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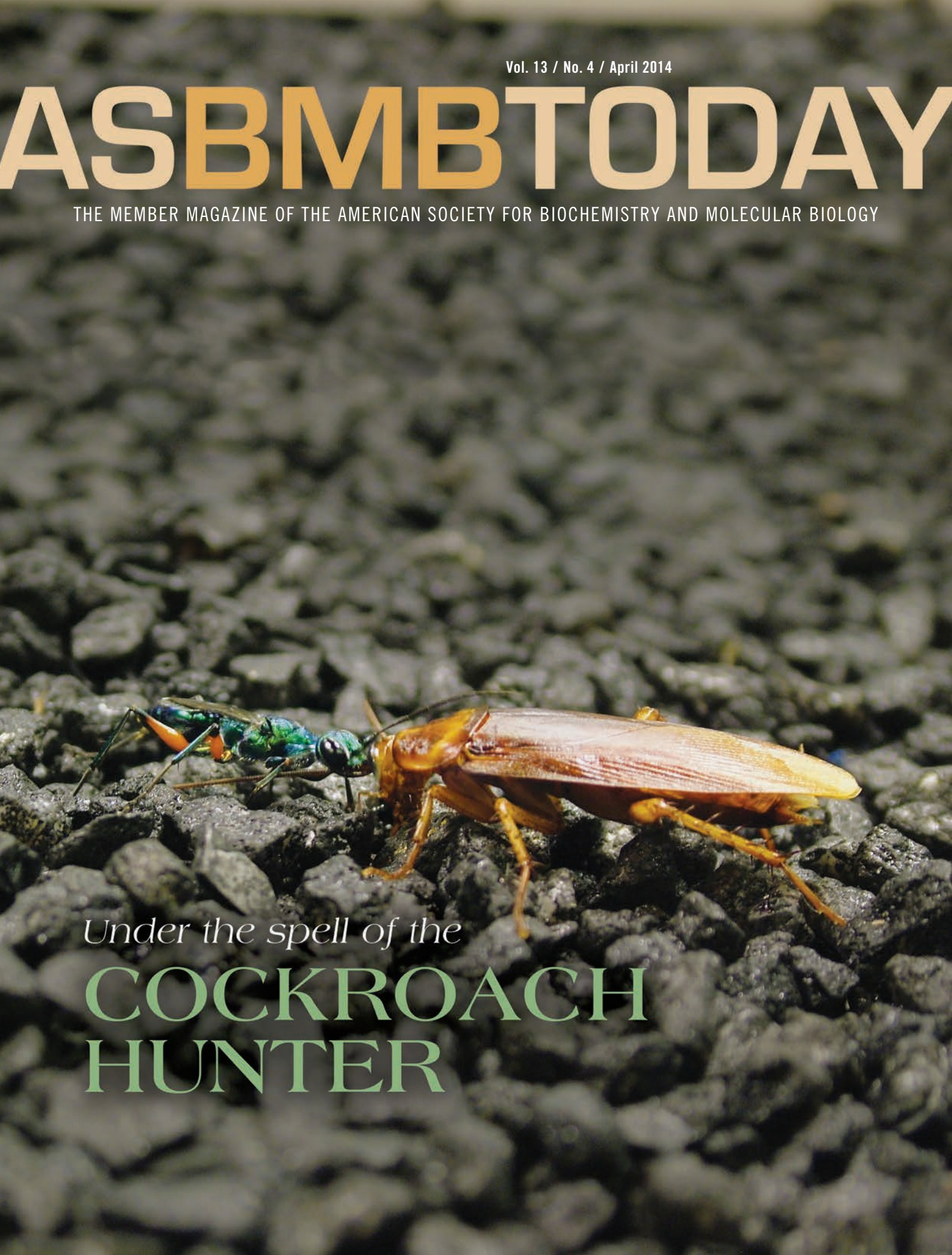

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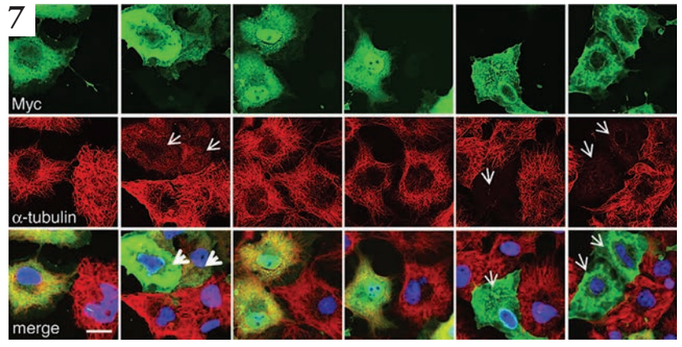

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In this month's cover story, science writer Rajendrani Mukhopadhyay writes about the jewel wasp, a fascinating parasite whose bewitching stings turn cockroaches into unwitting – and, simultaneously, willing – victims.

PHOTO BY VICTOR LANDA, UNIVERSITY OF CALIFORNIA, RIVERSIDE

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Serendipity and 'impact'

By Jeremy Berg

When I was a young faculty member at Johns Hopkins University, I served on the Ph.D. thesis committee of Suzanne Baker, a Ph.D. student in the laboratory of Bert Vogelstein, then an assistant professor in oncology. Baker's thesis project involved trying to identify a putative tumor-suppressor gene on human chromosome 17. Based on considerable work mapping deletions in numerous human tumors, she had reduced the search space to approximately one-fourth of the chromosome. To put the finishing touch on Baker's thesis, Vogelstein suggested that she sequence a gene that falls in the center of this region to rule out this gene as the sought-after tumor suppressor. The gene they selected was p53, the product of which had been shown to associate with a key protein from the tumor virus SV40 (1). To everyone's astonishment, Baker found point mutations in this gene in several tumors (2); they had stumbled on what turns out to be the gene that is most commonly mutated in human cancer (3).

While serendipity has been central to a number of important discoveries, the importance of serendipity can be overstated. The selection of the problem under study is also essential, as is a deep knowledge of the field in order to place incidental or unexpected findings in perspective; the great microbiologist and biochemist Louis Pasteur famously said "Dans les champs de l'observation le hasard ne favorise que les esprits prérparés" ("In the fields of observation, chance favors only the prepared mind"). Under ideal circumstances, scientific priority setting balances the benefits of exploring the unknown with its associated potential for truly novel discoveries against the selection of problems that, if substantial progress is made, will provide considerable benefit to society.

Estimating the importance of serendipity

Can we provide at least some boundaries on the balance between serendipity and problem importance? Significant discoveries can be primarily serendipitous; the result of incremental, step-by-step solving of a known, important problem; or a hybrid of the two. An example of a largely serendipitous discovery was recognized by the Nobel Prize in physiology or medicine in 2006 to Andrew Fire and Craig Mello for their discovery of "RNA interference-gene silencing by double-stranded RNA" (4).

This discovery was based on a chance observation made in the context of studies of gene regulation in C. elegans wherein a control experiment involving the simultaneous injection of both sense and anti-sense RNAs corresponding to the same gene resulted in a dramatic change in gene expression not observed for either the sense or anti-sense molecules separately. Their appreciation of this chance observation eventually revealed a widespread but largely unsuspected biochemical pathway.

In the same year, Roger Kornberg was awarded the Nobel Prize in chemistry "for his studies of the molecular basis of eukaryotic transcription" (5). This prize was primarily for the determination of the three-dimensional structure of eukaryotic RNA polymerase. This prize represents not a serendipitous discovery but rather the culmination of many years of effort by Kornberg and his co-workers on a well-recognized problem, namely the elucidation of the structure and associated mechanistic insights for a large and complex enzyme of central importance to biochemistry and molecular biology.

An example of a hybrid discovery is represented by the Nobel Prize to J. Michael Bishop and Harold Varmus in 1989 for their discovery "of the cellular origin of retroviral oncogenes" (6). They were working on a fundamental problem, namely the nature of cancer-causing genes from viruses. Identifying the nature of these genes, regardless of the answer, would have been of fundamental importance. The answer turned out to be of unanticipated significance, revealing that the viral genes were related to normal cellular genes that, when mutated in some ways, can contribute to cell transformation.

To look at the balance between serendipity and problem selection, I examined all of the winners of the Nobel Prize in physiology or medicine and chemistry over the past 25 years and scored each winner's contribution as either largely serendipitous, largely driven by solving a problem of known, fundamental importance or a hybrid of the two. Of the 117 Nobel laureates (as opposed to prizes, since in some cases individuals who shared a prize fell into different categories), I classified 14 as serendipitous discoveries, 72 as driven by the importance of the problem and 31 as hybrids. This classification is, of course, somewhat subjective. Furthermore, the choice of Nobel laureates for analysis clearly represents a highly selected group. With these caveats, the analysis reveals that serendipity was the primary driver in approximately 10 percent of these accomplishments and a substantial contributor to an additional 25 percent.

This misinterpretation of impact may be driving research toward the middle of the clinical-fundamental continuum – that is, away from fundamental studies toward translational ones, even if these are quite far removed from true clinical applications.

Judging potential impact

The balance between selection of important problems and the potential for unanticipated discoveries has been the topic of much discussion. Marc Kirschner of Harvard Medical School recently published an editorial in Science magazine titled "A Perverted View of 'Impact'" (7), in which he criticizes the use of "impact" and "significance" as criteria in peer review by the National Institutes of Health. I agree with Kirschner that the use of these terms has the potential to distort judgments about the potential consequences of supporting specific proposals. However, as someone who was involved in the NIH "Enhancing Peer Review" project (8) that led to the incorporation of these terms, I can provide some context.

First, what concerns about peer review led to the incorporation of these terms? Much of the discussion with stakeholders both inside and outside of the NIH focused on the fact that grant-application reviews often were preoccupied with the fine details of the scientific approach rather than the proposed problem. Many indicated that they felt the potential importance of the problem was receiving too little attention.

Second, the choice of the term "impact" was not intended to mean short-term influence on human health but rather the potential for changing the landscape of the research fields involved, regardless of whether these changes were close to a human health or clinical setting or were fundamental changes in our understanding of basic biology. Unfortunately, this broad perspective on potential impact sometimes has been lost during implementation, to some degree within the NIH but, in my opinion, to a greater degree by reviewers who interpret impact to mean translational impact.

This misinterpretation of impact may be driving research toward the middle of the clinical-fundamental continuum – that is, away from fundamental studies toward translational ones, even if these are quite far removed from true clinical applications.

This middle region may, in fact, be the least fertile area for real progress. Fundamental research often turns out to be most influential when it is addressing basic biological processes of which our understanding is incomplete (i.e., most processes), and important discoveries often are made in model systems that are most amenable to controlled, detailed study without regard to direct clinical translation. In contrast, research at the clinical end of the continuum often is most effective when a very well-defined clinical context is provided for the proposed study.

History has shown that many of the important applications of fun-

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damental knowledge could not have been anticipated, and pushing applicants to propose such applications can distort the basic research. Indeed, the National Institute of Neurological Diseases and Stroke recently reported a detailed analysis that supported the notion that applicants are moving away from truly fundamental research to the detriment of the long-term mission of the institute (9).

A balanced framework

One of my former colleagues at the NIH (now retired) described to me very succinctly what he felt he needed to make rational funding recommendations. He proposed three questions (which I have modified slightly):

(1) How important (either fundamentally or in terms of applications) is the project if it is successful?

(2) What are the chances that the project will be successful (in the hands of the investigators involved)?

(3) What are the chances that something unanticipated will be discovered along the way?

These questions capture the need to work on something important (with importance defined in a context-dependent manner) and an integrated view of the approach and the skills and previous accomplishments of the investigator(s) while acknowledging the potential for serendipitous discovery. I have found this to be a useful framework for guiding my own research planning, and I hope you may as well.

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Proposed American Cures Act is not a long-term solution to research-funding woes

By Benjamin Corb

U.S. Sen. Dick Durbin, D-Ill., recently sponsored a bill that would change how the federal government funds biomedical research. Called the American Cures Act, the bill would create a trust fund of sorts and mandate annual increases in the research budgets for the National Institutes of Health, the Centers for Disease Control and Prevention, the Department of Defense health programs and Veterans Affairs at a rate of inflation plus 5 percent. The goal, it seems, is to put an end to the repeated proposed increases for funding that do not even match inflation and have led to a loss of purchasing power for a decade.

The announcement came March 11 during a speech Durbin gave at the Center for National Policy in Washington. "In the last two centuries, U.S. government support for scientific research has helped split the atom, defeat polio, conquer space, create the Internet, map the human genome and much more. No nation has ever made such a significant investment in science, and no nation's scientists have ever done more to improve the quality of life on Earth," Durbin said. "But America's place as the world's innovation leader is at risk as we are falling behind in our investment in biomedical research."

In many ways, Durbin is absolutely right.

Research-funding levels in general and investments in the NIH and National Science Foundation specifically are not keeping pace with those of our global competitors. It should come as no surprise to many that, while the U.S. invests more in biomedical research than any other country (dollar for dollar), the gap is closing as countries — including China, Singapore, Australia, Germany and India — are investing increasingly larger percentages of their gross domestic products in research than the U.S. is.

The question, however, is how this proposed trust fund would be financed and whether such a funding stream is a good idea.

The details about where Durbin plans to find the money are sketchy at best. During his speech, he proposed a nearly $1 increase in the tobacco tax and suggested that increase alone would cover half of the spending needed to develop this new funding stream. But the source (or sources) of the other half remains unclear.

Plus, what happens when the funding streams dry up? Today, segments of the CDC and the Food and Drug Administration are funded on similarly well-intended, but not completely reliable, alternative revenue sources, putting those budgets in peril.

Finally, and perhaps most importantly, what about unintended consequences? While supporters of the Durbin bill today are confident this wouldn't happen, many policy analysts worry that funding the NIH through an alternative stream ultimately would reduce main-line appropriations. Meaning, appropriators will see a trust fund in place and begin decreasing the base investments in the NIH, figuring that the alternative funding will more than adequately fill the coffers. Should this happen, and, as many fear, should the trust fund income be less than expected, the NIH could end up in an even worse position than it is in at the present.

Durbin is an outspoken champion for biomedical research, and we all should commend him for his support and his effort to find creative solutions to today's research-funding problem. But the reality is that his plan does little more than put a Band-Aid on a wound that needs to be stitched.

The appropriations process has been hijacked by partisanship and near-sighted fiscal policies. The only real way to ensure reliable, long-term investments in the NIH is to fix the broken system by eliminating unnecessary and damaging austerity measures (like the sequester and discretionary spending cuts) and returning to the regular appropriations process.

Benjamin Corb (bcorb@asbmb.org) is director of public affairs at ASBMB.

Maxfield, Ory winners of NIH Clinical Center awards

MAXFIELD

ORY

The National Institutes of Health last month announced that 10 groups of researchers will be granted access to the agency's Clinical Center in Bethesda, Md. One group that won one of the three-year, renewable grants includes two members of the American Society for Biochemistry and Molecular Biology: Frederick Maxfield at Weill Cornell Medical College and Daniel Ory of the Washington University School of Medicine in St. Louis. While the NIH's extramural funding supports scientists beyond the agency's walls, these awards are unique in that they give the teams direct access to NIH's resources. Maxfield and Ory's team will conduct a clinical trial on a drug against the most common form of Neimann–Pick disease, NPC1, a fatal, inherited lysosomal-storage disorder. The trial will be on the drug Vorinostat, a histone deacetylase inhibitor that in early studies has show some promise in clearing cholesterol and other lipids from NPC1-mutant human cells. Maxfield and Ory's collaborators include Steven Walkley of Albert Einstein College of Medicine of Yeshiva University and Forbes Porter of the Eunice Kennedy Shriver National Institute of Child Health and Human Development.

AACR's Pezcoller fund award for Fuchs

FUCHS

Next month, Elaine Fuchs of the Rockefeller University will receive the 2014 Pezcoller Foundation–AACR International Award for Cancer at the American Association for Cancer Research's annual meeting in San Diego. Fuchs, a Howard Hughes Medical Institute investigator, was recognized for "her pioneering research on the biology of skin stem cells and how they go awry in human diseases of the skin, including cancer," Margaret Foti, chief executive officer of the AACR, said. Just last year, Fuchs was named as an inaugural fellow of the AACR Academy. She's also a member of the National Academy of Sciences, the Institute of Medicine, the American Philosophical Society, the American Academy of Arts and Sciences and the European National Academy of Sciences.

IN MEMORIAM: Boris Magasanik

MAGASANIK

Boris Magasanik of the Massachusetts Institute of Technology died late last year at the age of 94. A longtime member of the American Society for Biochemistry and Molecular Biology and a former editorial board member of the Journal of Biological Chemistry, Magasanik had spent decades studying microbial physiology and the regulation of gene expression. Upon learning of Magasanik's death, colleagues and former students recalled his storytelling ability and the breadth of his knowledge. Magasanik was born in Ukraine in 1919. His family fled to Vienna after the Russian Revolution. Magasanik was studying chemistry at the University of Vienna in1938 when Germany annexed Austria and Jews were expelled from the universities. He immigrated to New York City, later attending City College of New York. Drafted into the U.S. Army during World War II, Magasanik served in medical units in England and France. He earned his Ph.D. from Columbia University in 1948 and joined the Harvard Medical School faculty. In 1960, Salvador Luria recruited Magasanik to MIT, where he later led the biology department, which almost doubled in size during his tenure.

An endowed professorship for Hannun

HANNUN

Yusuf A. Hannun, director of the Stony Brook University Cancer Center, was granted an endowed professorship last month. Hannun's investiture makes him only the eighth endowed faculty member at the university, which has set its sights on having 100 within the next five years. Hannun's endowed professorship, established in 2001, is named after Joel Strum Kenny, the late son of the university's past president Shirley Strum Kenny. Joel Kenny, who died of leukemia, had been a scholar, teacher and rabbi. Hannun is a past winner of the American Society for Biochemistry and Molecular Biology's Avanti Award in Lipids.

Kinases control cytoskeleton response to cellular stress

By Mariana Figuera-Losada

When cells are exposed to stresses, such as heat shock, osmotic or chemical stress, inflammatory cytokines, proteasome inhibition and hypoxia, physiological responses promote the reorganization of the cytoskeleton to maintain structural integrity.

Understanding the regulation of cytoskeleton organization is fundamental for the control of cell division, migration, proliferation and differentiation. Cytoskeleton dynamics play a role both in physiological processes and in diseases such as cancer. In their recent article in the **Journal of Biological Chemistry**, Yan Y. Yip and colleagues at the University of Melbourne revealed new details about the complex signaling processes that determine cytoskeleton reorganization in response to cell stress.

When cells are exposed to stresses, such as heat shock, osmotic or chemical stress, inflammatory cytokines, proteasome inhibition and hypoxia, physiological responses promote the reorganization of the cytoskeleton to maintain structural integrity.

Microtubular cytoskeleton dynamics are in part determined by a small protein known as stathmin, or oncoprotein 18. Stathmin sequesters two tubulin dimers, destabilizing microtubules. It can be phosphorylated in various serine residues in response to stress. These post-translational modifications reduce the stathmin-dependent inhibition of microtubule assembly, stabilizing microtubules and preserving cytoskeleton structure.

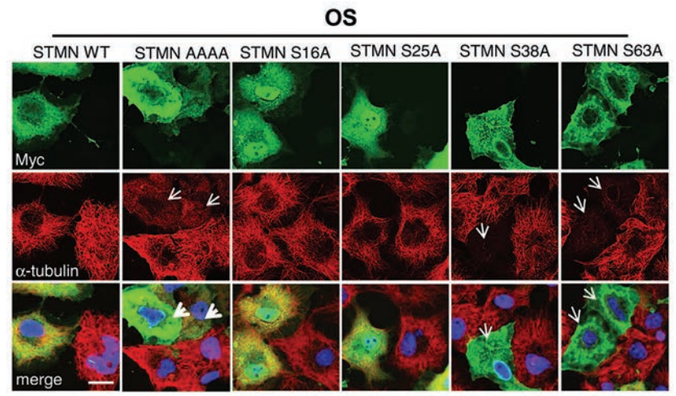
The regulation of stathmin function through phosphorylation is a complicated process. Multisite phosphorylation occurs and different residues get modified depending on the cellular and signaling context.

The authors confirmed that stathmin gets phosphorylated during hyperosmotic stress by c-Jun N-terminal kinase, or JNK, and cAMP-dependent protein kinase, or PKA. These post-translational modifications inhibit stathmin activity and preserve the integrity of microtubules.

These researchers found by mutagenesis that two residues, S38 and S63, are essential in the response to hyperosmotic stress and required to fully attenuate the inhibitory effects of stathmin.

S38 is phosphorylated by JNK early during the response to hyperosmotic stress, followed by PKA-dependent S63 phosphorylation. However, phosphorylation of stathmin in position S63 did not require prior S38 phosphorylation. Additionally, the authors proposed an interesting cross-talk between JNK and PKA in which JNK could possibly be involved in the down-regulation of PKA activity during hyperosmotic stress.

These results highlight some of the complexities of cytoskeleton regulation and the functional interconnection between signaling pathways during cellular responses to stress.



This figure from the Yip et al. paper illustrates the contributions of specific stathmin serine residues phosphorylation to microtubule preservation during hyperosmotic stress (OS). Arrows point at cells with destabilized microtubule cytoskeleton product of serine-to-alanine substitutions.

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Fast, cheap way to detect dyslipidemia genes

By Mary L. Chang

Researchers at the University of Western Ontario have developed a new sequencing method to detect genes responsible for abnormal lipid levels in a variety of patients.

Christopher T. Johansen and colleagues designed a targeted resequencing panel, which they call LipidSeq, that looks for genetic problems that can cause lipid abnormalities. In a paper appearing in the April issue of the **Journal of Lipid Research**, they report their results after using the panel to look for responsible genes in 84 patients with lipid abnormalities and comparing the results to those obtained by standard Sanger sequencing, the most widely used method to sequence DNA.

The authors report that there potentially are several major benefits to using LipidSeq. The first is speed: The researchers analyzed 12 DNA samples in a week using LipidSeq, whereas it would have taken much longer with Sanger sequencing. Second is overall cost: A LipidSeq sample costs about half (less than $500) of what a comparable sample for the Sanger method would (around $1,000). Additionally, the samples analyzed by LipidSeq were analyzed for 23 dyslipidemia genes and 50 other metabolic genes – a targeted approach revealing much more information than those analyzed by the Sanger method, which analyzed only three candidate hypercholesterolemia genes.

While Johansen et al. admit LipidSeq detects more genetic variants requiring investigation, they say that as more is learned about genomic variation in patients more insight will be gained about the subtypes of dyslipidemia, and hopefully this will drive development of targeted therapies.

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The invisible killer of research?

By Shirley H. Tan

Ever wonder why the results of cell culture experiments are sometimes difficult to replicate? A recent study in the journal **Molecular & Cellular Proteomics** may shed some lights on the secrets behind the complex biological mechanisms.

Protein phosphorylation, a common type of post-translational modification, plays critical roles in regulating signaling pathways involved in disease progression, including cancers. With the advancement of mass-spectrometry technology, phosphoproteomics now enables scientists to map in depth the delicate changes of protein biomarkers and allows them to interrogate important research questions. However, a team led by Pedro Casado and Pedro Cutillas at Barts Cancer Institute in London discovered that cells are extremely susceptible to environmental stress stimuli, including temperature, and consequently elicit numerous protein modifications that may lead to errant data interpretation.

The team tested the MCF7 breast cancer cell line in room temperature and on ice and then monitored the changes by mass spectrometry. Nearly 1.5 percent of 3,500 phosphorylation sites measured were changed after leaving the cells in room temperature for 15 minutes. In addition, while the effects were delayed compared with those in room temperature, maintaining cells on ice did not prevent the cells from responding to metabolic stress. The researchers found that ambient conditions at room temperature stimulated catabolic pathways involving AMPK and GSK3beta and inactivated anabolic pathways regulated by AKT, ERK and mTOR.

Autophagy also was induced by the environmental stress in this experiment. Cutillas' team used immunofluorescence microscopy to measure two common autophagic markers, WIPI2 and LC3. After two hours of exposure to room-temperature conditions, the number and size of the markers increased dramatically. The protein assay also confirmed the increased phosphorylation of numerous other autophagy markers.

This study raises an interesting question not frequently asked by the scientific community:

Is it a real biology response, or is it a response caused by sample retrieval?

The discoveries made by the Cutillas group provide another angle from which to interpret research data more carefully.

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Ptashne reflects on chemistry of gene regulation

By Jane Campanizzi

Mark Ptashne begins his "Reflections" article in the **Journal of Biological Chemistry** with a quote by French biochemist and Nobel laureate Jacques Monod: "(T)he truth of a theory lies in the deductive methods used to establish it and the experimental demonstration of its fundamental premises and consequences."

Ptashne's article reviews and puts into context many of his experiments on the molecular basis of gene regulation, beginning with bacteria and then moving to yeast and mammalian cells. He emphasizes how, at each stage, alternative answers to problems were confronted and how key experiments distinguished between them. He also emphasizes that the principles at work in bacteria apply as well in eukaryotes.

While an undergraduate at Reed College in Portland, Ore., in the 1960s, Ptashne first learned of "dazzling ideas" emerging from the Institute Pasteur in Paris. There, Monod and Francois Jacob, studying gene regulation in bacteria, proposed that regulatory molecules called "repressors," Ptashne explains, "turn off expression of specific genes unless inactivated by specific extracellular signals."

Ptashne wanted to know: Was this idea correct? What were "repressors," and how did they work?

In 1962, Ptashne entered graduate school at Harvard University. He writes that he and his colleagues were inspired by the dream that understanding "the repressor" would "illuminate development of a complex organism from a fertilized egg." By then it was strongly suspected that "formation of different body parts requires differential expression of common genes, and that different organisms can develop using essentially the same set of genes." And so regulation was the key.

Mark Ptashne and his cat, McCoy

The behavior of the bacteriophage lambda, as pointed out by the French scientists, represented a paradigm. In a lysogenic bacterium, one repressor (the bacteriophage lambda repressor) keeps most of the virus' nearly 40 genes in a dormant state (off). UV irradiation of these lysogens switches the regulatory program so that the silent genes are now on, and a new crop of phage is produced.

Lambda was particularly interesting to Ptashne and his colleagues because it exemplified the so-called "memory" problem. Once lysogeny was generated in a bacterium, he writes, "that state of gene expression was perpetuated for very many generations in the absence of an inducing signal. Neither 'remembering' nor switching requires any mutation."

Ptashne completed his Ph.D. in 1965, became a junior fellow of the Society of Fellows at Harvard from 1965 to 1968 and started his own lab. There, he and his colleagues isolated the repressor, a pure protein, not an RNA molecule and not attached to one. They showed that this protein could bind to specific DNA sites (operators) on DNA and later showed that it could prevent transcription of target genes. Ptashne notes that the experiments showing that repressor binds DNA specifically and many other experiments performed along the way demonstrate the power of combining genetics and biochemistry.

By 1971, Ptashne was a professor. His lab's next step was to determine how the repressor binds DNA. Their experiments, along with those of others, indicated that an α helix (the so-called recognition helix) at the repressor could insert into the major groove of B-form DNA. Amino acid functional groups extending from the helix would make specific contacts with base pairs.

But even repressor dimers, which recognize sites of two-fold rotational symmetry, did not bind with sufficient specificity. Ptashne's lab learned that cooperativity is essential; one protein (e.g., a repressor dimer) helps another dimer bind DNA by merely touching it. This simple binding reaction, it turned out, also explains transcription activation by a specific DNA-binding protein: The "activator" contacts RNA polymerase and helps it bind and work at a promoter that lies near the activator binding site.

As Ptashne explains, a DNA-bound activator recruits polymerase to a promoter. The simplicity of the activation mechanism means any gene can be brought under the control of any activator by apposing the activator and polymerase binding sites. And a suitably positioned

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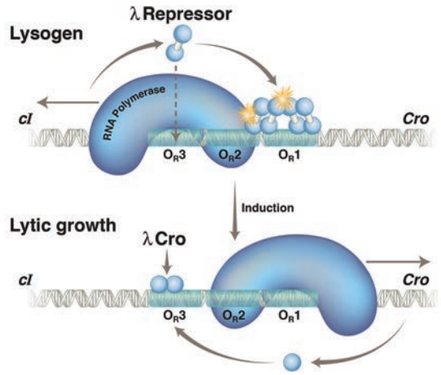
DNA-bound protein (e.g., lambda repressor) can turn off, or repress, certain genes as it activates others.

The solution to the lambda memory problem demonstrates that where an activator works on its own gene, that state of gene expression tends to self-perpetuate. As cells divide, the activator distributes to daughters, with the state maintained. Memory is thus a property of the system of basic elements appropriately arranged. "By combining these elements, nature can produce sophisticated switches, which allows genes to be expressed in alternate states, with sensitive and dramatic transitions between them in response to signals," he writes.

Over the following years, Ptashne and colleagues described lambda's switch as a complex set of interactions that guaranteed expression of alternate sets of genes with a rapid switch upon command.

The switch includes positive and negative feedback; a double negative circuit involving the repressor and the protein Cro; and cooperativity of repressor binding, including the example (demonstrated later by others) of interactions between proteins separated by 3,000 base pairs, with formation of a large DNA loop. A separate gene regulatory circuit establishes repressor synthesis in the first place. As Ptashne notes, only rather simple binding interactions are required to construct such a switch, and it is not hard to imagine how it might have evolved. These aspects of systems biology are widely found in gene regulatory circuits driving development of higher organisms.

Lambda "remains the best-understood integrated system we have, and perhaps one should ponder how we got it." He writes, "The switch was not deduced from general observations or theoretical or mathematical models. Its parts were assembled as we went along, its glorious integrated working revealed only near the end. At every stage we could test this or that aspect, challenging with genetics and biochemistry, trying to ensure that each bit was well in hand before going on." He implies that today this is a rare undertaking: "This approach is nowadays rather out of fashion. Instead we have the 'big picture,' many genes, obscure words and formulations."



Lambda repressor and Cro action at the right operator (Or) in a lysogen and following induction (bottom line).

Ptashne then turned his investigation to how the insights from the lambda work might apply to eukaryotes. He and his colleagues chose to work with yeast, a eukaryote that could be genetically manipulated almost as easily as bacteria. He writes that they "had no way of knowing, at the start, that studying λ repressor and its action would yield a coherent picture of a regulatory switch and even less indication that the principles of protein-DNA interaction and gene regulation, gleaned from the λ studies, would apply even in eukaryotes."

They showed, however, that eukaryotic activators (e.g., the yeast protein Gal4) work, as does lambda repressor, as an activator – by recruitment. Only simple binding interactions are required, and it is thus easy to see how "natural variation can throw up many regulatory-circuit options for natural selection to consider."

The fact that eukaryotic genes are wrapped in nucleosomes, whereas bacterial genes are not, presents a special problem for transcriptional activators, and Ptashne recounts his group's recent experiments that indicate the way this problem is solved as well.

He observes that today diagrams of gene regulatory circuits look like "a lot of lambdas" and that regulatory proteins, usually working cooperatively and in many different combinations, turn on sets of genes. Some of these genes encode inhibitors that block the effects of activators. Once positive feedback loops are established, they maintain states of gene expression unless they are perturbed, such as by a signal, thus permitting the system to move on to the next phase of gene expression. He speculates that the key is evolution: "(S)election must occur in small steps, and the simplest mechanism that works will be used over and over again, sometimes in so many guises that the underlying similarities are at first hard to see."

Ptashne ends his "Reflections" by noting that "one can make ever broader generalizations by solving basic problems, sometimes in near fanatical detail, and then seeing where those solutions can lead," instead of "looking at problems in general." In addition, he writes, "No part of the world can simply be read – it always must be interpreted, and those interpretations are subject to constant reevaluation."

Jane Campanizzi (jcmtechservices@gmail.com) is pursuing graduate studies in the science-medical writing program at Johns Hopkins University and serves on the Publications Committee of the American Medical Writers Association.

Talking about JBC's Best of 2013

In a podcast series, authors of four award-winning articles discuss their research

By Andrew Harmon

To celebrate the articles the editors of the **Journal of Biological Chemistry** named the Best of 2013, the journal has produced a podcast series featuring interviews with authors of four of the 22 articles that were honored. The series was launched in mid-February. In these interviews, authors offer personal insights into their work.

The first podcast, posted in mid-February, features my interview with Rachel Green, a professor at Johns Hopkins University School of Medicine. She is the corresponding author of the paper selected from the RNA category. Originally published in March 2013, Green's article illustrates how, in gene regulation, recognition of siRNA and microRNA structures by Argonaute proteins influences downstream effects on target RNAs. She discusses the way her article came about and the direction she sees this research moving.

In the second podcast, JBC Associate Editor Paul Fraser at the University of Toronto speaks with Nigel Hooper at the University of Leeds in the United Kingdom. Hooper is the author of the article selected from the neurobiology category. Also published in March 2013, Hooper's paper details how remodeling amyloid-β oligomers and disrupting the prion-LRP1-raft interaction can provide therapeutic targets for Alzheimer's disease. Fraser and Hooper talk about the progression of this work and where the research may lead.

The third podcast features a conversation between JBC Associate Editor Alex Toker at Beth Israel Deaconess Medical Center and Ron Bose, a medical oncologist and assistant professor at Washington University in St. Louis. Bose's article, published in August, was selected from the JBC's signal transduction category. It provides the first structural characterization of HER2-HER3 heterodimers, which are part of the receptor family used in the development of targeted cancer therapies. Bose talks about his more than 10 years of research in the study of tyrosine kinases. He also talks about where the research is going, the development of innovation where mass spectrometry is limited in the study of protein complexes that can't be crystallized, and the power of interdisciplinary studies for graduate students in science.

In the final podcast, we hear about the debate surrounding α-synuclein, which plays a critical role in Parkinson's disease. Is it an unfolded monomer? Is it a helically folded tetramer? Associate Editor Fraser speaks with Dennis Selkoe at Harvard Institutes of Medicine and Ulf Dettmer, a research fellow in neurology also at Harvard. Selkoe and Dettmer are co-authors of the chosen paper in the cell biology category. Published in March 2013, the article exhibits a new method for cross-linking α-synuclein in living cells that reveals a form consistent with a tetramer. In this conversation, we hear about the prior research leading to this article and what to look forward to as the debate continues.

You can find links to play all four podcasts at www.jbc.org/site/podcast.

Andrew Harmon (aharmon@asbmb.org) is the science and publishing technology manager for the American Society for Biochemistry and Molecular Biology.

FOUR-PART SERIES

The following Journal of Biological Chemistry papers were highlighted in the Best of JBC podcast series. Listen to them at www.jbc.org/site/podcast. See other selected papers at www.jbc.org/site/bestoftheyear.

RNA

Regulation of Argonaute Slicer Activity by Guide RNA 3′ End Interactions with the N-terminal Lobe, by Hur et al.

NEUROBIOLOGY

Prion Protein-mediated Toxicity of Amyloid-β Oligomers Requires Lipid Rafts and the Transmembrane LRP1, by Rushworth et al.

SIGNAL TRANSDUCTION

Carboxyl Group Footprinting Mass Spectrometry and Molecular Dynamics Identify Key Interactions in the HER2-HER3 Receptor Tyrosine Kinase Interface, by Collier et al.

CELL BIOLOGY

In Vivo Cross-linking Reveals Principally Oligomeric Forms of α-Synuclein and β-Synuclein in Neurons and Non-neural Cells, by Dettmer et al.

Richard Hanson, 1935 – 2014

By William C. Merrick, Vern L. Schramm and Michael A. Weiss

If we were to measure an individual by his dates on the earth, his number of publications, his prizes both local and national, we would find that Richard Hanson was a model of success — and yet we would totally miss the value of the man.

Richard was an accomplished scientist who started his career at Temple University and then in 1978 moved to become chairman of Case Western Reserve University's biochemistry department — the gluconeogenesis house of kings established by Merton Utter, the previous chairman. Both Mert and Harland Wood were giants in the exploration of the pathways of metabolism, Mert in mammals and Harland in bacteria. Richard spent the rest of his life studying the enzyme phosphoenolpyruvate carboxy kinase, or PEPCK, the rate-limiting enzyme in gluconeogensis, and establishing the cAMP-dependent regulatory mechanism that controlled PEPCK mRNA synthesis. Who would have thought you could become so famous studying just one enzyme, even when it gave rise to Mighty Mouse (the PEPCK-C^{mus} mouse that could run forever)?

But far greater were his contributions to the university; the American Society for Biochemistry and Molecular Biology; his beloved Journal of Biological Chemistry; and his colleagues, students and friends.

Richard was the best representation of a modern renaissance man, a scholar who was knowledgeable about science, art, music, literature, governing and life in general. And perhaps in spite of that knowledge base, Richard was the eternal optimist: The glass was always at least two-thirds full. Of the countless visitors who approached him for enlightenment, none was turned away, and all left with the feeling that they had a better understanding and could go forward with whatever decision or choices they had to make. He left a wake of people affected positively by their interactions with him.

Although Richard had few down moments, the only true one he had was when he was informed that he no longer would be teaching biochemistry to medical students. The new curriculum was going to feature self-directed learning or problem-based learning and not lectures. After polishing the delivery of metabolism to thousands of medical students for more than 30 years and generating the most highly rated section of the preclinical curriculum, he was no longer to be a participant.

Although Richard continued teaching undergraduates, the medical students were his true love. There was always the 70-kilogram man or 50-kilogram woman upon whom all the reference numbers for metabolism were based, and Richard would select such a student from each first-year class. What was the longest a medical student had fasted? Is the Atkins diet a good idea? Why is the woman on the pineapple diet not feeling well?

When students would return years later, while they remembered the preclinical years as being challenging, the one teacher they remembered was Richard – out of the hundreds they had seen. The sparkling blues eyes and truths delivered with humor and clarity motivated generations and served as a model of engagement to his teaching cohorts. He thrived on his interactions with students.

And it was not all about Richard. More than anyone at CWRU over the past 36 years, Richard was about, as they say, improving the breed – improving faculty (especially junior faculty), the department, the medical school and the university. He was recognized for that dedication with the Hovorka Prize for university service and scholarly accomplishment and with a distinguished university professorship.

Richard took advantage of his position as department chairman, associate editor of the Journal of Biological Chemistry and his presidency of the ASBMB to introduce CWRU faculty to the community of peer-reviewed science or the functioning aspects of a scientific society.

The 1980s and 1990s often were referred to as the golden years in the medical school as department chairmen Les Webster, Mike Lamb, Fritz Rottman and Richard presented a unified force for the improvement of the school. Their cooperation led to the establishment of the Reinberger Laboratories, the correlated curriculum in cell and molecular biology (lecture and laboratory), and the Biomedical Sciences Training Program, an umbrella program to recruit Ph. D. students into all of the departments of the medical school.

But what Richard really cherished were his interactions with others.

The biochemistry department's Winter Solstice party was a highlight. Richard was a prominent character in the faculty skit (when the heat's on, the ham sizzles). He praised the delicious dishes representing many tastes and heritages the department members brought to the feast.

Richard found great joy from playing the banjo (obviously a Pete Seeger wannabe) and leading the department in song (tunes we all knew, he said, which meant tunes from the '60s and '70s). Ken Neet and Dave Goldthwait (on accordion) would be lead vocalists in "On Top of Spaghetti" and "Alouette," respectively. This past December's was the only Winter Solstice party that Richard did not attend. It was a party that he, though perhaps a not-ready-for-prime-time performer, wouldn't miss.

Many of Richard's talents were widely recognized. His banjo playing was well known throughout the medical school and, alas, throughout his home. His doodles, known affectionately as "Riccasos," are featured in a gallery in the biochemistry department and as a set of note cards prepared by the ASBMB. Richard also supported the Cleveland artistic community as seen through countless acquisitions he made, which are displayed in the department.

The phrase often associated with Will Rogers was that "he never met a man he didn't like." For Richard, the phrase might be "he never met an individual he couldn't say something positive about." And this was not restricted to just his scientific colleagues but included individuals in the public eye as well, especially the arts.

Richard's opinions were universally sought for problems large and small. He was the campus sage. But most of all, he generated a warm feeling in everyone he met. His conversations were characterized by his blue eyes and dimples, the easy laughter, the quiet concern.

Another quality of Richard's was that he didn't have to be right. Any discussion entered was about opinions and facts and how they might be best interpreted, understood or used as a place to move forward from. It was not personal that he didn't agree with you or you with him; it was just about interpretation. As a result of this honesty, there was never a question of his motives, never a question about the truth of his statements, never a question about his leadership. His transparency provided a secure calm in which his department, his collaborators and his colleagues could operate and flourish. Everyone left better for the interaction, and perhaps this is for what he will be most measurably missed. He was a most wonderful human being who made all of us better.

RICHARD HANSON SCHOLARSHIP FUND

Checks payable to Case Western Reserve University should be sent to:
Development and Alumni Affairs
Case Western Reserve University
School of Medicine
10900 Euclid Avenue
Cleveland, OH 44106-7035
Please include a memo:
Richard Hanson Endowment Fund

SEIDMAN CANCER CENTER

Checks payable to University Hospitals should be sent to:
University Hospitals
Institutional Relations
and Development
11100 Euclid Ave.
MCCO 5062
Cleveland, OH 44106
Please include a memo:
in memory of Dr. Richard Hanson

William C. Merrick (wcm2@case.edu) is a professor in the biochemistry department at Case Western Reserve University. Vern L. Schramm (vern.schramm@einstein.yu.edu) is chairman of the biochemistry department at Albert Einstein College of Medicine of Yeshiva University. Michael A. Weiss (maw21@cwru.edu) is chairman of the biochemistry department at Case Western Reserve University.

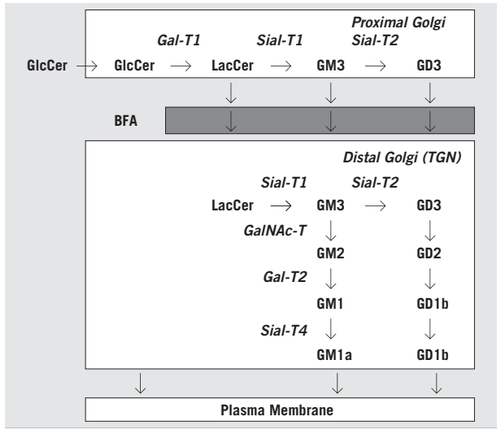
Organization of glycolipid biosynthetic enzymes in the Golgi complex

By Hugo J.F. Maccioni

Glycolipids play diverse biological roles – from serving as receptors of toxins and growth factors to overseeing molecular recognition at the cell surface. These molecules are composed of a ceramide backbone to which monosaccharide (sugar) molecules are attached. The order in which different sugars are attached to the ceramide backbone is a crucial feature in determining the precise role of a glycolipid. Understanding the machinery that regulates the glycosylation of the ceramide backbone, therefore, is critical to our understanding of the biosynthesis of these important lipids and provides insight into the mechanisms underlying diseases resulting from aberrations of their synthesis. Interestingly, the organization of the glycosylation machinery within the Golgi is linked intimately to the supramolecular organization and dynamics of the Golgi complex itself.

The enzymes responsible for catalyzing the stepwise addition of monosaccharides to ceramide and ceramide-bound oligosaccharides are the glycolipid glycosyltransferases, or GGTs (reviewed in 1). Researchers have given considerable effort to understanding the organization of GGTs within the Golgi.

Like other Golgi glycosyltransferases, GGTs that use GlcCer and more complex glycolipids as acceptors show a modular organization, with their N-terminal domain bearing a transmembrane domain flanked by a short cytoplasmic tail and a flexible lumenal stem region to which a large C-terminal domain bearing the sugar nucleotide and acceptor glycolipid binding sites is appended (reviewed in 2).



A simplified scheme of ganglioside biosynthesis, showing the topological distribution of the GGT in Golgi compartments as deduced from the block imposed by Brefeldin A (marked gray) in metabolic labeling studies with CHO-K1 cells.

Notably, the GGTs are unlike glycoprotein glycosyltransferases, which alternate with glycosidases in the processing of oligosaccharides, in that they are not strictly distributed along the Golgi in the order in which they act. Instead, they organize as distinct homo- and hetero-multienzyme complexes, which in many cases involve their N-terminal domains (3).

Deducing the sub-Golgi localization and organization of GGTs has been challenging. Our current understanding results mainly from studies involving activity determinations in Golgi subfractions, cell metabolic labeling in the presence of pharmacological reagents that disrupt Golgi dynamics and structure like Brefeldin A, single-cell imaging, and immunoprecipitation of epitope-tagged versions (reviewed in 4). Such studies have demonstrated interesting differences in the organization of specific GGTs.

For example, in CHO-K1 cells, the N-terminal domains of GalT1, SialT1 and SialT2 (see figure) participate in a heterocomplex in the Golgi and the trans-Golgi network, while the complex formed by GalNAcT and GalT2 localizes instead in the trans-Golgi network (5). Recent studies in FAPP2 knockout mice reveal that the synthesis of Gb3 in the TGN uses LacCer synthesized from GlcCer transported by nonvesicular (FAPP2) intermediates, while the track for synthesis of GM3 in the Golgi uses LacCer

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A physicist's view of the role of lipids in membrane curvature and fission

By Patricia Bassereau

The definition of lipid rafts has evolved considerably over the past 15 years. They now are recognized as dynamic "nanoscale assemblies of sphingolipids, cholesterol and proteins that can be stabilized into platforms" (1) and no longer viewed as static microdomains (2). Confusion occurred because of the different methods used to reveal and characterize the lipid rafts and in part because of the unfortunate concomitant revival of membrane physics, which was boosted by the possibility of observing phase separation in giant unilamellar vesicles, or GUVs, with confocal microscopy (3, 4).

Physics studies with reconstituted simple lipid mixtures generally were made at equilibrium, whereas cell lipid membranes are clearly not. Nevertheless, the interplay between cell biology and membrane physics inspired other physics studies, in particular investigations into the role that membrane curvature plays in sorting lipids. It was suggested, based on in vivo observations of fluorescent lipid homologs, that lipids could be redistributed upon budding due to the high curvature of the membrane (5, 6).

The development of new in vitro systems was crucial to understand and quantify the corresponding sorting mechanisms. Using membrane nanotubes pulled from GUVs made of simple lipid mixtures and controlling their radius in the 10 to100 nanometer range by setting membrane tension, different groups of physicists quantitatively assessed the conditions and the efficiency of this lipid-sorting process (7 – 9). An enrichment in membrane nanotube in unsaturated phosphatidylcholine, or PC, lipids as compared to sphingomyelin was measured (8), and it was shown to result from the reduction of the energy used to bend the membrane.

Another interesting aspect ... is that lipid domains in membrane accompany a constrictive force acting at the periphery of the domains, the line tension, resulting from the nonmiscibility of the different phases.

Indeed, PC-rich membranes are more flexible than those enriched in sphingomyelin (8). However, this effect was not detected for arbitrary mixtures, and proximity to lipid demixing, and hence lipid-lipid interactions, were critical for observing sorting (7 – 9); otherwise, the mechanical gain is too small and completely dominated by the mixing entropy of the lipids.

Observation of macroscopic lipid domains on giant plasma membrane vesicles blebbing from cells (10) suggests that this membrane could be, at equilibrium, close to demixing and that this sorting mechanism might be relevant at this level in cells. Nevertheless, interactions between lipids and proteins probably are more efficient for redistributing the lipids than the membrane shape only, as they can amplify (8, 9) or completely reverse (11) curvature-induced lipid sorting, depending on the affinity of the protein for curved membrane. (For reviews on these questions, see references 12 through 14.)

Another interesting aspect revealed by membrane physicists, both theoretically and with their model systems, is that lipid domains in membrane accompany a constrictive force acting at the periphery of the domains, the line tension, resulting from the nonmiscibility of the different phases. The energy relative to line tension is proportional to the perimeter of the domain; thus, by reducing the domain contour length, line tension can induce the bending of the domains in moderately tensed GUVs (4) and even squeeze the bud down to scission (unpublished data). Squeezing of membrane nanotubes also occurs when lipid domains are present and can lead to their spontaneous scission even in the absence of any protein (7).

A combination of in vitro and in

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synthesized from GlcCer transported by vesicular intermediates (6).

GGT organization, however, is only part of the story. How GGTs and Golgi-resident proteins are maintained in the Golgi while plasma-membrane-destined proteins exit the Golgi remains a mystery. Bioinformatics data indicate that transmembrane domains, or TMDs, of Golgi proteins (which represent about 80 percent of putative glycosyltransferases) are four to five amino acids shorter than those of plasma-membrane proteins (9, 10), but the significance of this to GGT organization is unclear.

An interaction of amino-acid motifs at GGTs' cytoplasmic tails with coat proteins has been proposed to mediate retention in yeast (7). Additionally, it has been suggested that a hydrophobic mismatch between the short TMDs of some glycosyltransferases and the increased bilayer thickness of Golgi membranes at export domains, due to the addition of order-inducing sphingolipids and cholesterol and/or to the concentration of proteins with long TMDs, segregate them from these domains (8).

Studies using chimeric proteins have provided some hints on this point. Swapping the hemi-transmembrane domains of Golgi and plasma-membrane-resident proteins (the yeast SNAREs Sft1 and Sso1, respectively) showed that, in addition to the short length, the presence of voluminous amino acids in the exoplasmic hemi-TMD is a crucial parameter for Golgi localization. Proteins with longer TMDs and less voluminous exoplasmic halves exit the Golgi and localize to the plasma membrane both in yeast and in mammalian cells (10).

These studies highlight the role of the shape of TMDs in the fitness of glycosyltransferases (or their oligomeric associations) in either processive or export lipid domains of Golgi membranes.

Clearly, we are learning a lot about the localization and topology of these important enzymes. But the story is far from complete. Studies like these, as well as others intended to enhance our understanding of these enzymes, will keep the glycolipid community busy for a long time.

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LIPID NEWS CONTINUED

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vivo experiments now demonstrate that this squeezing effect can occur during membrane budding if lipid heterogeneities form induced by actin filaments (15). This might be the case also upon BAR-protein assembling at the neck of the bud (16, 17).

In conclusion, lipids can give a hand to specialized proteins to produce forces that remodel membranes. But, conversely, when membranes get deformed by coats, cytoskeleton or molecular motors, lipids and proteins can be relocalized because of shape changes in the membrane matrix.

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Public-private initiative aims to speed drug development for three illnesses

The NIH, industry and nonprofits announce Accelerating Medicines Partnership focused on Alzheimer's, diabetes and autoimmune disorders

By Sapeckshita Agrawal

It takes several years and millions of dollars for a new drug to come to market, starting from the time that its properties are first studied at the bench. That's a lot of time and money. What's even more stupefying is that only a fraction of drug candidates make it to market. Clearly, a new approach to drug development is needed – one that not only expedites and increases the availability of drugs but also maintains the high standard of quality needed to ensure safety and efficiency.

A new collaboration announced earlier this year called the Accelerating Medicines Partnership seems to promise a viable solution. The collaborators include 10 of the world's leading pharmaceutical companies, the National Institutes of Health and several nonprofits. The goal: to develop new treatments earlier for three serious conditions – Alzheimer's disease, type 2 diabetes and autoimmune disorders, namely rheumatoid arthritis and lupus.

"Patients and their caregivers are relying on science to find better and faster ways to detect and treat disease and improve their quality of life," NIH Director Francis S. Collins said in the announcement.

The syndicate has pledged more than $230 million over the next five years for research aimed at identifying biological targets and characterizing new biomarkers. The parties have agreed unanimously to make the resulting data and analyses publicly available despite conventionally being competitors. The expected consequence is the stitching together of a vast knowledge network needed to solve the big problems of pharmaceutical research.

Accelerating Medicines Partnership participants

Government	Industry	Nonprofits
FDA	AbbVie	Alliance for Lupus Research
NIH	Biogen Idec	Alzheimer's Association
	Bristol-Myers Squibb	American Diabetes Association
	GlaxoSmithKline	Lupus Foundation of America
	Johnson & Johnson	Lupus Research Institute
	Lilly	Foundation for the NIH
	Merck	Geoffrey Beene Foundation
	Pfizer	PhRMA
	Sanofi	Rheumatology Research Foundation
	Takeda	USAgainstAlzheimer's

Mikael Dolsten, president of worldwide research and development at Pfizer, a participant of AMP, optimistically prognosticated that "this type of novel collaboration will leverage the strengths of both industry and NIH to ensure we expedite translation of scientific knowledge into next-generation therapies to address the urgent needs" of patients.

The research will be overseen by steering committees with representation from both the public and private sectors. Offering even more hope to patients and families is the possibility of extending AMP to other diseases and conditions through advances made by the milestone-driven pilot projects in the three disease areas.

Capturing the spirit of the collaboration, Rupert Vessey of Merck said, "Our most critical health challenges require new, innovative ways to develop medicines and vaccines. Collaborations such as this, that exchange data, share insights and generate knowledge, will be important to unraveling the mysteries of the diseases that cause suffering for individuals and are a burden to our society."

Sapeck Agrawal (sapeck.srivastava@gmail.com) earned her Ph.D. in molecular microbiology and immunology from the Johns Hopkins University. For more stories, visit sapeckagrawal.wordpress.com.

How you can spread the good news

We need your help with getting the word out

By Angela Hopp

Experimental Biology 2014 is just around the corner, so it's time to start thinking about how you'll communicate your science and the science presented by others in San Diego.

Don't forget to use the hashtag!

If you plan to tweet at the annual meeting, please use the #xBio hashtag. Additionally, if you tag @ASBMB in your tweet, we'll do our best to retweet you to our followers. If you're on Instagram, we'll be looking for #xBio-tagged images and will include them in post-meeting collections. If you follow us on Facebook, you can check there for posts about big events each day. Not a fan of our page yet? Like us at www.facebook.com/asbmb.

Join us for #breakfast

When: *7 a.m. to 8:15 a.m. Sunday, April 27*

Where: *San Diego Convention Center, Room 14A (Mezzanine Level)*

Start your meeting experience right by joining ASBMB staff to learn Twitter tips and tricks to use during the annual meeting and beyond. We welcome a group of diverse professionals from a variety of areas including academia, nonprofits, industry, media, etc. Attendees will leave the breakfast informed, equipped and caffeinated.

Don't be afraid to do a little of your own PR

You still have time to work with your institution's media relations office on a press release about the research you'll be sharing at the meeting. A couple of years ago, ASBMB Today published a handy guide for starting the media-outreach process. You can find it at http://bit.ly/zQghRK. We strongly recommend that you work with your institution to generate press interest in your findings. Reporters these days don't have time to wade through the thousands of abstracts to find you, so do them and yourself a favor and reach out to them. If you send a copy of your press release to media@faseb.org by April 15, our media relations team will include it in the materials issued to reporters who visit the on-site press room.

Plan on blogging while at the meeting?

Last but certainly not least, we're taking applications from members who are interested in serving as official meeting bloggers. The American Society for Biochemistry and Molecular Biology will cover your meeting registration fee, and you'll gain entry to the press room (read: free food and wifi) and access to the scientific sessions of all six EB-sponsoring societies. Official meeting bloggers may write on their own blogs or on ASBMB's official meeting blog, The Interactome. The deadline for applications is April 15. Contact Angela Hopp at ahopp@asbmb.org if you're interested.

Angela Hopp (ahopp@asbmb.org) is editor of ASBMB Today.

Your annual meeting checklist

Be prepared for meeting highlights, and avoid meeting fails

By Shaila Kotadia

1. Download the meeting app.

It is great to browse on your flight and plan your schedule, especially now that program booklets are not sent prior to the meeting. Find the app soon at www.experimentalbiology.org.

2. Hang onto your poster!

Yes, you have your glossy poster ready to go, but what if you accidentally leave it at airport security because that lady behind you rushed you along because she decided to show up 20 minutes before her flight? Be sure to pack your poster printed out on sheets of paper as a backup. Carry the handouts with you in case you need to explain your work on the fly.

3. Have your data nicely organized on your laptop.

If you bring your computer to show off your data, have it labeled and easily accessible. You don't want to make someone wait while you look around in your folders. It gets awkward really quickly.

4. Get your devices ready.

For some reason, I need to travel with my laptop, tablet and cell phone. And they seem to all need to be charged at the same time. Remember to bring a charger for each. For international participants, bring a converter! Those are not easy to find at the last minute.

5. Pack a notebook and pen.

It seems old-school but they're handy when perusing posters, taking notes at talks or quickly writing down someone's contact info. It is also way lighter than carrying around a laptop or tablet all day.

6. Nonacademic careers are all the rage these days.

If you are looking to branch out from the lab, business cards are a must when networking. Nothing too fancy — just your name, job title and contact info. Adding your poster or talk title and presentation number makes it easy for others to find you later or to view your work.

7. Give your feet a break.

We all want to look good, but heeled or tight shoes can be hard on the knees or feet after a full day of conferencing. Pack a pair or two of (stylish) comfortable shoes. While you're at it, throw in some Band-Aids just in case.

8. Bring an extra pair of pants.

OK, boys. I know most of you travel with one pair of pants and then you get caught in the rain or some other disaster. Just bring an extra pair, especially if you are going to meet colleagues — even if they are scientists.

9. Remember pain killers and other meds.

Seriously, talking to scientists all day can give anyone a headache, and you know those little packets of two at the hotel cost as much as the whole bottle back home. For those of you with bad allergies, bring extra pills. New environments can produce some adverse effects.

10. Importantly, bring your I.D.

You want to get on the airplane. Enough said.

Shaila Kotadia (skotadia@asbmb.org) is an ASBMB science policy fellow.

Plan your meeting break time!

By Shaila Kotadia

While the science presented at the American Society for Biochemistry and Molecular Biology annual meeting is bigger and better than ever, there is always down time. And part of the fun of a conference is traveling and checking out a new city. So why not take a break and explore San Diego?

Whether you're looking for family-friendly spots or places where you can let loose, San Diego offers plenty of options. Here are some places and events to check out:

Are you traveling with family and children?

The famous San Diego Zoo boasts animals ranging from condors to giant pandas to wombats. A one-day pass for an adult is $46 and for a child (aged 3 to 11) is $36 and includes a guided bus tour, access to the circulating Kangaroo Express bus, access to the Skyfari aerial tram and the entry fees for any ongoing shows.

Other family-friendly venues include Sea World ($84 for adults and $78 for children) and Legoland ($83 for adults and $73 for children).

Looking for a good time out?

The Gaslamp Quarter is the place to go out for dinner and drinks — and dancing and shows. And it is just a few steps away from the San Diego Convention Center, where the meeting will be held.

The weather is bound to be gorgeous, so check out a rooftop bar. Get a fantastic view at the ALTITUDE Sky Lounge.

Not into rooftops? How about an underground bar with no cover and a good dance scene like The Red C Lounge?

If a pub is more your style, try The Field.

And if none of these sounds like your scene, that's OK. There are plenty of other bars just around the corner.

Tired of the food at the convention center?

The restaurant Searsucker gets top billing on Yelp and features main courses from the ocean, farm and ranch. The French Café Chloe provides a more intimate space. For those of you on a budget, San Diego is known for its fish tacos. Be sure to ask around for the best. You're bound to get several suggestions.

Finally, for vegetarians, try out an ethnic option like Pokez Mexican Restaurant or Royal India. (These offer lots of meat options as well.)

Want to check out the Pacific shore?

San Diego is known for its beautiful beaches. The water probably will not be warm enough to swim in, but lying in the sand and checking out the gorgeous waves will be well worth it. If you're lucky, you may spot some ocean wildlife — seals, dolphins and maybe even a whale!

Below are just a few in a long list nearby beaches. Be sure to ask locals for their favorite spots.

- **Mission Beach:** The most well-known beach in San Diego, Mission has a famous boardwalk and is attached to Belmont Park, where the Giant Dipper roller-coaster resides.
- **Coronado Beach:** This beach is loved by the locals and by tourists for its vast beauty. Year after year, this beach receives many votes for the best beach.
- **Tourmaline:** Always wanted to try to surf? This break has a calmer wave, making it a good spot for beginners. This will require renting a board and wetsuit, and an instructor will make a huge difference, especially if this is your first time out. Also, be sure to check when the surf is good, because no waves means no surfing.

Those who want to watch surfers, rather than doing the surfing, and those more experienced surfers should check out Oceanside and Ocean Beach. Both have piers with good views. And those looking for more advanced adventures can take the long walk from the Torrey Pines area to discover Black's Beach.

Want a special event never to forget?

In addition to the relationships you build and the science you learn at the conference, you can make lifelong memories by attending a local event. It is even better if you attend with new friends you meet at the conference!

The Adams Avenue Unplugged Festival takes place once a year on Adams Avenue in the Normal Heights neighborhood. The music festival hosts more than 100 acts in local establishments. The neighborhood also offers an array of restaurant, bars, coffee shops, art galleries and antique shops. This year the festival will be Saturday, April 26, and Sunday, April 27.

Shaila Kotadia (skotadia@asbmb.org) is an ASBMB science policy fellow.

Bringing science to San Diego

By Geoff Hunt

The American Society for Biochemistry and Molecular Biology annual meeting once again will feature a full slate of programming from the Public Outreach Committee. If you are interested in getting involved with outreach or just curious about what outreach is, come check out one of our events.

Outreach poster session

When: *after the opening lecture Saturday, April 26*

Where: *San Diego Marriott Marquis, Marriott Hall 3, North Tower*

To get things rolling, we will host a special outreach-themed poster session after the opening lecture on the night of Saturday, April 26. Posters will showcase various outreach and informal science-education programs from around the country.

Examples include Trainee Meetings Outside the Box (1), a graduate-student-run mentorship and science-communication program at the University of Texas Health Science Center in San Antonio (1), as well as the ASBMB Undergraduate Affiliate Network chapter at San Francisco State University, which will highlight its collaborations (2) with Bay Area Science Festival and Guerilla Science, a collective that combines science with cultural activities. Take this opportunity to chat with your fellow scientists about their experiences and see for yourself how outreach is getting done at the ground level.

Communication workshop

"You Can't Say That on Television (or to Congress, or to Students)"

When: *12:30 p.m. Monday, April 28*

Where: *San Diego Convention Center, Room 14A, Mezzanine Level*

Effective public outreach relies on your ability to communicate about science with a wide variety of audiences in a plethora of different formats and venues. With that in mind, we've put together a workshop that will train you on how to do just that.

A roomful of communication experts will help you tailor your research description for different stakeholders, including the media, K – 12 students and policymakers. Bring your poster or talk abstract and get expert feedback and advice on how to ensure that your message resonates with your audience.

The workshop will serve as an introduction to several science-communication programs that we are developing. You can register at http://bit.ly/P5YHyM.

Science café

"Game Changer — How a Computer Game Can Turn You into a Real-Life Hero"

When: *7:30 p.m. Monday, April 28*

Where: *Southpaw Social Club, 815 J. St., San Diego, Calif. 92101*

Are you a protein biochemist? Do you like communicating with people about the joys and wonders of science? Do you just want a break from posters and lectures? If you answered yes to any of these questions, then join us for our annual EB science café, which will take place in the heart of the San Diego Gaslamp District.

UNESCO has designated 2014 as the Year of Crystallography to celebrate 100 years of X-ray diffraction with the goal to "increase public awareness of the science of crystallography" (3). The ASBMB is getting in the spirit by hosting a public science café on protein structure.

The café will focus on FoldIt (4), an interactive game developed by David Baker and his lab at the University of Washington. Users play the game by using amino-acid sequences and general rules of protein folding to solve complex protein structures. Lab member Brian Koepnick will lead a hands-on demonstration of the game at this event, showing how players from any background can participate, potentially even ending up as co-authors on scientific publications (as happened in 2011 for a group working on folding algorithms) (5).

Opportunities for outreach at every turn

We hope that those of you attending the annual meeting will interact with the nonscientist attendees, because, in our opinion, the best way to get involved with outreach is to get involved with outreach.

So once you get your fill of science at the meeting, come to our sessions to see how you can do a little bit more. We'll see you out in San Diego.

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Geoff Hunt (ghunt@asbmb.org) is the ASBMB's public outreach manager.

On the path to sustainability

Addressing the problems of an unbalanced research enterprise

By Chris Pickett

These are stressful times for biochemists and molecular biologists. Funding which has been stagnant for some time — took a significant hit last year when sequestration kicked in. Funding levels have yet to recover. The available faculty positions for up-and-coming scientists are few and far between, and formal job training for careers away from the bench can be hard to come by. Interactions and collaborations among academia, government and industry are often strained due to the very different cultural goals and needs of each stakeholder. Inefficient and ineffective collaborations among stakeholders, the potential of continued poor funding and a lost generation of scientists threaten the underlying stability of the American biomedical research enterprise.

To address this threat, the Public Affairs Advisory Committee of the American Society for Biochemistry and Molecular Biology has launched a project with a goal of moving the biomedical research enterprise onto a sustainable path. The first stage of this project, as discussed by ASBMB President Jeremy Berg in August, was to draft a white paper outlining a vision for this enterprise. This vision included improving education opportunities for trainees to prepare them for the variety of careers available; providing a new framework for more efficient cooperation among the academia, government and industry stakeholders and setting the entire enterprise on a path to predictable increases in funding.

But how can this vision be implemented in times of government austerity and significant regulatory and cultural roadblocks to interactions among the stakeholders? The second stage of the PAAC's sustainability initiative will explore this question at the Experimental Biology meeting in April in San Diego. A panel session on the second day of the meeting will address the barriers to sustainability and discuss possible mechanisms to overcome these impediments. Sitting on this panel will be four distinguished guests with experience bridging the divides among academia, government and industry:

Lana Skirboll has a unique perspective on industry and government, as she worked on science policy issues for more than two decades at the National Institutes of Health before becoming the vice-president of academic and scientific affairs at Sanofi. **Michael Marletta** serves as the president and chief executive officer of The Scripps Research Institute, and he has a firm understanding of industry through his own startup ventures.

As the director of the Massachusetts Institute of Technology Technology Licensing Office, **Lita Nelsen** has extensive experience overcoming barriers between academia and industry to enable the movement of technology and expertise between the two. And Paula Stephan, author of "How Economics Shapes Science" and Science Careers' 2012 Person of the Year, is an economist who brings an outsider's view of the strengths and weaknesses of the scientific enterprise.

We want to hear from you, the meeting attendees, as well. This is why we have reserved half of the 90-minute session for the panel to interact with the audience to hear your ideas and questions about building a sustainable biomedical research enterprise. In addition, an informal mixer will follow the session for panel participants, audience members and PAAC members to mingle and continue discussions about this very important topic.

With the biomedical research enterprise so far off balance, the PAAC panel session at the Experimental Biology meeting surely will generate some lively discussion. We hope to see you there!

Chris Pickett (cpickett@asbmb.org) is a policy analyst at ASBMB.

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RUTH KIRSCHSTEIN DIVERSITY IN SCIENCE AWARD

Hrabowski and Summers recognized for their support of underrepresented minorities

By Anna Shipman

The American Society for Biochemistry and Molecular Biology has named Freeman Hrabowski III and Michael Summers the winners of the Ruth Kirschstein Diversity in Science Award. The award recognizes outstanding scientists who show a strong commitment to mentoring and encouraging underrepresented minorities to enter the sciences.

Hrabowski, president of the University of Maryland, Baltimore County, cofounded the Meyerhoff Scholars Program in 1988 with philanthropist Robert Meyerhoff. The program's goal is to help underrepresented minorities pursue advanced degrees and research careers in science and engineering. Since 1993, there have been more than 800 graduates from the program, and most have earned or are working toward graduate or professional degrees. The program has been lauded as a national model, and Hrabowski has published several articles and books based on the results of the program.

"The Meyerhoff program is one of the best programs in the country for developing undergraduates for future scientific training, including students from groups that are underrepresented in science," says Jeremy M. Berg, the ASBMB's president and the associate senior vice-chancellor for science strategy and planning at the University of Pittsburgh. "Part of the power of the program is the deep involvement of outstanding research scientists who provide tremendous research opportunities for undergraduates."

As a Howard Hughes Medical Institute investigator at UMBC, Summers has collaborated with the Meyerhoff Scholars Program by mentoring a large number of students in the program. The research focus of his lab is the use of nuclear magnetic resonance and other biophysical methods to examine RNA structural elements involved in the genome packaging of viruses.

Chianna Paschall, a chemistry student in the program, worked with Summers to create a model of one of the proteins that makes up HIV, a model of which was featured on the cover of The Journal of Molecular Biology in 1994. Summers' most recent paper on HIV-1 genome packaging, published in Science, included 10 undergraduate co-authors.

Summers has designed and directs both graduate and undergraduate training programs at UMBC. The Doctoral Diversity program supports underrepresented minorities in Ph.D. programs in biomedical sciences there and at the University of Maryland–Baltimore. This program is considered a model due to the high retention rates and increased enrollment of minorities into Ph.D. programs.

At the undergraduate level, Summers mentors UMBC students as part of the HHMI Biological Sciences Training Program and non-UMBC students in the Summer Biomedical Training Program. In addition to this, Summers has mentored several postdocs and high-school students in his lab.

Hrabowski earned an M.A. in mathematics and a Ph.D. in higher education administration and statistics from University of Illinois at Urbana–Champaign. In 2012, Hrabowski was named one of the Top 100 Most Influential People in the World by Time Magazine and was named as chair of the President's Advisory Commission on Educational Excellence for African-Americans. Hrabowski's research primarily focuses on science and math education, especially minority involvement. Hrabowski gave a TED Talk in 2013 in which he shared some of the approaches used at UMBC to help more students from all backgrounds succeed in science and math.

Summers earned his B.S. in chemistry from the University of West Florida and a Ph.D. in bioinorganic chemistry from Emory University in Atlanta. Summers has been an HHMI investigator since 1994 and is a distinguished university professor of chemistry at UMBC.

"Mike Summers has built an absolutely world-class research program primarily around undergraduate students, many of whom have continued in graduate school and then to their own independent careers," says Berg.

Hrabowski and Summers will receive the award during the 2014 ASBMB annual meeting in San Diego, where Summers will give a lecture. The presentation will take place at 9:05 a.m. April 28 in Room 6A of the San Diego Convention Center.

It has been a tremendous privilege to work with Freeman for the past 25 years on activities that are so important to science and society. I am especially proud to be a member of ASBMB, an organization that has played major roles in helping ensure that science education and science careers are broadly accessible.

– MICHAEL SUMMERS

I am honored to be receiving this award with my colleague Mike Summers. His passion for science and for supporting students inspires me every day. The Meyerhoff Program and UMBC's other diversity initiatives have been successful because our culture emphasizes high expectations, hard work and support for all. Like Mike, faculty and staff are committed to inclusive excellence.

– FREEMAN A. HRABOWSKI III

Anna Shipman (alsnpc@mail.umkc.edu) received her B.S. in biology–biotechnology from Missouri Western State University and is a Ph.D. student in the School of Biological Sciences at the University of Missouri–Kansas City.

HERBERT A. SOBER LECTURESHIP

Carroll acknowledged for his work on genome editing with targetable nucleases

By Kyeorda Kemp

Dana Carroll, professor of biochemistry at the University of Utah School of Medicine, has won the 2014 Herbert A. Sober Lectureship award from the American Society for Biochemistry and Molecular Biology.

Carroll, whose early scientific interests were in the physical sciences, won the Sober lectureship for developing the use of zinc-finger nucleases as reagents for making site-specific double-strand breaks in the chromosomes of living cells. These reagents have allowed researchers to make targeted genome modifications in a wide range of organisms.

"Gene-targeting procedures have been available for fungi and for mouse (embryonic stem) cells for many years, but the absolute frequencies of targeted modification were low, and the approaches were not applicable to other organisms," says Carroll's colleague Martin Rechsteiner. "Carroll's insight was that the genomic target is essentially inert for recombination and that double-strand breaks in the target DNA will substantially stimulate the process. He then sought DNA cleavage reagents that could cut at specific, but arbitrarily chosen, sites."

Carroll first showed the ability of zinc finger nucleases to make germline modifications in the Drosophila melanogaster genome, and his lab generated targeted mutagenesis and gene replacement in the germline in more than 10 percent of cases in this organism. The lab also has used this approach in nematodes, plants and silkworms. Other nucleases that target the genome have been developed based on this approach, and this technology is being used to target genes for deletion and modification in a number of organisms.

In a 2010 interview with the corporate publication Biowire, Carroll stated, "People can now contemplate making very specific mutations in their genes of interest, which was only previously possible in yeast and some simple organisms, and in mice. With ZFN technology, this targeting capability is available for lots of different organisms. So that's been a big change for geneticists, but the field is still expanding. The number of applications is still increasing as we learn more about how we can use them."

Indeed, phase I clinical trials are under way using ZFNs as a treatment for HIV, and preclinical studies using these procedures to treat animal models of human diseases have proved successful, indicating that there is potential for this technology to be used for gene therapy.

"It is my opinion that textbooks of biochemistry and molecular biology will place Dr. Carroll's development of zinc finger nucleases as tools for genome editing alongside Sal Luria's and Ham Smith's work on restriction — namely in the class of fundamental discoveries that have indelibly altered academic, industrial and medical biotechnology," says Philip D. Gregory, chief scientific officer and vice president for research at Sangamo BioSciences Inc.

Carroll earned his bachelor's degree at Swarthmore College and his Ph.D. at the University of California, Berkeley. He also completed postdoctoral stints at the Beatson Institute for Cancer Research and at the Carnegie Institution of Washington.

This award has special meaning for me because Herb Sober was a family friend as I was growing up. In addition to people in my laboratory and my collaborators, I am grateful to the many researchers around the world who have taken the basic targeting technology, improved it and applied it in ways I had not imagined. It's been a lot of fun.

– DANA CARROLL

Carroll, who has received a number of awards and accolades over his career, including the 2012 Novitski Prize from the Genetics Society of America and an American Cancer Society Scholar in Research Award, will receive his Sober award from the ASBMB during the Experimental Biology 2014 conference in San Diego. His award lecture will take place at 9 a.m. Wednesday, April 30, in Room 6A of the San Diego Convention Center.

Kyeorda Kemp (kkemp134@gmail.com) will be starting as an assistant professor of biology at Northeastern State University in the fall.

ASBMB AWARD FOR EXEMPLARY CONTRIBUTIONS TO EDUCATION

White called 'one of the most interesting, engaging and genuine individuals'

By Shaila Kotadia

Harold B. White III, professor of biochemistry and director of the Howard Hughes Medical Institute Undergraduate Science Education Program at the University of Delaware, is the winner of this year's American Society for Biochemistry and Molecular Biology Award for Exemplary Contributions to Education.

The annual award is granted to a scientist who excels in leadership, writing, research, mentoring or public engagement to teach biochemistry and molecular biology effectively.

"Hal is a consummate teacher whose influence on his students goes well beyond the classroom. Indeed, many of his undergraduate students report that he has directly affected their career choices," said Judith Voet of Swarthmore College and Donald Voet of the University of Pennsylvania in their nomination of White for the award.

White's dedication to serving students is exemplified by his having been a program director with HHMI funding since 1998. He, with colleagues, has received numerous grants to implement the problem-based approach to learning. He is also a co-founder of the Institute for Transforming Undergraduate Education at the university. There, professors from colleges and universities attend workshops that use problem-based learning to teach undergraduates how to solve complex problems that connect to real-world issues.

White also spends a significant amount of time in the classroom. Marilee Benore at the University of Michigan at Dearborn, a former graduate student in White's lab, said, "Hal White is one of the most interesting, engaging and genuine individuals to ever grace a biochemistry classroom full of rapt students."

Prior to devoting his career to undergraduate education, White researched the structure, function and evolution of vitamin-binding proteins and was an early advocate of the "RNA World" hypothesis, publishing more than 100 papers on these and other subjects. White has had nearly 80 undergraduate research students in his laboratory over the years. Kathleen Cornely at Providence College noted, "About one-fourth of the undergraduate students in Hal's lab appear as co-authors on research papers resulting from the work of his group."

White started out as a curious undergraduate majoring in biochemistry at the Pennsylvania State University, where he conducted undergraduate research and was elected to honor societies in chemistry, biology and mathematics. His research career began in earnest during his graduate studies in biochemistry at Brandeis University. He then took a postdoctoral research fellowship in chemistry at Harvard University with Konrad Bloch, a 1964 Nobel Prize winner and 44th president of the ASBMB. White has been at the University of Delaware since 1971.

White has received multiple awards for his efforts, including the University of Delaware College of Arts and Sciences 2005 award for outstanding teaching and its 2007 award for outstanding service, and the 2011 Howard Barrows Award for exceptional undergraduate teaching from McMaster University. He was named the 2013 CASE–Carnegie Delaware Professor of the Year and recently was elected a fellow of the American Association for the Advancement of Science.

He will receive his award at the 2014 ASBMB annual meeting in San Diego, where he will give a presentation. The presentation will take place at 12:30 p.m. Sunday, April 27, in Room 6A of the San Diego Convention Center.

I thank the students and colleagues who nominated me for this award that recognizes my efforts to promote and use problem-based learning in undergraduate education. Receiving this award is humbling because there are so many other biochemistry and molecular biology educators worthy of the honor. Thus I see my recognition as symbolic of the efforts of all educators whose passion is rewarded by the enthusiasm of their students who accept intellectual challenges and glow when their efforts are rewarded with deeper understanding.

– HAROLD B. WHITE III

Shaila Kotadia (skotadia@asbmb.org) is an ASBMB science policy fellow.

BERT AND NATALIE VALLEE AWARD IN BIOMEDICAL SCIENCE

Gottesman recognized for his accomplishments in multidrug resistance in cancer

By Natalie Osayande

Michael M. Gottesman, deputy director for intramural research at the National Institutes for Health, is the inaugural winner of the American Society for Biochemistry and Molecular Biology's Bert and Natalie Vallee Award in Biomedical Science.

The award was established by the Bert and N. Kuggie Vallee Foundation in 2012 to recognize established scientists with outstanding accomplishments in basic biomedical research. Gottesman's research focuses primarily on multidrug resistance in cancer, which is the main impediment to successful chemotherapy.

Lawrence E. Samelson at the National Cancer Institute, who nominated Gottesman for the award, says: "For nearly three decades, Dr. Gottesman has made seminal contributions to the understanding of multidrug resistance in cancer cells, through the use of a variety of approaches and techniques involving biochemistry, cell biology and molecular genetics. (His) work has resulted in a new field of study of ATP-dependent transporters, has advanced the field of molecular diagnosis of multidrug resistance, has contributed to a new understanding of the pharmacokinetics of most drugs in common use, and promises to lead to new approaches to the treatment of drug-resistant cancers."

Gottesman and co-workers cloned the gene encoding the first-known mammalian ATP-dependent transporter and described the mechanism by which it confers multidrug resistance. He was first to propose that multidrug transporters recognize substrates while in the plasma membrane and expel them from the cell.

Harold Varmus, who as NIH director recruited Gottesman to head up the intramural research program, says that he knew at the time of Gottesman's integrity, scholarship and reputation but that he was "astounded by the quality of his leadership, the soundness of his judgments and the energies he brought to the task of running the (intramural program) in the more than 20 years since then."

Gottesman's concern and impact on trainees also makes him a suitable candidate for this award, says Samelson, chief of the Laboratory of Cellular and Molecular Biology at the Center for Cancer Research. Echoing that sentiment, Paul A. Insel at the University of California, San Diego, says: "Michael has been a leader in education and the training of scientists: For example, he established the Undergraduate Scholarship Program, the NIH Academy, and the Clinical Research Training Program. He has consistently been a voice for data-driven studies that influence the research and training environments in biomedical science in the U.S."

Insel also noted that Gottesman also has had many editorial responsibilities for The Journal of Cell Biology, Molecular Cancer Therapeutics and Molecular Pharmacology and has still maintained a very active and successful research program.

"Michael has been a star for his entire career," says Insel.

Gottesman graduated from Harvard College with a bachelor's in biochemical sciences and earned his medical degree from Harvard Medical School, where he trained in Bert Vallee's lab. After his residency at the Peter Bent Brigham Hospital in Boston, he did a postdoctoral stint studying molecular genetics with Martin Gellert at the NIH, joined the Harvard faculty and returned to the NIH, where he has held several positions. Today, while serving as deputy director for intramural research, he heads up the Laboratory of Cell Biology at the National Cancer Institute.

I am deeply honored to be the first recipient of the Bert and Natalie Vallee Award in Biomedical Science. Bert Vallee was a pioneer in metalloenzyme characterization and a mentor to many successful scientists. Through their foundation, he and his wife Natalie (Kuggie) were generous supporters of innovative and interactive science and scientists.

– MICHAEL M. GOTTESMAN

Gottesman will receive his award during the Experimental Biology 2014 conference in San Diego, where he will deliver an award lecture. The presentation will take place at 8:30 a.m. Sunday, April 27, in Room 6A of the San Diego Convention Center.

Natalie Osayande (natalie.osayande@spartans.ut.edu) is an undergraduate at the University of Tampa studying biochemistry.

ASBMB-HOWARD K. SCHACHMAN PUBLIC SERVICE AWARD

Rice University undergrad called 'champion of science education'

By Shaila Kotadia

Zack Kopplin, science-education advocate, is the winner of the American Society for Biochemistry and Molecular Biology's 2014 Howard K. Schachman Public Service Award.

The award recognizes an individual who demonstrates dedication to public service in support of biomedical science as exemplified by the award's namesake, who served as chairman of the ASBMB's Public Affairs Advisory Committee from 1989 to 2000. The award, instituted in 2001, is given annually by the society's Public Affairs Advisory Committee.

Jeremy Berg, president of the ASBMB and director of the University of Pittsburgh's Institute for Personalized Medicine, said, "Zack has been a true champion of science education, which has become all the more important in these times where educational standards are being debated. Zack has tirelessly fought for the teaching of evolution in classrooms."

As a high-school student, Kopplin, a native of Baton Rouge, La., was infuriated to learn that the 2008 Louisiana Science Education Act had passed. The act allows supplemental teaching materials to be used to critique or objectively review scientific theories. Kopplin's upbringing with a political influence (his father was the former chief of staff to Louisiana governors Mike Foster and Kathleen Blanco and was recognized nationally as a political activist) taught him the power of using his voice to effect change. Thus, Kopplin used his voice to raise concerns about the act. "All the Louisiana Science Education Act does is create an unconstitutional loophole to sneak the teaching of creationism or intelligent design in public school science classes," he said.

After writing a research paper on the act for an English class, Kopplin launched a campaign to repeal the act. Though the law was not overturned, Kopplin did succeed in rallying students and scientists throughout the country, including 78 Nobel laureates, in his campaign.

Now 20 years old, Kopplin continues to speak out against the teaching of creationism, often appearing on such shows as HBO's "Real Time with Bill Maher" and MSNBC's "Hardball with Chris Matthews." Kopplin also wrote an open letter to President Obama, saying, "Denying and misteaching evidence-based science like evolution and climate science will confuse our students about the nature of science and stifle future American scientists and scientific innovation."

Benjamin Corb, director of public affairs for the ASBMB, said, "Zack is an impressive young advocate for science. He exemplifies how his generation can begin a larger discussion on issues important to the teaching of science. We applaud Zack's continuing efforts to protect the integrity of science education."

It's a huge honor to receive this award. I'm thrilled to be coming to D.C. to help remind Congress that science funding and education must not be politicized.

– ZACK KOPPLIN

Kopplin has received multiple awards for his efforts as a science-education advocate, including the Friends of Darwin Award and the Hugh M. Hefner First Amendment Award in education. Kopplin received the Schachman Award at an ASBMB Public Affairs Advisory Committee reception on April 1 in Washington, D.C.

Shaila Kotadia (skotadia@asbmb.org) is an ASBMB science policy fellow.

WILLIAM C. ROSE AWARD

Maquat, 'a pioneer in the field of mRNA regulation'

By Shaila Kotadia

This year's winner of the American Society for Biochemistry and Molecular Biology William C. Rose award is Lynne Maquat, director of University of Rochester's Center for RNA Biology and professor in the biochemistry and biophysics department.

Established more than three decades ago and named after a former president of the American Society of Biological Chemists, ASBMB's precursor, the Rose award recognizes outstanding contributions to biochemical and molecular biological research and a demonstrated commitment to the training of younger scientists.

Maquat began her career as an undergraduate at the University of Connecticut Storrs Campus and continued on to the University of Wisconsin–Madison, where she earned a Ph.D. in biochemistry. She remained at UW–Madison for a postdoctoral fellowship in molecular biology and human disease at the McArdle Laboratory for Cancer Research. Early in her career, she was making groundbreaking discoveries in the field of RNA.

Jeffrey Hayes, professor at the University of Rochester and chairman of the biochemistry and biophysics department, said of Masquat's postdoctoral research: "Importantly, her studies established that the premature termination of mRNA translation can trigger rapid mRNA degradation due to a process termed nonsense-mediated mRNA decay … Thus, even as a postdoc, Lynne was a pioneer in the field of mRNA regulation, and she has continued to make seminal contributions to this field ever since."

Maquat joined the faculty at Roswell Park Cancer Research, the oldest cancer center in the U.S., before moving to her current professorship at the University of Rochester. During her tenure as a professor, she has trained a large number of graduate-student and postdoctoral researchers who've had a great deal of success when moving on to their own laboratories. Olaf Isken, one of Maquat's former postdoctoral researchers, said that Maquat "showed to me a remarkable commitment to promote my professional career." As the founder and chair of the University of Rochester Graduate Women in Science Program, Maquat is also a mentor beyond her lab.

In light of her many achievements and commitment to research and mentorship, Maquat is an inspiration to her fellow colleagues. Cecilia Arraiano, professor at the Universidade Nova de Lisboa in Portugal, said, "Throughout her career, Lynne has been an inspiring mentor, supporter and motivator for other people in science, including myself."

In addition to this latest honor, Maquat has received much recognition, including election to the National Academy of Sciences, the American Association for the Advancement of Science, and the American Academy of Arts and Sciences. She also is a past recipient of the Davey Memorial Award for Outstanding Cancer Research.

This is an honor to be shared with many others. I feel very privileged to have worked with so many talented graduate students and postdocs, without whom my lab's research accomplishments would not have been possible. When I mentor others, I do so with gratitude for those who made my research career possible – supportive professors when I was younger and supportive colleagues, friends and family after I started my own lab.

– LYNNE MAQUAT

Maquat will receive her award at the 2014 ASBMB annual meeting in San Diego, where she will give a presentation. The presentation will take place at 2:55 p.m. Sunday, April 27, in Room 6A of the San Diego Convention Center.

Shaila Kotadia (skotadia@asbmb.org) is an ASBMB science policy fellow.

HERBERT TABOR RESEARCH AWARD

Stillman recognized for significant research accomplishments toward better understanding DNA replication

By Natalie Osayande

Bruce Stillman, president of Cold Spring Harbor Laboratory and director of the the CSHL Cancer Center, is the winner of the American Society for Biochemistry and Molecular Biology's Herbert Tabor Research Award. The award recognizes scientists whose excellent research has made major impacts on the field and the scientific community.

As a researcher, Stillman has made foundational discoveries that contributed greatly to our understanding of DNA replication, and as director and president of CSHL for the past 20 years, he has nurtured and developed outstanding programs in cancer, molecular biology, neuroscience, plant biology and genetics/genomics.

Nobel laureate James Watson, who nominated Stillman for the award, said, "In addition to his impressive research record, Bruce has been a leader throughout his career and has made significant contributions to the scientific community."

Watson noted that Stillman's studies of SV40 DNA and others projects led "to an understanding of DNA replication mechanisms that duplicate eukaryotic cell chromosomes." Stillman was able to characterize the mechanism by which chromosomal DNA replication is initiated in yeast and human cells. A third major contribution was Stillman's clarification of how DNA replication and chromatin assembly are molecularly linked.

Stephen Bell, professor of biology at the Massachusetts Institute of Technology, a Howard Hughes Medical Institute investigator and a former postdoctoral fellow at Stillman's lab, said that Stillman has led the field of eukaryotic DNA replication into "new important directions." Stillman's discoveries have helped scientists better understand diseases, including cancer. His discoveries also have encouraged research in the fields of DNA repair and eukaryotic genomic stability.

"Bruce has also been a generous citizen of science," said Anindya Dutta, a former postdoctoral fellow in Stillman's lab and currently the chair of biochemistry and molecular genetics at the University of Virginia, noting that Stillman has trained many young scientists who went on to make significant impacts on the fields of DNA replication, cell cycle and genomic stability. Bell echoed that sentiment, saying: "His students and postdocs have also gone on to become leaders in their own fields."

Stillman earned a bachelor's degree from the University of Sydney and earned a Ph.D. from the Australian National University. He completed a postdoctoral fellowship at the CSHL and has since held many positions there, including his current position as president and chief executive officer. He has received many honors and awards.

I am thrilled by this major recognition from ASBMB of contributions made together with many talented students and postdoctoral fellows in figuring out how our genome is inherited.

– BRUCE STILLMAN

Stillman will receive his award during the Experimental Biology 2014 conference in San Diego, where he will deliver the opening lecture of the ASBMB meeting. His presentation will be at 6 p.m. Saturday, April 26, in the San Diego Marriott Marquis Hotel, North Tower, Hall 4. The ASBMB opening reception will follow the lecture.

Natalie Osayande (natalie.osayande@spartans.ut.edu) is an undergraduate at the University of Tampa studying biochemistry.

Under the spell of the COCKROACH HUNTER

The venom of the female jewel wasp renders her victims docile so that her offspring can feast. Scientists wonder if this strange brew might teach us a thing or two about human neurobiology.

By Rajendrani Mukhopadhyay

PHOTOS BY VICTOR LANDA, UNIVERSITY OF CALIFORNIA, RIVERSIDE

For centuries, the jewel wasp has captivated entomologists with its beauty and, in the case of the female, its hunting prowess. The wasp doesn't kill its prey right away. Instead, it injects a special venom into its cockroach victim, putting it into a bewitched state. The wasp then builds a burrow, drags in the zoned-out cockroach, lays an egg on it and buries it. The larva that emerges gradually eats the cockroach alive.

Over the past two decades, researchers have been trying to tease out the molecular composition of this unusual venom. Not only could the results help researchers understand how this venom acts on an animal's central nervous system, but they also could lead to a better understanding of certain human neurological disorders that have some of the same symptoms as those found in the entranced cockroach.

The female Ampulex compressa and its taming of cockroaches were most vividly described in a 1942 paper by the entomologist Francis Xavier Williams (1).

"Ampulex compressa is a large, beautiful wasp with a shining blue-green body and with the femora or thighs of the second and third pairs of legs red … Mrs. Williams, who took great interest in this scintillating blue-green insect, very aptly named it the 'jewel wasp.'"

From 1916 to 1948, Williams was an employee of the Experiment Station of the Hawaiian Sugar Planters' Association. In May 1940, his employer sent him to New Caledonia, an archipelago in the southwest Pacific Ocean 750 miles east of Australia. Williams was to survey insects and catalog those that might devastate Hawaii's sugarcane industry. In those days, Pan American Airways ran clippers between Hawaii and New Zealand, stopping off at New Caledonia for refueling; the concern was that the clippers inadvertently would carry insects from New Caledonia to Hawaii and harm the state's economically valuable crops.

But Williams knew that New Caledonia was one of the tropical homes of the jewel wasp. He saw this survey trip as an opportunity to bring the wasp to Hawaii and use the animal as roach control. He described the story of traveling with his wife to Noumea, the capital of New Caledonia, to bring back both male and female wasps to Hawaii.

"The jewel wasp puts up a wonderful exhibition of boldness, skill and strength in the attack on her often huge prey, once to the effect that a French scientist upon witnessing such a battle in our hotel room laboratory in New Caledonia, much impressed, exclaimed: 'C'est formidable!'"

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In the late 1980s, Frederic Libersat was a postdoctoral fellow at Hebrew University in Israel working on cockroaches. "I was interested in how the nervous system generates movement," he says. "Cockroaches are a good model to study, because their nervous system is less complicated than that of a mammal. You can find some rules of organization of the nervous system to produce movement."

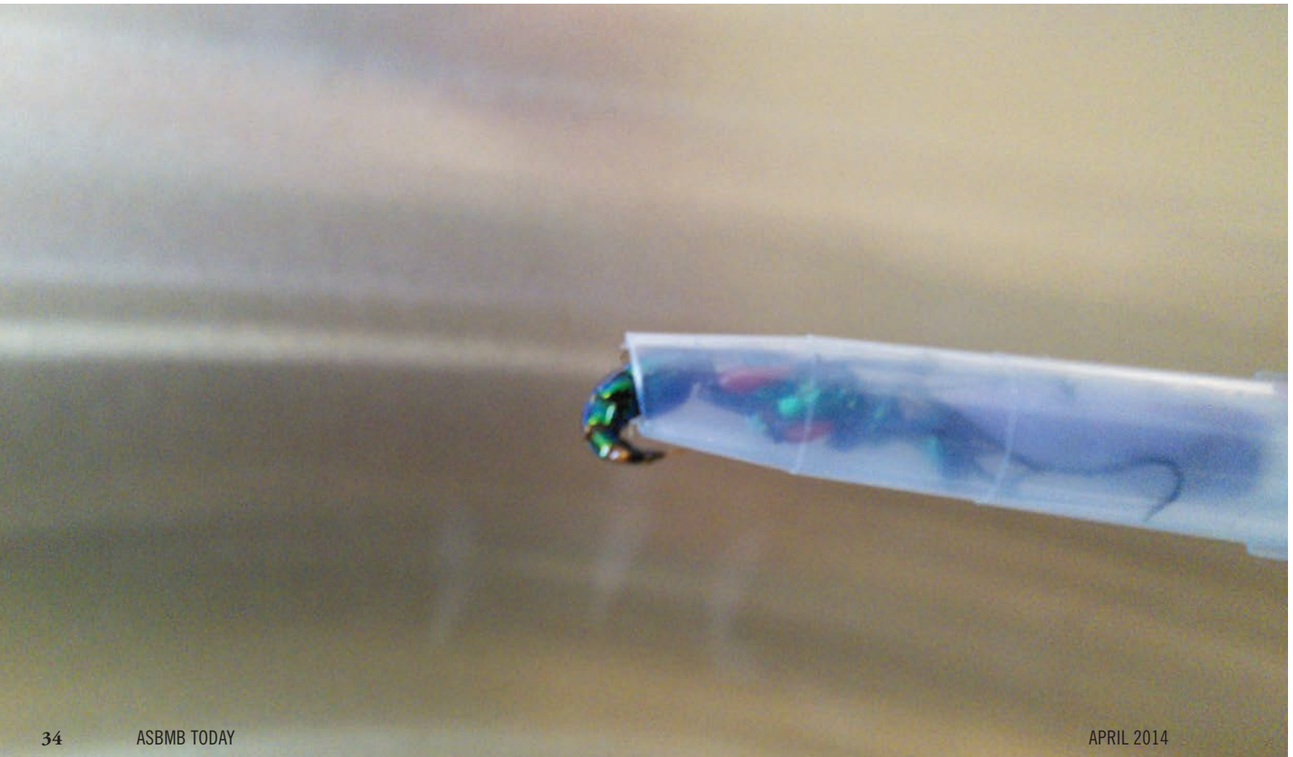
At Hebrew University, Libersat met a visiting German scientist, Werner Rathmayer. Rathmayer was studying the bee wolf, a wasp that hunts bees, but he happened to have a jewel wasp in an aquarium in his office in Germany.

At that time, not much was known about how the female wasp managed to tame the cockroach. Given Libersat's work on cockroaches, Rathmayer told him about the wasp and how it was capable of manipulating the cockroach's central nervous system in mysterious ways. The wasp's venom somehow made the cockroach unable to initiate walking on its own, putting it in a state known as hypokinesia. But when the wasp grabbed the cockroach by its antennae with its mandibles, it could lead the cockroach like a reined horse.

"I thought this would give me some window into understanding how walking is initiated in an insect, or any animal, as a matter of fact," says Libersat, now at Ben Gurion University in Israel. Movement can be initiated by a stimulus, such as food, a sexual partner or scent. "But sometimes, an animal also initiates what's called exploratory movement," says Libersat. What causes animals to make these movements that don't have clear-cut rewards?

And so began Libersat's careerlong interest in the female jewel wasp and its unusual manipulation of Periplaneta americana, the inch-long, dark brown flying cockroach that sends many of us screaming from the room.

Researchers place a wasp stinger-first into a pipet tip to extract its venom.



About 15 years ago, Libersat noticed the work that Michael Adams was doing with spider venom. Libersat invited Adams, who is based at the University of California, Riverside, to spend some time with his group in Israel to work on the jewel wasp venom. Libersat was immersed in understanding the neurological effects of the venom on the cockroach, but he also wanted to know the chemical composition of it. Libersat and Adams have collaborated over the years, and now both are working on the molecular composition of the venom.

Both groups have taken a proteomic sequencing approach. In collaboration with SongQin Pan, also at UC Riverside, Adams' graduate student Ryan Arvidson used an approach called multidimensional protein identification technology, better known by its acronym, MudPIT. This mass-spectrometric analysis is useful for studying complex protein mixtures.

The investigators earlier had built two databases of RNA sequences in collaboration with Peter Arensburger, now at the California Polytechnic State University, which they used for their MudPIT analyses to confirm that the protein identifications they made matched up with the transcripts in their databases.

To analyze wasp venom, one has to collect it. The approach is "artisanal," jokes Libersat, whose group developed it. A researcher first stretches parafilm across a Petri dish with a 5-µL droplet of water. Then he or she puts a female wasp in a pipette tip, abdomen first, so that the wasp's stinger protrudes from the opening. The pipette tip then gets attached to a syringe. Then, as Arvidson delicately puts it, "we antagonize the wasp."

The researcher positions the trapped wasp over the parafilm-covered Petri dish and pushes the plunger of the syringe to bang the wasp on the head. The

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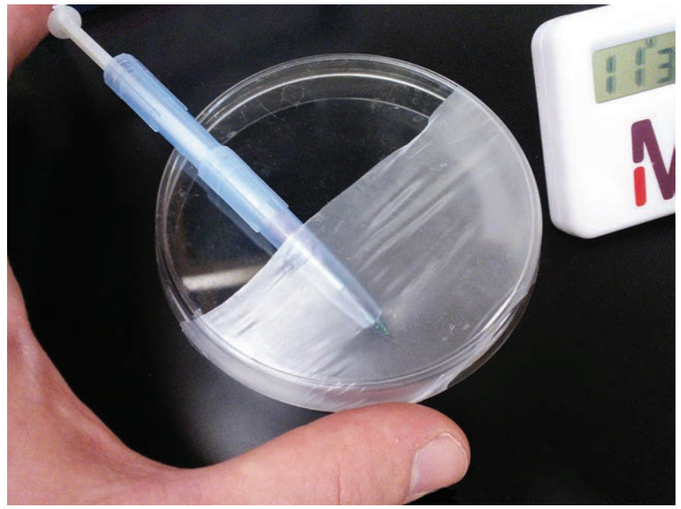

A female Ampulex compressa releases 50 nL of venom in a single sting.

The proteomic analysis

ARVIDSON

If you'd like to learn more about wasp venom, check out Ryan Arvidson's poster at the ASBMB annual meeting in San Diego. Arvidson will be presenting his poster, "Developing the venom of the parasitoid wasp Ampulex compressa," between 12:15 p.m. and 1:45 p.m. on Monday, April 28, at poster board number D235. The abstract number is 4947.

Photo provided by Ryan Arvidson.

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infuriated wasp pierces the parafilm in an attempt to sting the offender. The piercing action triggers venom release, and the wasp deposits about 50 nL of venom into the water droplet in the dish. The sample is then flash-frozen. A wasp can be milked up to 40 times. For their proteomic analyses, Arvidson says, they needed to milk about 50 wasps to get a sufficient amount of sample.

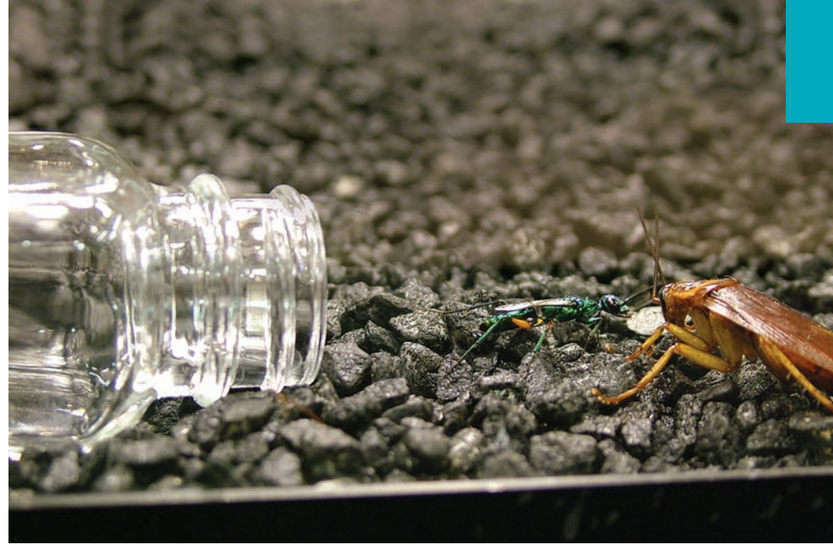
Arvidson thinks they may have found peptides that are known to affect motor function. The investigators also have found some novel peptides: These peptides are present in the venom at particularly high concentrations and seem to be involved in inhibiting entry of calcium into neurons through a G-protein-coupled receptor pathway. "When we put the venom on cell culture, we see inhibition of calcium dynamics. We can talk a lot about how affecting calcium entry into a neuron can prevent it from firing, but as far as that leading to the hypokinesia, we haven't made that connection yet," says Adams.

Unlike some other venoms, the jewel wasp's venom doesn't cause paralysis in victims. Rather, it changes the cockroach's behavior. It's important to remember, says Libersat, that the wasp itself doesn't use the cockroach as a food source. The wasp's offspring needs the cockroach as food. The wasp "wants to keep (the cockroach) very much alive and fresh," says Libersat. "The last thing it wants is muscular paralysis, which would prevent, for instance, gas exchanges and blood circulation. That would make the prey, which is the food item, rot within a few hours."

Williams observed:

"As a rule, Ampulex attacks the cockroach soon after the latter's introduction into the jar. The wasp, then becoming very alert and with antennae directed towards her intended victim, approaches it from the side in front and with a short lightning leap … Immediately directing her flexible abdomen forward and underneath the cockroach's thorax, she extends the point of her abdomen in search of a vital place in which to plunge her sting … The cockroach, now thoroughly frightened, struggles furiously, twisting, straining and describing short jerky circles, parrying with its legs, and striving particularly to tuck in its chin so that the tenaciously clinging wasp will not sting its throat."

Libersat explains that the wasp takes a two-pronged approach in taming its victim. The wasp first inflicts a sting to the cockroach's thorax. The first sting's venom causes a temporary paralysis of about two to three minutes at the cockroach's forelegs, which allows the wasp to get a better grip of the cockroach's front end and position its stinger over the cockroach's head. The first



The wasp prepares a burrow inside the jar for its bewitched victim.

venom's action has been worked out by using patch-clamp analyses and other approaches, says Libersat. The first venom, which contains a high concentration of GABA, causes chloride channels to open up and inhibit synaptic transmission at the neurons.

"It receives a sting in the thorax, its struggles become more feeble, and as the Ampulex thrusts her sting deep into its throat the head is thereby forced outwards on a membranous neck. After a few moments of injecting the poison, the wasp releases her hold and now backs off to view her work alertly. She may even grasp the cockroach and make pretense at dragging it away but usually leaves it in place — a wretched spectacle, head down and helpless though not immobile and later regaining considerable activity."

The second venom goes directly into the cockroach's brain. Known neurotransmitters, including dopamine, GABA and taurine, have been found in the venom. The dopamine is thought to kick off a grooming response in the cockroach. The cockroach stands in one spot, cleaning its antennae and forelegs, while the wasp busies itself in getting a burrow ready.

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The hunter scrutinizes its prey.

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After this 30-minute grooming stage, the cockroach falls into the zoned-out state of hypokinesia.

Once the wasp has prepared a burrow and pulled the cockroach in, it glues an egg to the underside of the bug and buries it. The egg hatches, and the larva grows latched on the cockroach. Once the larva has grown its final set of mandibles, it begins to chew into the roach, eventually climbing in completely. Inside the still-living host, the larva enters the pupal stage, forms a cocoon and matures. It emerges as a fully formed wasp.

"The last pair of jaws are large and stout-toothed, and it is with these that the larva immediately bites through the cockroach's body to enter it and feed within … The larva now feeds ravenously within its weakening host, hollowing out its body even to the base of the legs. The cockroach soon perishes — having provided the wasp during its life as a grub with a continuous supply of fresh meat."

Another notable attribute of the venom, besides not causing paralysis, is that it's reversible. If, for some reason, the wasp egg doesn't hatch, the stung roach regains its senses five days later inside its tomb. Laboratory studies have shown "stung cockroaches tend to live as long as control cockroaches after the sting, can lay eggs, have babies and go on about their normal lives even after the encounter with the wasp," says Adams. Libersat adds that it's interesting to note that five days is exactly the time it takes for a larva to eat through a cockroach.

Reversible effects of biomolecules are not unusual, points out Libersat. "There are things that are secreted by your own brain that can affect you for periods of weeks or months, like a woman's menstrual cycle," he explains. "You can imagine that there is something in the venom that has an effect that lasts for a week."

Given the evolutionary conservation of the dopaminergic system between insects and humans, the experts think that the study of the insect system may have an impact on human illnesses, such as Parkinson's.

"One of the hallmarks of Parkinson disease is the inability of people to generate movement. One of the treatments of Parkinson disease is to supply them with a precursor to dopamine because the dopaminergic system is malfunctioning," says Libersat. "The dopaminergic system is involved in controlling the initiation of locomotion in insects as well."

The wasp venom's dopamine probably attacks the cockroach's dopaminergic synaptic transmission. "The cockroaches show the classical freezing movements of Parkinson-disease patients," says Libersat. "The roaches are immobile, but they can generate movement in specific conditions, such as being led by the antennae by the wasp."

So much like scientists of yesterday, present-day scientists continue to be fascinated by the parasitic jewel wasp and her manipulative ways with her cockroach victim. As Williams described, it wasn't just scientists who found this wasp to be a wonder to behold:

"On our Pan American Airways voyage from Nouméa to Honolulu, we stopped for a day and a half at the equatorial atoll of Canton. Here the two Ampulex jars were brought out of their travel bags, a large cockroach was given to each of the wasps, and the airplane passengers, the airplane and the ground crews were treated to an exciting rough-and-tumble performance."

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2. Arnaud, P.H. Jr. *Occasional Papers California Acad. Sciences,* **80** (1970).

Francis Xavier Williams

Williams contributed more to the science of entomology than just his detailed observations and illustrations of the female Ampulex hunting behavior. A globetrotter, Williams traveled through the Galapagos Islands, the United States, the Philippines, parts of Central and South America, and East Africa in his pursuit of insects.

In his expedition to the Galapagos Islands alone, between 1905 and 1906, he collected more than 4,000 insects from which scores of new species were described. Williams himself proposed 146 new taxa in three orders of Insecta, including five genera, one subgenus, 132 species, six subspecies and two replacement names (2).

In his career of six decades, Williams published 286 scientific papers as well as the 400-page reference book "Handbook of the Insects and Other Invertebrates of Hawaiian Sugar Cane Fields." In 1946, Williams published a popular book, "Mike the Minah," which he had coauthored with his wife Louisa Clark Williams. He died in California, the state where he was born, in 1967 at age 85.

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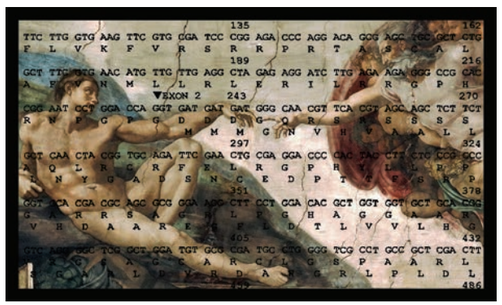
Thank God for overlapping genes

By Harvey J. Armbrecht

Sometimes I feel weighed down as a scientist. Sometimes I feel overwhelmed by grant deadlines, unwritten papers, finicky experiments, endless forms, and so forth. Why am I doing this? Isn't there an easier way to earn a living? During times like this, I'll sometimes glance over to the corner of my desk. There I display pictures of special people and things – my wife, my children, my grandchildren … and a DNA sequence. Now, pictures of family are understandable, but why a DNA sequence?

The DNA sequence I have on my desk is from the INK4a/ARF gene locus. The DNA sequence (shown in black) and the corresponding proteins it codes for (shown in blue and red) read in part:



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INK4a DNA:      …ATT CAG GTG ATG ATG ATG GGC AAC GTT CAC GTA GCA GCT…
INK4a protein:  …Ile-Gln-Val-Met-Met-Met-Gly-Asn-Val-His-Val-Ala-Ala…
ARF protein:                 …Asp-Asp-Asp-Gly-Gln-Arg-Ser-Arg-Ser-Ser…
```

This DNA sequence is an exquisite example of an overlapping gene. Overlapping genes are genes where a single stretch of DNA sequence codes for parts of two proteins. In the case of INK4a/ARF, the in-frame reading of the DNA codes for the amino acids of the INK4a protein (shown in blue above) in a perfectly conventional way. But in the middle of this, the DNA also codes for different amino acids for a completely different protein – the ARF protein (shown in red above). It does this by shifting the reading frame of the triplet code. This results in an alternate reading frame – hence the name ARF protein. Amazingly, the overlapped coding of these two proteins continues for 105 amino acids. The same DNA sequence produces long stretches of two completely different proteins with different three-dimensional structures and functions!

I first heard about overlapping genes years ago in the virus PhiX174. The amount of DNA in the genome of this virus is too small to produce the 11 proteins it needs. To overcome this, the genome contains multiple overlapping genes. I was intrigued by this clever strategy, but it was only a virus. Then it gradually became clear that it was not just a virus thing. Examples of overlapping genes in mammals gradually accumulated. I became more excited. Now it is estimated that least 10 percent of mammalian genes contain overlapping sequences. To me, the fact that interlocking DNA sequences produce unique, functional proteins across the biological spectrum is remarkable. I feel that I am looking at something that transcends mere biology.

As I reflect on these overlapping genes, I am thankful for several reasons – some obvious, others perhaps not so obvious. At the functional level, many of these genes are essential for disease prevention, longevity and life itself. I display on my desk the sequence for the INK4a/ARF gene because, as a gerontology researcher, this locus is very important to me. These proteins play a major role in tumor suppression and perhaps the aging process itself. These two proteins are regulated by separate promoters, and they function in independent tumor-suppressor pathways. Mutations in this locus result in a marked increase in tumors in mouse models, and these genes are frequently inactivated in human tumors.

At the personal level, I am thankful for overlapping genes because they remind me of the beauty of the things we biochemists study. These genes come in a wide variety of motifs. Sometimes the overlap is on the same coding strand, as it is for the INK4a/ARF gene locus. But sometimes the code for the second protein is on the complementary (antisense) strand. It can even be on the complementary strand read backward!

Probably my favorite overlapping sequence involves the yeast protein Tar1p. Here the messenger RNA sequence that codes for Tar1p also codes, on the antisense strand, for a ribosomal RNA. Ribosomal RNA serves as a structural backbone for protein-synthesizing ribosomes. This is a completely different RNA function than that of messenger RNA. Scientists who study overlapping genes use words like "novel," "remarkable," "striking" and "statistically improbable" to describe them.

When life is difficult, I look at the DNA sequence on my desk. From its intricate beauty, I draw strength and hope for the future.

At the spiritual level, overlapping genes give me a glimpse of a reality that transcends our everyday world. Writers as different as Richard Dawkins ("An Appetite for Wonder"), Stephen Jay Gould ("Wonderful Life"), Ursula Goodenough ("The Sacred Depths of Nature"), Stuart Kauffman ("Reinventing the Sacred") and the author of Psalm 139 ("I am fearfully and wonderfully made") make the point that what we study is wonderful, transcendent, even sacred. To me, overlapping genes point to something greater than myself. When life is difficult, I look at the DNA sequence on my desk. From its intricate beauty, I draw strength and hope for the future.

Since this is a letter of thanks, who then do we thank? Who do we thank for the function, beauty and spirituality of these overlapping genes? Depending on one's worldview, a person might thank God, nature, evolution or perhaps all of these. Being a person of faith, I would thank God first. But whatever one's answer, it is a question that these genes confront us with.

I think that all of us as scientists have our overlapping-genes moments. Something in our field of study stirs our soul and evokes wonder. It may not be a DNA sequence. It could be a protein with amazing properties, an intricate signal=transduction network, a cell with marvelous abilities or a novel organism that provides new insights. But whatever it is, for a moment it captivates us. And if we take time to reflect on it, maybe it will lighten our daily burden of grants, papers and paperwork.

Looking at the big picture, we scientists can be thankful that we get to study biochemical systems as wonderful as overlapping genes. We get to apply our knowledge of them to the treatment of human diseases. We get to talk and write about them and perhaps inspire others. We get to enjoy their beauty and the meaning that they bring to our own lives. And maybe we even put a picture of them on our desk.

Harvey J. (Jim) Armbrecht (armbrech@slu.edu) earned a B.S. in physics from Drexel University and a Ph.D. in biophysics from the University of Rochester Medical School. He is a research biochemist at the St. Louis VA Medical Center and professor emeritus in the Division of Geriatric Medicine and the Department of Biochemistry and Molecular Biology at St. Louis University School of Medicine. His major research interests have been age-related changes in calcium and vitamin-D metabolism. More recently he has been studying age-related memory loss in animal models. His current interests are in the biochemistry of aging and dementia and caregiving.

Enjoying the Open Letters series?

We've extended the submission deadline to Oct. 1. Send yours to asbmbtoday@asbmb.org.

Petsko on the Ph.D. pipeline

Former ASBMB president weighs in on mentoring, postdoctoral training and alternative careers in science

By Lymor Ringer-Barnhard

Gregory Petsko, a structural biologist at Brandeis University and a former president of the American Society for Biochemistry and Molecular Biology, sat down recently for a Google Hangout to answer questions from students and postdoctoral fellows regarding the Ph.D. pipeline, postdoctoral training, careers in science and funding issues. In his interview, which is archived online (1), he emphasizes the need to make major changes to Ph.D. and postdoctoral training programs in the U.S.

The conversation with Petsko was hosted by iBiology, an initiative started in 2006 to make scientific presentations available to the public. Petsko's talk is one of more than 300 produced by iBiology.

Many audience members asked Petsko about careers beyond academic research. Petsko was cautious when describing those careers as "alternative" because, in fact, most Ph.D. graduates do something other than academic research. When asked about what needs to be done to familiarize Ph.D. students with careers outside of research, Petsko said that he believes that responsibility lies mainly with graduate schools, likely in the form of postdoctoral or career-training offices. He also said graduate schools should provide internship opportunities in nonacademic fields, such as in industry.

One audience member asked why many mentors are hesitant to support students pursuing careers outside of research. Petsko said this is not simply the single-mindedness of the mentor but rather "plain stupidity."

He continued: "The idea that there can be no plan B is simply a failure on the part of the mentor to be a proper mentor. The job of the mentor is not to provide clones of him or herself. The job of the mentor is to help the person become the best that they can be." To further stress his point, Petsko added that "If they don't see that as the job, then they've got no business mentoring."

Petsko said he does not think that Ph.D.s should do postdoctoral fellowships unless they plan to stay in academia, but if you are a postdoc who does not want to continue along the academic track, Petsko recommends that you "stay until you stop learning." He also stressed that the point of a postdoctoral period was to provide advanced training – in research.

For postdoctoral fellows to obtain jobs outside of academia, Petsko indicated that the responsibility lies largely with the institution to provide proper career guidance. He also mentioned the importance of professional societies to host job fairs showcasing a variety of career types. If this is not happening, it is up to the young scientists to petition for it, he said.

"Every scientific society that I am aware of is scared to death about the fact that their membership tends to look like me: white, middle-aged males. If the young members of a society got together and made enough noise, societies would be responsive to what they want, because societies desperately need their young members right now."

Meanwhile, Petsko said that fewer postdoctoral positions should exist in order to pay postdocs higher salaries. The goal is to not "make postdocs the default," he says but rather to make it a desirable position that is competitive and that people pursue to stay in academia. "We need to have much (closer to) the correct number of graduate students becoming postdocs relative to the number of postdocs that find advanced positions," says Petsko.

When asked about the most effec-

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"The idea that there can be no plan B is simply a failure on the part of the mentor to be a proper mentor. The job of the mentor is not to provide clones of him or herself. The job of the mentor is to help the person become the best that they can be."

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tive way for a postdoc to get the best mentoring, Petsko replied, "I think the best mentees are those that make sure I don't forget them; they don't fall between the cracks." He also mentioned that what you get out of a postdoc is "highly individualistic" and that it is a research training position, so postdocs need to make sure they continue learning. To be successful, postdocs should be proactive and ask their mentors to let them help with paper review, proposal writing, teaching and so forth to further challenge themselves, he said.

Petsko also said that he is a firm believer that labs in the U.S. should take some pointers from European labs and create more nontenure track, permanent research positions. In Europe, people who obtain positions like that are "exceptionally well-trained to do high very high-powered research," he said, adding that "it's stupid to assume that the only way to do good science at an academic institution is being a faculty member." Petsko admitted funding those types of positions would be the main hurdle for creating them, but he said that he believes it would be possible.

To see the complete video of Petsko's interview and a full breakdown of each question and answer, go to http://bit.ly/1fjHPOH.

Lymor Ringer-Barnhard (lymor.ringer@gmail.com) earned a Ph.D. in tumor biology from Georgetown University. She is a postdoctoral fellow at Johns Hopkins University.

REFERENCE

1. http://bit.ly/1fjHPOH

2014

ASBMB ANNUAL MEETING

April 26–30, 2014 • San Diego, CA

ASBMB SPECIAL EVENTS

Saturday, April 26

Fostering Partnerships Among Colleges, Universities and K-12 Schools*
San Diego Marriott Marquis Hotel
9 a.m. – 1 p.m.

Start Trek the Next Generation of Scientists: Undergraduate Program
San Diego Convention Center
Events all day

Professional Development Program for Trainees*
San Diego Convention Center
9 a.m. – 4:30 p.m.

Opening Reception & Science Outreach Posters
San Diego Marriott Marquis Hotel,
North Tower, Marriott Hall 3
7:30 p.m. – 9 p.m.
(immediately following the Opening Lecture)

Sunday, April 27

ASBMB Twitter Breakfast*
San Diego Convention Center, Room 14A
(Mezzanine Level)
7 a.m. – 8:15 a.m.

Building A Sustainable Research Enterprise
sponsored by the ASBMB Public Affairs Advisory Committee
San Diego Convention Center, Room 6B (Upper Level)
12:30 p.m. – 2 p.m.

ASBMB Welcome Reception
hosted by the ASBMB Minority Affairs Committee
San Diego Marriott Marquis Hotel, Marina Ballroom D
7:30 p.m. – 9:30 p.m.

Monday, April 28

Science Communication Training Workshop "You Can't Say That on Television (or to Congress, or to Students)"
Sponsored by the ASBMB Public Outreach Committee
San Diego Convention Center, Room 14A,
Mezzanine Level
12:30 p.m. – 2:30 p.m.

ASBMB Science Cafe
South Paw Social Club, J St. & 8th Ave.
7:30 p.m. – 9 p.m.

Tuesday, April 29

Women Scientists Networking Event
San Diego Convention Center, Room 14A
(Mezzanine Level)
6 p.m. – 8 p.m.

**Pre-registration is required*

ASBMB
American Society for Biochemistry and Molecular Biology

www.asbmb.org/meeting2014