes, a major improvement over protein-based targeting.²¹ They have demonstrated the generality of their method by applying TCO-based tags for the endoplasmic reticulum, the mitochondria, plasma membrane, and, importantly, the elusive Golgi complex, whose organization and dynamics have proven so challenging to unravel over the decades.²²

David Tirrell (California Institute of Technology) delivered the closing lecture, entitled “What are Non-Canonical Amino Acids Good For?” Professor Tirrell laid out a rhapsody on the important and complex biological questions one can interrogate using the ingenious chemical technology, bio-orthogonal noncanonical amino acid tagging (BONCAT).²³ The lecture began with a brief overview of how combining an arsenal of noncanonical amino acids together with aminoacyl-tRNA synthetase engineering has enabled time-resolved probing of proteome dynamics in a cell-selective manner.

The talk then focused on its broader utility toward generating cell-specific proteomic “atlases,” in particular through the stable isotope labeling with amino acids in cell culture (SILAC)–BONCAT coupled strategy. The multi-faceted nature of the method was exemplified by recent work in various model organisms spanning from worms²⁴ to fruit flies,^{25,26} beyond *E. coli* and cultured mammalian cells. For instance, with the use of the *myo-2* promoter that drives pharyngeal muscle cell-specific expression of the mutant aminoacyl-tRNA synthetase in worms, temporally modulated patterns of pharyngeal muscle proteomes were selectively captured in response to user-defined environmental cues.²⁴ Commercial availability of BONCAT reagents was also noted, ultimately offering ready access to this versatile toolset.

The Cornell Baker Symposium has, in recent years at least, been organized by pretenure faculty at Cornell. These junior faculty are given the opportunity to highlight scientific developments from their young laboratories. This year the Cornell Chemical Biology community was represented by Professors Jeremy Baskin and Yimon Aye.

Jeremy Baskin, whose lab was established at Cornell in August 2015, closed out the morning session with a seminar titled “Illuminating the Chemistry and Biology of Phospholipid Signaling.” Phospholipids such as phosphatidic acid (PA) can act as second messengers that help cells transduce extracellular signals into changes in physiology and behavior. How a single signaling agent can cause many different outcomes remains a mystery, motivating the development of imaging tools to visualize these messengers. The seminar highlighted a chemical strategy that the Baskin Lab has developed for imaging cellular sites of PA synthesis by phospholipase D (PLD) enzymes using clickable primary alcohols to generate PA mimics that are subsequently tagged with fluorophores using click chemistry.²⁷ These tools revealed novel subcellular localizations and unexpected heterogeneities of PLD activity and appear poised to decipher physiological and pathological functions of PLDs.

Yimon Aye's talk, given the enigmatic title, “Swiss Army Man: A Single Molecule That Interrogates Cause and Consequences of Precision Redox Signaling,” discussed a method her lab has developed over the past four years.^{28–30} This technology, called Targetable Reactive Electrophiles and Oxidants, or “T-REX,” is a method to selectively tag a specific redox-sensor protein using a native reactive electrophilic signal (RES) *in vivo*. This method uses a tailor-made photocaged RES and sidesteps the toxicity and off-target effects associated with uncontrolled bulk electrophile exposure, which modifies many proteins at once. The talk disclosed several “privileged sensors” the Aye lab has identified as being uniquely reactive to innate RES under electrophile-limited conditions and whose function is also markedly changed upon modification. At the end of her talk, she discussed an unbiased, proteome-wide method to identify privileged sensors using the same molecule employed in the original T-REX method.

CONCLUDING REMARKS

This one-day symposium, with its excellent speaker lineup and enthusiastic participants—from undergraduate students to faculty across 10 different institutions—in our opinion has been a unique success. The spirit of the symposium went hand in hand with the title itself to provide an atmosphere embracing the limitlessness of chemical biology. As with the 11 Finger Lakes that decorate the natural beauty surrounding Cornell, the science from the five external lecturers spoke volumes about many enchanting trajectories of chemical biology that are sure to push forward the future horizons of science and medicine.

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Figure 1. External speakers for the 2017 Baker Symposium in Chemical Biology. From left: Professors David Tirrell, Jon Clardy, Laura Kiessling, Alanna Schepartz, and Christopher Chang. Photo credit: Jessica Daughtry (Cornell University).