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ASBMB TODAY

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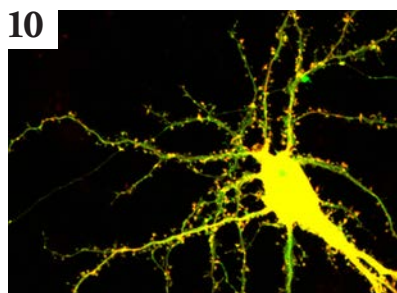
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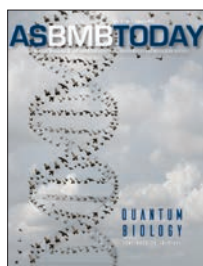


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PRESIDENT'S MESSAGE

PCP addict

By Steven McKnight

No — I'm not talking about phencyclidine or angel dust but instead PCP as an abbreviation for three words: phenomenon, curiosity and paradox.

My 1973 edition of Webster's New Collegiate Dictionary defines a phenomenon as "a rare or significant fact or event," a curiosity as "one that arouses interest especially for uncommon or exotic characteristics," and a paradox as "a tenet contrary to received opinion." I'm always on the lookout for any PCP worthy of study. Once I find a good one, I see the opportunity to make a discovery.

Before discussing ways of finding PCPs, let's first question the value of this strategy.

With respect to practicality (careerism), this approach is a bad idea. Committing to a project that is unusual, exotic or contrary to opinion is not easy. Granting agencies tend to choke on ideas that are new, different or a challenge to conventional wisdom. They want us to add incrementally to the existing knowledge base; they want to know that what we propose in our grant applications will work. Nothing I've ever known for sure will work and proceeded to do has added anything of significance. If a project is perceived as likely to succeed, building on what already is known and accepted, it is far more digestible to most review committees than a project seeking to challenge dogma or break new ground.

Were it up to me — and as I have admitted over and over, it is not — I would never fund a research project that did not do one of two things. A worthy project should either question our existing assumptions or propose an uncharted pathway directed toward an unexplained biological phenomenon.

Knowing that my advice is anti-theoretical to the status quo, I start with the truth-in-advertising warning that the thoughts presented herein are anti-professional. Follow this advice, and you are almost certain to get your grant application triaged.

PCPs abound in biology. They hit us in the face without even looking for them. Some may defy conventional wisdom and be paradoxical, others may constitute little more than weird curiosities, and still others may rest on a newly observed phenomenon of interest.

I bump into PCPs on a regular basis. Here are several examples that I thought of without getting up from my chair.

Starting with the phenomenon category of the PCP triad, I recount a conversation I had recently with my colleague, Betsy Goldsmith. Betsy is interested in how cells respond to changes in osmotic pressure. Much to her surprise, Betsy found an enzyme that is pressure sensitive and involved in a signaling cascade that responds to extracellular osmolarity. How crazy and cool is this? An enzyme that is

Correction

The article "More good news about aspirin" in the October 2015 issue of ASBMB Today incorrectly referred to salicylate as an acetylated form of aspirin. It is an unacetylated form of aspirin.

pressure sensitive! Betsy sticks her enzyme in a test tube, pumps up the pressure, and the enzyme activates magically. Talk about a cool phenomenon!

Moving to the curiosity category, I turn to a gene my lab has studied for a while — the gene encoding a transcription factor that we call neuronal PAS domain protein 3, or NPAS3. The NPAS3 gene has ridiculously large introns. Two of the introns span nearly a million base pairs. Geez, it takes the RNA polymerase II enzyme five to 10 hours simply to transcribe the gene from end to end. Other genes are big, so the whalelike size of NPAS3 introns is not all that perplexing. Cool and unexpected is the fact that the introns of the NPAS3 gene contain hundreds of ultraconserved elements 100 to 300 base pairs in length. These elements have been conserved for upward of half a billion years, going back to the evolutionary time when our ancestors diverged from teleost fish.

The intronic sequences of the NPAS3 gene are conserved to an extent equal to the handful of exons that encode the polypeptide sequence of the NPAS3 protein. If we knew nothing about exons, introns, proteins — nothing about the central dogma of molecular biology — yet were able to sequence and comparatively align the NPAS3 genes from dozens of vertebrates, evolution would be telling us to pay just as much attention to

the ultraconserved intronic elements of the NPAS3 genes as to its protein-coding exons. This is a curiosity.

I'll close with a paradox. Several years ago, my trainees and I stumbled onto the fact that low-complexity sequences associated with many DNA and RNA regulatory proteins can polymerize into amyloidlike fibers. Intuition and certain experimental observations led us to hypothesize that there might be biologic utility to LC sequence polymerization. Whether we are right or wrong on this remains open to question. The paradox that is clear, however, is that the amyloidlike fibers polymerized from LC sequences are labile. This is crazy. As visualized by electron microscopy, LC amyloids look just like pathogenic amyloids that are rock solid and at the heart of many forms of neurodegenerative disease. How can two amyloid fibers look the same yet be entirely different with respect to lability?

I happen to believe that these three PCPs are pregnant with discovery. That is the good news, and that is what causes me to adore my job. The bad news is that I can't be sure that studies of Betsy's pressure-sensitive enzyme, the ultraconserved intronic elements of the NPAS3 gene or our labile amyloids will illuminate our understanding of biology. Instincts tell me they will, but these are the sorts of projects that most grant review groups would automatically reject — the

technical hurdles might be way too high, or our instincts may simply be dead wrong.

PCP projects are risky. We all know this. What if our system of grant funding, instead of betting on sure winners guaranteed of incremental advance, instead demanded that each funded project aim at a unique phenomenon, curiosity or paradox? A small fraction of the annual budget of the National Institutes of Health is indeed devoted to high-risk, high-reward projects — perhaps 1 percent in aggregate. Why do we not devote a higher fraction of biomedical research funding to crazy exploration?

The success rate of PCP-funded projects would be modest. Many would fail. By contrast, the small number of wins might accelerate our understanding of how biological systems actually work. The careers of scientists crazy enough to expend their shot on the goal of a four-year period of grant funding on a wild and crazy project might well decay and die on the journey. Despite this risk, I'm thinking that the line for those bold enough to give PCP a try might be long.



Steven McKnight (steven.mcknight@utsouthwestern.edu) is president of the American Society for Biochemistry and Molecular Biology and chairman of the biochemistry department at the University of Texas-Southwestern Medical Center at Dallas.

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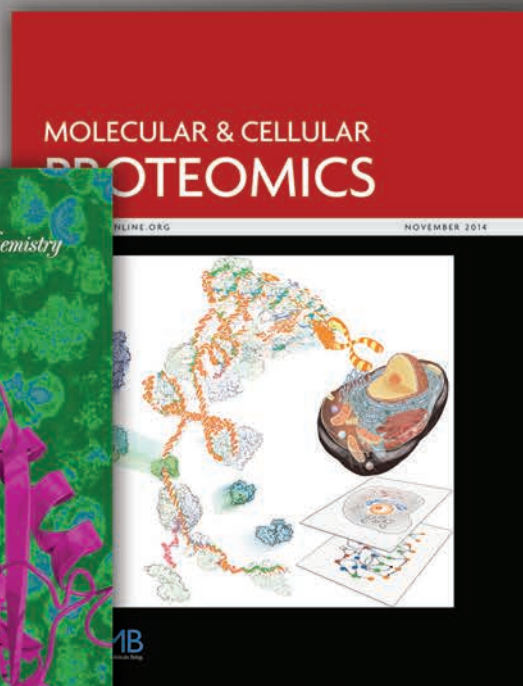
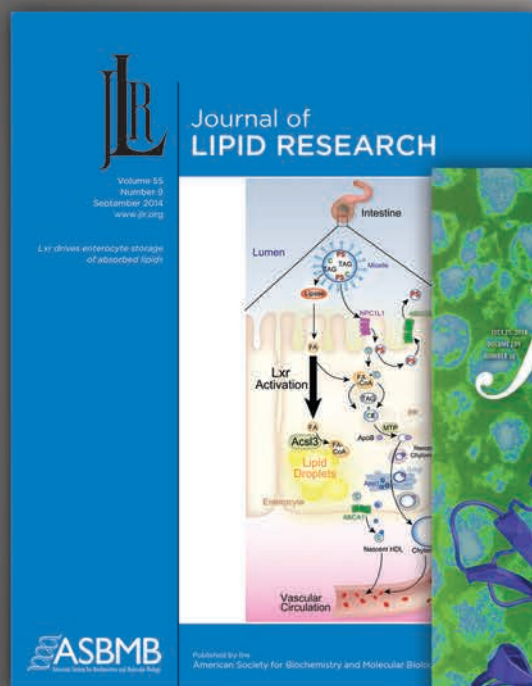
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What's on tap for 2016

By Benjamin Corb

As the calendar turns to 2016, our attention shifts to what concerned scientists can expect from Washington during a presidential election year. Let's dust off the crystal ball and make some predictions for the coming year.

Funding

With the 2015 Bipartisan Budget Act, we got a total spending level established for fiscal year 2017. Add this to the fiscal year 2016 spending bill, which provided measurable increases to the National Institutes of Health's budget, and it feels as though a lot of the fiscal advocacy heavy lifting has been done. Considering that 2016 is not only a presidential election year but also an election year for the entire U.S. House of Representatives and one-third of the U.S. Senate, we know that Congress will be in recess more often than usual, leaving less time for legislating. Thus, we anticipate a continuing resolution will be the most likely outcome of the appropriations process this year.

Thanks to the hard work of U.S. Reps. Fred Upton, R-Mich., and Dianna DeGette, D-Colo., who pushed the 21st Century Cures Act through the House of Representatives last summer, the research community should keep an eye out for nonap-

propriations opportunities. This year the Senate is expected to release and discuss its own bill aimed at helping researchers: the Innovation for Healthier Americans Act. These two bipartisan legislative initiatives, which are intended to help the research community develop treatments for those suffering with diseases, have the potential to move quickly and become feel-good stories of bipartisan legislating done right in 2016.

Sustaining the enterprise

Over the past several years, the American Society for Biochemistry and Molecular Biology's Public Affairs Action Committee has focused on the issue of sustaining the biomedical research enterprise. We are very excited to announce that next month we will hold a stakeholders summit on the topic. During the summit, thought leaders will develop ideas about how best to sustain the enterprise, and following the summit, the ASBMB will announce an advocacy strategy designed to implement those ideas.

New initiatives

Your public affairs staff isn't stopping with funding and sustainability. We're exploring new ways to engage

those society members who want to play more active roles in our advocacy efforts, including developing local opportunities for postdocs to present their science in a way that promotes not only amazing research but also pride in their home states. We're continuing to strengthen and broaden our blog (policy.asbmb.org), so it's the source for goings-on in Washington, D.C., that may affect your laboratory. We'll also be publishing a monthly advocacy newsletter to make information even more accessible to you. Finally, we are beginning an analysis of basic science study sections at the NIH to try to identify ways the NIH can better serve the needs of the basic science community.

This year, like every year, is about our members — how we can best serve you and represent you to the policymakers here in the capital. If you like what we're doing, have questions about what we're doing or want to share your ideas, reach out to us. We'd love to hear from you.

We are available via email at publicaffairs@asbmb.org or on Twitter (www.twitter.com/ASBMB).



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



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Ohsumi to receive Rosentiel Award



OHSUMI

Yoshinori Ohsumi, a cell biologist at the Frontier Research Center at the Tokyo Institute of Technology,

will receive the 45th Lewis S. Rosenstiel Award for Distinguished Work in Basic Medical Research. Brandeis University presents the award annually to scientists whose discoveries are of particular originality and importance to basic medical research. Brandeis is recognizing Ohsumi for his “pioneering discoveries of molecular pathways and biological functions of protein degradation by autophagy.”

Autophagy is a form of degradation and recycling and elimination of unnecessary cellular components. Ohsumi used budding yeast as a model organism to identify protein components of the autophagic machinery as well as mutations in many of the genes that code for these proteins. He and his colleagues also discovered some of the regulatory proteins of autophagy.

According to Brandeis, though “the lysosome was first identified in the 1950s, it was not until Dr. Ohsumi’s work that the many protein components of this degradative machine were identified.”

Written by Alexandra Pantos

Yamamoto appointed UCSF vice chancellor



YAMAMOTO

Keith Yamamoto is the inaugural vice chancellor for science policy and strategy at the University of California, San Francisco. Yamamoto long has been a

leading advocate for communication between policy makers and scientists. As part of his new role, he will contribute to policy at state and national levels, working in tandem with other leading officials in the scientific community to shape the development of scientific research and education.

Yamamoto also will help maintain UCSF’s ranking as the No. 1 public recipient of National Institutes of Health funding and its reputation as one of the primary institutions for science research and education in the country.

Yamamoto brings a wealth of knowledge and experience to his new position. He joined the UCSF faculty in 1976 and has served as professor of cellular and molecular pharmacology, vice dean of the School of Medicine, and the vice chancellor for research — all positions he will continue to occupy. Yamamoto also runs a research lab that studies signaling and transcriptional regulation by nuclear receptors.

WUSTL’s Goldberg named distinguished professor



GOLDBERG

Daniel E. Goldberg has been named the first David M. and Paula L. Kipnis distinguished professor at Washing-

ton University School of Medicine in St. Louis. Goldberg is a professor of medicine and molecular microbiology and has been co-chief of the school’s division of infectious diseases for 15 years.

This professorship honors the late David Kipnis, a pioneering scientist and educator who was with the university for nearly 50 years, and his wife, Paula Kipnis. David Kipnis was instrumental in developing the university’s medical school, which he led for two decades. His late wife was

considered an unofficial ambassador for the university.

Goldberg has contributed groundbreaking research on malaria and was director of the school’s medical scientist training program from 1997 to 2007.

Goldberg has had a highly decorated career, and in 2013 the American Society for Biochemistry and Molecular Biology recognized him with the Alice and C. C. Wang Award in Molecular Parasitology.

Zuk tapped to direct NIGMS division



ZUK

Dorit Zuk has been selected as the director of the National Institute of General Medical Sciences’ Division of Genetics and Developmental Biology.

To help advance prevention, treatment and diagnosis of a variety of diseases, GDB funds research that studies the cellular and molecular mechanisms underlying inheritance, gene expression and development.

A molecular biologist with a background in science policy and communication, Zuk is a former deputy editor of *Cell* and was the editor of *Molecular Cell*. Previously the science policy adviser to the National Institutes of Health deputy director for extramural research, she currently serves as director of the Office of Policy, Communications and Strategic Alliances at the NIH’s National Center for Advancing Translational Sciences.

Zuk also has held science policy fellowships with the American Association for the Advancement of Science and the American Academy of Arts and Sciences. She has been with the NIH since 2007.

Written by Erik Chaulk

Baumann a BioArt contest winner



BAUMANN

Heinz Baumann at the Roswell Cancer Research Institute in Buffalo, N.Y., is one of the 2015 winners of the Federation of

American Societies for Experimental Biology BioArt contest. The contest highlights artistry in biomedical and life sciences by recognizing the often spectacular images and videos produced in the course of research. Laboratory-based images produced by federally funded investigators, contractors, trainees or members of FASEB societies are eligible for the contest.

Baumann is part of a research group that seeks to identify genetic changes that contribute to pancreatic cancer. The team labeled and tracked the tumor origins of cancer cells through the use of “confetti” fluorescent



labeling in a mouse model. Cell descendants carried on a color induced in their parent cells, and the technique created a stunning, colorfully abstract proof of concept image.

Written by Erik Chaulk

Upcoming ASBMB events and deadlines

- JAN.** **Jan. 9:** ASBMB workshop Developing and Sharing Best Practices: From Concept to Classroom, Melbourne, Fla.
- Jan. 23:** ASBMB workshop Developing and Sharing Best Practices: From Concept to Classroom, Hattiesburg, Miss.
- Jan. 23:** ASBMB workshop Developing and Sharing Best Practices: From Concept to Classroom, New York City
- Jan. 28:** Late-breaking abstract deadline for the ASBMB 2016 Annual Meeting, San Diego

- FEB.** **Feb. 23:** Discounted housing closes for the ASBMB 2016 Annual Meeting, San Diego
- Feb. 27:** ASBMB workshop Developing and Sharing Best Practices: From Concept to Classroom, Westerville, Ohio

- MAR.** **Mar. 1:** Early discounted registration closes for the ASBMB 2016 Annual Meeting, San Diego
- Mar. 1 – 4:** ASBMB is a sponsor at the Deuel Conference
- Mar. 15:** Accreditation deadline

- APR.** **Apr. 2 – 6:** ASBMB annual meeting



NIH retiring 50 reserve chimpanzees

By Chris Pickett

The National Institutes of Health announced that it is ending its chimpanzee research program and will retire all of the agency's remaining chimpanzees. The news comes two and a half years after the NIH announced plans for a dramatic reduction in the number of chimpanzees used for biomedical research. In 2013, the NIH retired the majority of its chimpanzees and kept 50 in reserve for research needs. The new move will retire these 50 chimpanzees.

"We reached a point where ... the need for research (using chimpanzees) has essentially shrunk to zero," said NIH Director Francis Collins in an interview with *Nature*. "I think this is the natural next step of what has been a very thoughtful five-year process of trying to come to terms with the benefits and risks of trying to perform research with these very special animals."

The original set of retirements came after a 2011 report by the National Academies made a series of recommendations for improving the treatment of research chimpanzees. Since the 2013 announcement, the number of requests to use chimpanzees for research has dropped so significantly that the NIH decided the maintenance required for the remaining 50 chimpanzees was not worth the price.

A rule change by the U.S. Fish and Wildlife Service also may have played a part in the NIH's decision. Until mid-2015, wild chimpanzees were listed as an endangered species, but a loophole exempted captive chimpanzees from protected status. In June,



NATIONAL INSTITUTES OF HEALTH

Pumpkin is a retired chimpanzee living at the Alamogordo Primate Facility in New Mexico.

the USFWS closed this loophole and listed captive chimpanzees as endangered along with their wild brethren. This ruling does not eliminate the possibility of conducting research on chimpanzees, but it does add new rigorous requirements for justifying new chimpanzee research, including a determination that any research would have to benefit wild chimpanzees.

While the NIH has committed to retiring its entire chimpanzee colony, the speed with which retirement will be accomplished is not clear. First, only a portion of the chimpanzees slated for retirement in 2013 have

been moved to sanctuary facilities. Second, Chimp Haven in Louisiana, the only federally accredited facility to handle retired research chimpanzees, is nearing capacity. While the NIH no longer owns chimpanzees for research purposes, the agency will still pay for chimpanzee facilities for several years until the entire U.S. research chimpanzee colony is moved to retirement locations.



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

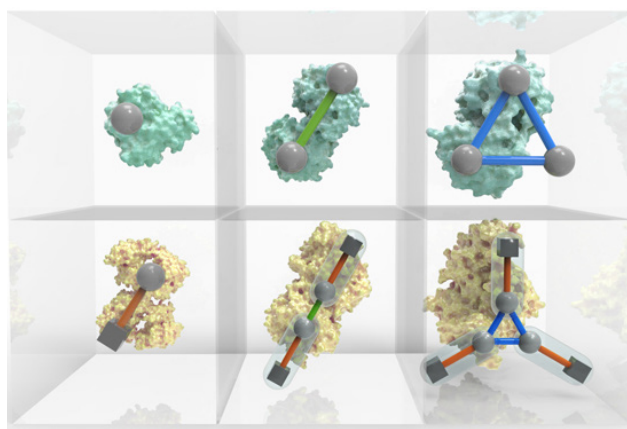
Proteins get their own periodic table

By Rajendrani Mukhopadhyay

Much like Legos, proteins can come together in a number of ways to create complex structures. The various ways make it hard to organize protein complexes into categories.

But now, in a paper just out in the journal *Science*, researchers describe an approach to classify protein complexes that creates a periodic table, like the periodic table that's used in chemistry to organize elements. "We're bringing a lot of order into the messy world of protein complexes," says Sebastian Ahnert at the University of Cambridge. Ahnert is the first author on the paper.

Many proteins spend much of their time interacting with other proteins and assembling into complexes in order to carry out their functions. But the interactions and functions are specific, much like in the way different Lego bricks can latch onto each other only in certain ways. The underlying principles of protein interactions and assembly are not yet fully understood.



EMBL-EBI / SPENCER PHILLIPS

An interactive periodic table of protein complexes.

But by organizing the different ways protein comes together into a table, Ahnert, along with Sarah Teichmann at the European Molecular Biology Laboratory–European Bioinformatics Institute, Joseph Marsh at the University of Edinburgh and others, wanted to see if some of the fundamental steps in protein complex evolution would become apparent.

They did. The investigators organized complexes based on simple rules so that they could find the most basic structures. "In the end, we discovered that three possible steps of interface

evolution, combined in very specific ways, give rise to almost all known structures of protein complexes," says Ahnert.

The investigators say that the fact that almost all known protein complexes could be arranged into a periodic table is revealing and will help understand how protein complexes come about.

"Most heteromeric protein complexes — ones with more than one protein type

— consist of identical repeated units of several protein types," says Ahnert. "Because of this, heteromeric protein complexes can, in fact, be viewed as simpler, homomeric protein complexes — ones that only consist of a single type of protein — if we think of these repeated units as larger 'single proteins.'"



Rajendrani Mukhopadhyay (rmukhopadhyay@asmb.org) is the chief science correspondent for ASBMB. Follow her on Twitter at twitter.com/rajmukhop.



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Implicating proteins in synaptic plasticity

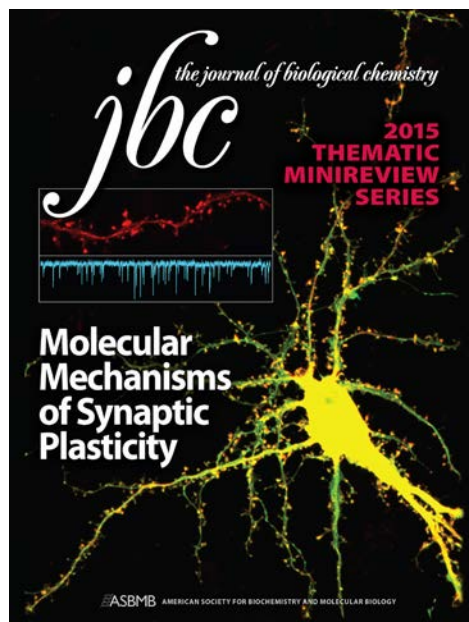
By Mariana Figuera-Losada

The activity of synapses, those fundamental biochemical units and cellular structures that allow nerve-impulse transmission between neurons, is not constant. Rather, synaptic strength can weaken or intensify over time in response to activity levels and other factors. Changes in activity also are associated with changes in the size and shape of synapses. This synaptic plasticity is thought to play a critical role in various forms of learning and memory, and understanding its molecular bases has become a thriving area of neuroscience research.

Synapses contain hundreds of proteins, including neurotransmitter receptors, cell-signaling molecules, scaffolding proteins and cytoskeleton components. These proteins are involved directly in synaptic activity. To understand how the brain truly works, we need to comprehend the role of proteins in synaptic plasticity.

The **Journal of Biological Chemistry** recently published a collection of thematic minireviews edited by Roger J. Colbran of Vanderbilt University. Titled “Molecular Mechanisms of Synaptic Plasticity,” the series includes four reviews that discuss recent advances in understanding the mechanisms that modulate synaptic protein production and function as well as the effects of these mechanisms on synaptic plasticity.

Marc P. Lussier at the University of Quebec at Montreal, Antonio Sanz-Clemente at Northwestern University and Katherine W. Roche at the National Institute of Neurological Disorders and Stroke discuss one of the mechanisms of synaptic plasticity in the first review. The authors detail the consequences of three types of post-translational modifications —



phosphorylation, ubiquitination and palmitoylation — on the stability, trafficking and synaptic expression of ionotropic glutamate N-methyl-D-aspartic acid, or NMDA, and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, or AMPA, receptors, the workhorses of excitatory synapses. The review also addresses the effects of these modifications on two major forms of synaptic plasticity: long-term potentiation, or LTP, and long-term depression, or LTD.

Kevin M. Woolfrey and Mark L. Dell’Acqua at the University of Colorado provide an additional in-depth discussion of post-translational modifications. These authors discuss experimental evidence supporting the idea that the balance between phosphorylation and dephosphorylation of glutamate receptors and ion channels mediates LTP and LTD. Moreover, the dynamics of these signaling events are dictated by the association of protein kinases and protein phosphatases with postsynaptic scaffold proteins.

Next, a minireview by Erin F.

Spence and Scott H. Soderling at Duke University covers the molecular processes involved in the regulation of synaptic cytoskeleton within the dendritic spines in the context of human neurodevelopmental and psychiatric disorders. This review emphasizes actin filament assembly and disassembly and its role in synaptic plasticity, because it is the most abundant cytoskeleton component in the dendritic spines.

Finally, Beatriz Alvarez-Castelao and Erin M. Schuman at the Max Planck Institute for Brain Research discuss an important mechanism of inducing long-term synaptic plasticity that involves regulation of synaptic protein synthesis and proteasome-dependent degradation.

The authors present an exhaustive discussion of the evidence to date that explains where and how synaptic protein turnover occurs; which proteins are affected by these processes; and the long-term effects of these events on learning, memory and behavior.

Understanding how changes in synaptic activity are connected to modulation of protein expression and degradation, post-translational modifications and cytoskeleton dynamics is essential to determining the molecular bases of physiological and pathological processes that occur in the human brain. In addition, this knowledge could contribute to the development of novel therapies for disorders — such as Parkinson’s disease, schizophrenia and autism — that have been associated with unresponsive or overactive synapses.



Mariana Figuera-Losada (fmariana@hotmail.com) is an associate scientist at Albert Einstein College of Medicine in the Bronx.

When the good and the bad make the ugly

By Rajendrani Mukhopadhyay

At first, no one took them seriously. In 1991, Rafael Radi, Joseph Beckman, Kenneth Bush and Bruce Freeman published a paper in the **Journal of Biological Chemistry** demonstrating that a molecule called peroxynitrite, the product of a reaction between nitric oxide and superoxide radicals, selectively attacked sulfhydryls in proteins. “Nobody believed much of any of it,” recalls Beckman at Oregon State University. “It was considered an unproven theory. I was surprised we even got the paper accepted in JBC.”

Today, “Peroxynitrite Oxidation of Sulfhydryls” is recognized as a JBC Classic (1). The paper has been cited in the scientific literature more than 2,100 times.

Until 1990, the chemistries of nitric oxide and oxygen radicals were thought to be unrelated. Nitric oxide was known to physiologists as the molecular radical that caused vasodilation, played a role in neurotransmission and killed invasive pathogens. The chemistry of superoxide and other oxygen radicals fell under the purview of biochemists interested in the damage wreaked by these reactive entities. Neither group considered that its radical of interest had anything to do with the other.



BECKMAN

That view was challenged in 1990 with a paper in the Proceedings of the National Academy of Sciences, with Beckman as the first author and Freeman as the corresponding author. At that time, the group was at the University of Alabama at Birmingham. Freeman

held a faculty position. Beckman was a tenure-track assistant professor who had done a postdoctoral fellowship with Freeman.

In the PNAS paper, the authors described how nitric oxide reacted with superoxide to form peroxynitrite. “We proposed that nitric oxide was toxic because it reacted with superoxide to form peroxynitrite,” explains Beckman.



RADI

Radi, who had joined the Freeman group as a postdoctoral fellow, had been working on oxygen radicals at the Universidad de la República in Uruguay (he later returned to the institution as a principal investigator). For the JBC paper, he and Beckman analyzed the reaction kinetics of peroxynitrite with bovine serum albumin and cysteine and discovered that peroxynitrite was capable of directly oxidizing sulfhydryls, much more so than hydrogen peroxide. “This completely opened a new paradigm of oxygen-radical-dependent toxicity by means of the crosstalk with the nitric oxide pathway,” says Radi. Bush, the third author on the paper, was a research technician who later became a lawyer.

Radi says he and Beckman found inspiration from Clint Eastwood’s 1966 movie “The Good, the Bad and the Ugly.” It was unthinkable to physiologists that nitric oxide could “be converted in such a nasty molecule just because of the reaction with superoxide,” says Radi. “Nitric oxide was the good guy. Superoxide was the bad and peroxynitrite the ugly.”

These days, peroxynitrite is

recognized as an oxidant and nucleophile that can attack mitochondria and lead to cell death by a slew of oxidation and nitration reactions.

Radi explains that peroxynitrite has a dual personality. It can be “liberated by our immune cells to kill invading pathogens,” says Radi. But he adds that the molecule has been implicated in atherosclerosis, hypertension, type 2 diabetes and neurodegenerative conditions, such as amyotrophic lateral sclerosis.



FREEMAN

Peroxynitrite can break down to form secondary molecules, such as nitrogen dioxide and hydroxyl radicals. Freeman says nitrogen dioxide is capable of nitrating protein tyrosine and tryptophan residues and unsaturated fatty acids. The latter reaction leads to products with signaling capabilities that modulate metabolic and inflammatory responses. The fatty-acid reaction with nitrogen dioxide is being scrutinized as a drug target.

But back in the early 1990s, “it took a few years and redundant ways to show that these reactions were of any importance in biology,” says Radi. Beckman sees the silver lining in having naysayers: Not too many others were interested in working on peroxynitrite. The field was left wide open for investigators like him, Radi and Freeman to get a head start on peroxynitrite research. He says, “The moral here is don’t get discouraged if people don’t immediately jump to your ideas.”



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JLR co-editor-in-chief steps down

By Mary L. Chang

Joseph L. Witztum has stepped down as co-editor-in-chief of the **Journal of Lipid Research**.

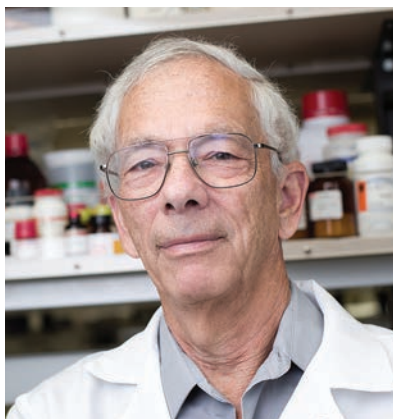
A distinguished professor at the University of California, San Diego, Witztum joined the JLR leadership as deputy editor in 2003. In 2008, he was named co-editor-in-chief alongside Edward A. Dennis.

JLR Associate Editor William Smith at the University of Michigan was named Witztum's replacement as co-editor-in-chief. His term began Jan. 1.

Witztum has worked in the field of lipoprotein metabolism for more than 40 years, much of that time with the late Daniel Steinberg, who invited him to join the faculty at UCSD in 1979. The two worked on deciphering how oxidized, low-density lipoproteins and the body's immune system played roles in atherogenesis. Steinberg and Witztum led the clinical trial unit at UCSD as one of the units of the Coronary Primary Prevention Trial (1). The 10-year study, which ended in 1984, was the first large, randomized, double-blind study to show a statistically significant decrease in heart disease as a result of cholesterol-lowering drug therapy. Witztum and Steinberg's results sent ripples through the medical community and significantly changed how physicians treated patients' high cholesterol levels.

According to Dennis, also of UCSD, "Joe is one of the foremost researchers on lipoprotein metabolism and especially the role of oxidized LDL in the pathogenesis of atherosclerosis, and his knowledge and wisdom in this area have been invaluable for the JLR. It has been a wonderful period of working closely with such a creative and devoted scientist."

Throughout his time at the journal, Witztum was recognized



DAVID AHNTHOLZ

Joseph Witztum

for his detailed reviews of submitted work. He evaluated every submitted manuscript to determine if it met the journal's stringent submission guidelines and took extra time to consult with one or more associate editors about papers that went to peer review. If he didn't feel a manuscript met the journal's guidelines or felt it was more suitable for publication elsewhere, Witztum would write a detailed letter to the authors explaining his decision. He made it a priority to respond to authors quickly, maintaining that if he were submitting a manuscript to the JLR he would want to be shown similar respect.

The journal staff regularly received positive replies from authors about Witztum's decision emails. They were often effusive in their praise of Witztum, thanking him for the care he took with his letters. A recent email reads, "Thank you very much for taking the time to write such a considered and informative decision letter. It has been very much appreciated by the authors and a pleasant change from the standard rejection letter issued by many journals."

Dennis says he and Witztum oversaw significant milestones during their time together at the journal.

"From the beginning, we worked closely together with a shared goal of continuing and expanding on the almost 50-year tradition of JLR of being the leading journal in lipid metabolism. Over the first five years, we doubled the number of submissions and brought the acceptance rate to about 30 percent. We expanded the Thematic Review Series and, for our 50th anniversary, published a special golden issue with 75 reviews covering the latest in all of lipid metabolism. We also initiated the JLR Lectureship at selected specialized lipid meetings each year."

Witztum graduated magna cum laude with a bachelor's degree in chemistry from Vanderbilt University in 1965 and earned his medical degree at Washington University at St. Louis in 1969. An internship and residency in internal medicine at Mt. Sinai Hospital in New York City and a position as chief medical officer at Winnebago Indian Hospital on a Native American reservation in Nebraska followed. He later took a fellowship in endocrinology and metabolism and then a faculty position at Washington University in St. Louis before being recruited to UCSD in 1979. Witztum has an active research lab and is an internist, continuing to see patients in a lipids clinic.

For his many contributions to the journal, Witztum was honored at a special dinner in New York in October. He won't be cutting his ties to the journal completely, however. As of Jan. 1, he will become an associate editor.



Mary L. Chang is publications manager at ASBMB.

The details of DNA end resection

By Aurelia Syngkon

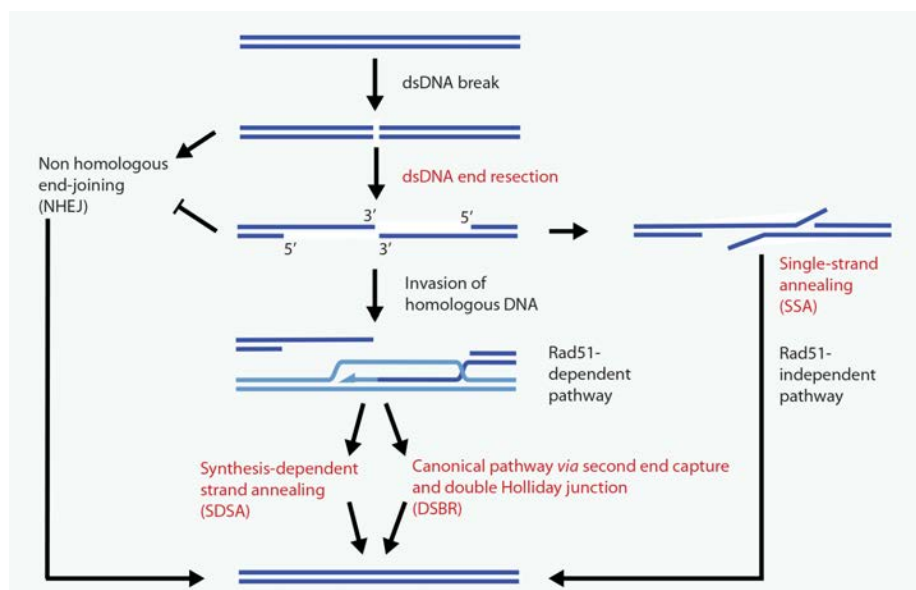
Cells are exposed continuously to challenges, such as ionizing radiation and collapsed replication forks, that cause double-strand DNA breaks. Such breaks can lead to cell death or provoke chromosomal rearrangements that make a cell susceptible to cancer. As a result, cells have adapted a couple of highly efficient repair systems to keep these double-strand DNA breaks in check.

The most common repair mechanism is nonhomologous end joining, which reattaches broken DNA strands with minimal processing and without regard to missing nucleotides. The other repair mechanism, which is less error-prone, is homologous recombination, in which a single-strand overhang invades a similar or identical strand from a sister chromatid and uses it as a template to repair breaks. This repair process is the focus of a recent minireview published in the **Journal of Biological Chemistry**.

“The repair of DNA double-strand breaks by homologous recombination commences by nucleolytic degradation of the 5'-terminated strand of the DNA break,” which results in 3'-overhangs, explains author Petr Cejka at the University of Zurich.

In the yeast *Saccharomyces cerevisiae*, end resection has two steps

The first step depends on a complex of three proteins — a nuclease, Mre11; an ATPase, Rad50; and an associated protein, Xrs2 — together termed the MRX complex. Mre11 has both an endonuclease and 3'→5' exonuclease activity.



DNA end resection is required for all recombination processes. The resection of the 5'-terminated DNA strand is required for all recombination pathways, including the SSA, synthesis-dependent strand annealing, and canonical double-strand break repair pathways. DNA end resection prevents mutagenic NHEJ. Microhomology mediated end-joining was omitted from the scheme and text for simplicity.

Based on various biochemical and genetic studies, the author is in support of a short-range bidirectional resection model. He writes: “(U)pon the initial endonuclease cleavage, the Mre11 exonuclease proceeds back towards the DNA end via its 3'→5' exonuclease activity.” This would explain how MRX is able to resect DNA with secondary structures or proteins dangling on their sides and obstructing exonucleases. “The endonuclease cut can create an entry point for long-range resection enzymes,” Cejka writes.

The second step is carried out by either the helicase/nuclease activity of Sgs1–Dna2 enzymes or the nuclease activity of Exo1 enzyme, which advances the process by resecting long stretches of DNA. The Sgs1–Dna2 tag team unwinds dsDNA in the 3'→5' direction using Sgs1 helicase, while Dna2 nuclease loads onto the other strand in the 5'→3' direction and

resects ssDNA. Exo1, however, does not have to pair up with a helicase. It can degrade directly the 5'-terminated end within dsDNA.

The author also highlights the regulation of the resection process by phosphorylation of the Sae2 protein, which in turn activates Mre11. This control mechanism is carried out by cell-cycle protein kinase CDK (Cdc28) to ensure DNA is resected only in the S/G2 phase of the cycle where homologous template is available and also by DNA-damage checkpoint proteins in response to breaks. This is how cells decide if DNA resection would be a viable option, and then the “nucleases team up with the right partners to initiate (homologous recombination),” writes Cejka.



Aurelia Syngkon (aurelia.syngkon@gmail.com) is a biotechnologist and a former postdoctoral research fellow in the biochemistry and pharmacology department at New York University.

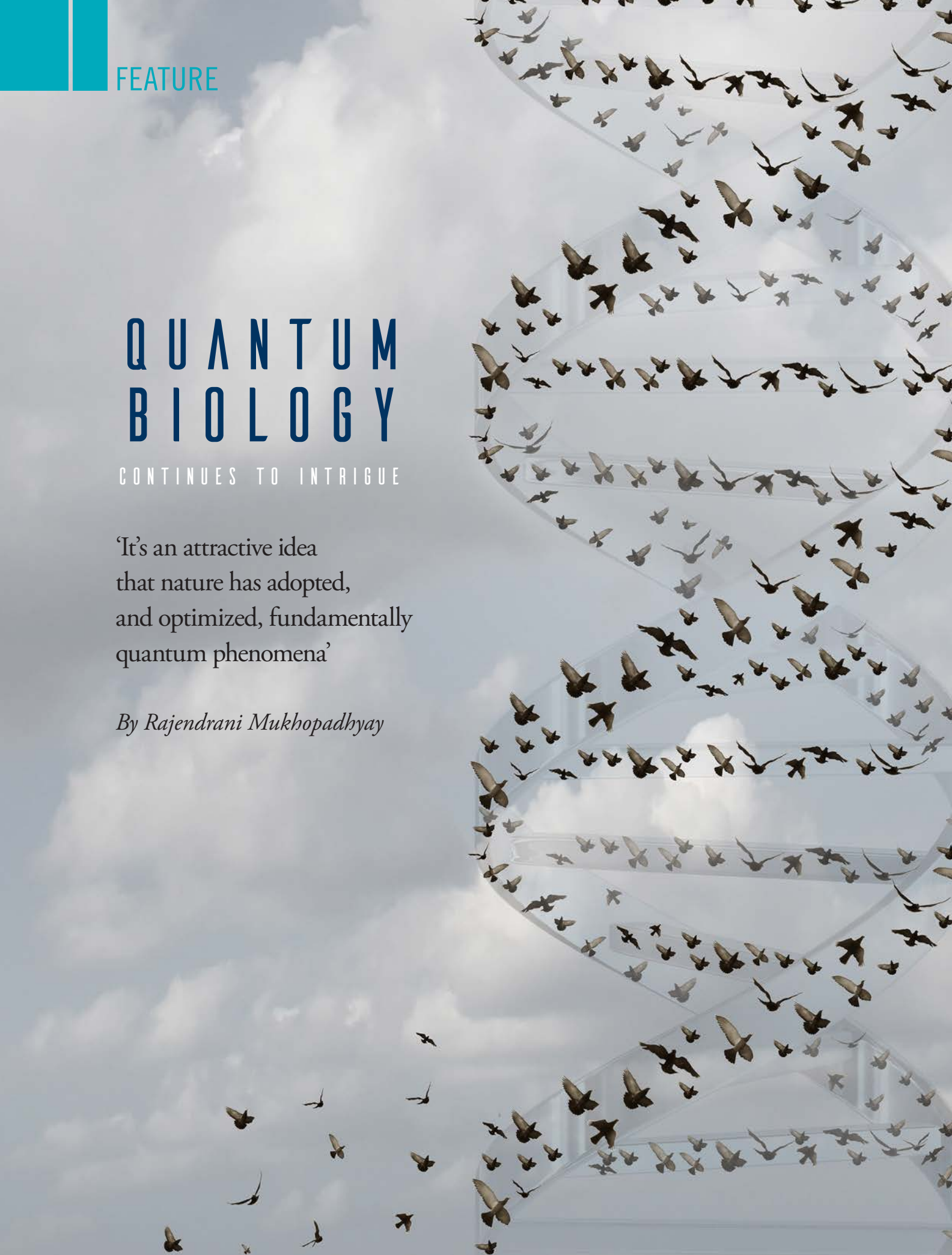
FEATURE

QUANTUM BIOLOGY

CONTINUES TO INTRIGUE

‘It’s an attractive idea
that nature has adopted,
and optimized, fundamentally
quantum phenomena’

By Rajendrani Mukhopadhyay



What if you were told that a single proton or electron can influence the behavior of an entire biological molecule? Would you snort with derision or give the idea some serious thought?

The loosely defined field of quantum biology, which is permeated in equal parts by speculation, skepticism and unbridled excitement, looks to that strange realm of physics called quantum mechanics where energy starts acting funny. Researchers working in this niche are asking if some critical biochemical reactions rely on the split personality of energy as waves and particles.

Superficially speaking, quantum mechanics pervades all chemical reactions including ones in the specialized collection called life. “If you delve into chemistry deep enough, you inevitably come across quantum mechanics, in the sense that the orbital structure of atoms is based on quantum mechanics,” says Johnjo McFadden at the University of Surrey in the U.K. So, in a sense, he adds, “quantum mechanics is everywhere.”

Quantum effects tend to fade at the level of whole atoms and molecules. At this level, classical mechanics, the realm of forces laid out by Isaac Newton and others, begins to dictate the movements of objects. Quantum mechanics also is thought to be most noticeable at temperatures close to absolute zero. The general thinking goes that there is no way quantum effects could persist at the relatively balmy temperatures of life.

But what if — just what if — they did?

A pressing problem with the field of quantum biology is the inability to test and prove unequivocally many of the ideas within its purview. For that reason, even the most ardent supporters of quantum biology are its biggest skeptics. “I’m always the biggest critic as well as a fan,” says Greg Scholes of Princeton University, who is studying quantum effects in photosynthesis.

Jim Al-Khalili at the University of Surrey, who has gone as far as giving a TED talk and co-writing a book with McFadden on quantum biology called “Life on the Edge,” says that the field needs to be treated with caution. “We have to be skeptical,” he says.

Quantum mechanics brushes against genetics

The concept of quantum biology first arose in the late 1920s. Quantum physics was in its heyday after the discovery that particles existed as discrete packets of energy that could act like waves. The word “quantum” refers to those wave-particle packets of energy.

When quantum physicists established the mathematical basis for quantum mechanics in the early 20th century, they “strode out of their labs around Europe, arrogantly looking around for other problems to solve,” says Al-Khalili. “The biologists looked like they needed some help — they couldn’t understand what a gene was.”

At this time, biologists were wrestling with understanding what a gene was made of, how it functioned and how it propagated from one generation to the next. It was natural for scientists to wonder if genetics at the atomic level could be explained by quantum phenomena. After all, certain areas of physics and chemistry, such as condensed-matter physics and computational chemistry, make sense only in view of quantum mechanics. Why would biology be different?

Physicists who pondered the atomic and molecular processes of life included Max Delbrück and Erwin Schrödinger. Delbrück was an author on a paper that considered the effects of ionizing radiation on genetic matter. That paper, “On the nature of gene mutation and gene structure,” inspired Schrödinger’s book “What is Life?” The book devoted much attention to quantum effects in biology, with Schrödinger postulating how

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order at the level of the hereditary material could lead to order on the organismal level.

“What is Life?” is said to have motivated James Watson and Francis Crick to think about the structure of DNA. In 1953, Watson and Crick published the double-helix structure. “What came thereafter was that there was this strong sense that quantum mechanics was no longer needed in biology,” says Al-Khalili. “Molecular biology was doing very well without quantum mechanics, thank you very much.”

The notion that quantum effects may play important roles in molecular biology went out of fashion. But beginning in the 1970s, quantum effects started to be considered again in disparate subject areas: Do quantum phenomena occur when some species of birds migrate? Are they present during the first stages of photosynthesis? Do they influence enzyme catalysis?

Biological relevance

What makes quantum biology of today different from the science of yesterday is that researchers are designing experiments and developing theoretical models based on experimental data. As Alexandra Olaya-Castro at the University College London says, quantum biology is “now driven by experiments.”

But hesitation abounds in calling quantum biology an actual field of study, even among the scientists who work on quantum phenomena in various biological processes. “I’m not sure about calling it quantum biology. It’s clearly in vogue at the moment,” says Peter Hore at the University of Oxford in the U.K., who is interested in understanding the molecular mechanism by which migratory birds sense Earth’s magnetic field. “It’s an attractive idea that nature has adopted, and optimized, fundamentally quantum phenomena for its own purposes.”

But, he adds, “my sense is that it has really not (been) established yet that any of these phenomena are genuinely quantum mechanical.”

Much of the skepticism is rooted in the fact that quantum mechanical experiments are hard to do. Typical experimental conditions in quantum mechanics are near absolute zero, under vacuum and vibrationally isolated — hardly physiological. Biochemical analyses are another ball of wax. Measuring quantum phenomena in molecular biology can be an artful arrangement of experimental compromises. But then the problem becomes proving that the quantum effects being measured in experimental systems actually happen in the real world. It’s challenging to show unambiguously quantum effects in biological experiments.

And then comes the question of relevance — are quantum phenomena making a difference in biochemical processes, or can they simply occur without having any meaningful effects? The very fact that most molecular biologists and biochemists don’t contemplate quantum mechanics in their line of work says something. “Right now, biologists don’t care” about quantum mechanics, says Scholes. “We have to listen to that. It means we haven’t proven biological relevance.”

The poster children

So far, researchers have demonstrated quantum effects most clearly in enzyme catalysis and photosynthesis. Both areas are most advanced in their experimental data and theoretical underpinnings. Another line of work is avian migration; the centuries-old question of how migratory birds navigate from one part of the globe to another continues to dog researchers.

Enzymes. Judith Klinman at the University of California, Berkeley, has been studying quantum effects in enzyme catalysis since the late 1980s.

She seems surprised that her body of work is held up as one of the prime examples of quantum biology. “I never thought it would be called a field,” she says.

Over the years, Klinman’s group and collaborators have shown that hydrogen tunneling occurs in enzymes. The fact that electrons can tunnel, which means to cut across an energy barrier instead of going over it, is undisputed. Hydrogen tunneling is another matter. Hydrogen is 2,000 times heavier than an electron. It wasn’t clear, when Klinman and her team began looking at isotope effects in enzymatic reactions in the late 1980s, that this heavy entity had that requisite quantum duality of wave and particle.

But in doing the kinetic isotopic effect experiments with enzymes such as alcohol dehydrogenase and soybean lipoxygenase for more than two decades, Klinman and colleagues showed that hydrogen tunneling was occurring in biological molecules at room temperature. The experiments involved replacing hydrogen with its heavier isotopic counterpart deuterium and measuring how the catalytic pace of the enzyme changed.

Initially, Klinman says, the data suggested that a simple tweak to an existing theory based on semiclassical mechanics would explain what was going on. But as more data accumulated, it became obvious the tweak wouldn’t suffice. A new explanation was needed. “I didn’t really believe it at first,” says Klinman, recalling her reaction when she first had to consider that quantum mechanical behavior was occurring.

That new explanation was that a hydrogen, like an electron, was cutting through an energy barrier rather than going over the hump. New data suggest motions of the enzyme are critical for the quantum phenomenon to occur. The motions of the enzyme bring two sites, the acceptor and donor that are needed for the reaction

to take place, very close together — so close that the hydrogen can move like a wave to get from one site to another.

The emerging picture is a “very different view of catalysis,” says Klinman. “The role of the whole protein, through these fluctuating conformations, is to bring things so close that quantum mechanics starts to take over, even at room temperature.”

Photosynthesis. A longstanding question in biology is how the energy from sunlight gets transferred through chlorophyll molecules to the photosynthetic reaction centers with nearly 100 percent efficiency and within picoseconds.

In 2007, Graham Fleming’s group at Berkeley published a paper that suggested a role for quantum mechanics in photosynthesis. They described their analysis of the Fenna–Matthews–Olson complex. The FMO complex appears in green sulfur bacteria that live in the Black Sea and other sulfide-rich waters. The FMO complex contains a type of chlorophyll, a class of molecules that can absorb photons and transfer the electronic excitations, which are created during the absorption process, to the reaction center of the photosynthetic apparatus. These electronic excitations are quantum mechanical entities called excitons.

The investigators used an ultrafast spectroscopic technique that allowed them to study the complex. In analyzing the data, “we saw a long-lived oscillatory signal that was lasting far longer than we would have expected,” says Greg Engel, who was the first author on the paper as a postdoctoral fellow working with Fleming. “It was lasting, interestingly, on the timescale of the energy transfer times in these complexes.”

The collective electronic excitations of interacting chlorophylls were thought to cause the oscillatory signal. How the oscillatory signal came about became a pressing question in the



Researchers are trying to determine if quantum phenomena are present during the first stages of photosynthesis.

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European robins navigate during migration using magnetoreception.

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field. But after years of debate, says Olaya–Castro, a quantum phenomenon was the answer. The data suggested that the energy was traveling by multiple routes in the chlorophyll molecules simultaneously, all within a couple of picoseconds.

McFadden uses a traffic jam to explain the quantum phenomenon: “You can go one way or another way to escape the traffic jam. But you never know, once you’ve taken one route, whether the other route would have been better. But for the energy in photosynthesis, it travels through all routes and then crashes down on the one that works out the best.”

A criticism of the 2007 observation was that the isolated FMO complexes were analyzed at -196°C , a temperature far from being physiologically relevant. In 2009, the group of Ian Mercer at University College Dublin reported similar observations at ambient temperatures with the light-harvesting complex II of a photosynthetic bacterium. In 2010, Scholes’ group demonstrated the phenomenon in aquatic algae, and Engel, now an independent investigator at the University of Chicago, repeated the FMO experiments at higher temperatures. The observation has been extended beyond bacteria and algae to protein complexes in spinach.

As more research has gone into the mechanism of excitation transfer within chlorophyll molecules, it’s becoming apparent, as it has for enzyme catalysis, that specific motions of the pigment are critical for allowing the quantum phenomenon to occur. “Normally in biology, you focus on the paradigm of structure–function, but these observations are adding an element to that paradigm that should be structure–dynamics–function,” notes Olaya–Castro.

However, researchers still feel they are not getting a proper look at the mechanism of excitation transport.

“What we need is to develop new kinds of measurements,” says Scholes. The kind of new measurements he’s thinking of will allow researchers actually to see the energy moving through the chlorophyll molecules to the reaction centers.

But that’s easier said than done. “We lose so much information as complexity scales,” says Scholes. “That’s one of the issues here. We can do these pretty deep analyses and incisive experiments on these isolated light-harvesting complexes, but what happens when you have 100 of them working together in an organism which has other things to worry about as well?”

Avian magnetoreception. Before the onset of winter every year, European robins make their way from Scandinavia to the Mediterranean or North Africa. Since the 19th century, zoologists have wondered if migratory birds follow the Earth’s magnetic field. It wasn’t until 1976, with work done by the husband–wife team of Wolfgang and Roswitha Wiltschko, that the answer became obvious. Yes, birds like the European robins navigate by magnetoreception, which means by sensing the Earth’s magnetic field. But now the question was how.

In 2000, Klaus Schulten’s group at the University of Illinois Urbana–Champaign proposed that magnetoreception relied on cryptochromes, a class of molecules ubiquitous in many species, as the internal compass in birds.

Cryptochromes are found in the eyes of most animals. Although cryptochromes are implicated in regulating circadian rhythms, Schulten’s group put forward the idea that cryptochromes play a role in photosensitive magnetoreception. Inside the cryptochrome, the authors suggested, there was a coupling between unpaired electron and nuclear spins. The coupling is a quantum phenomenon known as entanglement.

The proposal had a historical



There are hints that cryptochromes in monarch butterflies, which migrate, are sensitive to magnetic effects.

context. Back in the 1970s, Schulten originally had suggested that, in the presence of light, unpaired spins coupled in a way that was sensitive to a magnetic field. The 2000 paper by Schulten's group pinpointed the spins to cryptochromes, which "gave us all a specific molecule to think about," says Hore. (In their book, Al-Khalili and McFadden call that paper "one of the classic papers of quantum biology.")

Since then, there are some hints that cryptochromes in fruit flies and monarch butterflies (like European robins, monarch butterflies also migrate) are sensitive to a magnetic field. For example, in 2008, Steven Reppert's group at the University of Massachusetts published a paper demonstrating that fruit flies missing cryptochromes were insensitive to magnetic field effects.

The question now dogging researchers studying avian magnetoreception is how a single molecule sitting in an animal's eye can sense Earth's very weak magnetic field, do some quantum mechanics and set the animal in the right direction. "Those

are challenging experiments to do," notes Hore, whose group has been working in the area.

Just on the molecular-biology front, "we have no idea about what the environment of these proteins might be inside the cell," says Hore. "We really have no idea about what the binding partners are of the cryptochromes in the context of magnetic sensing. It's almost certain the proteins will have to be immobilized to stop them rotating inside the cell, because if they do rotate then they won't be able to sense the rotation of the magnetic field, merely its presence. That's not enough for a compass."

Then come the issues of proving that the phenomenon actually happens. All molecules possess thermal energy simply because of their random motions. This energy may override weak magnetic effects. Skeptics have pointed out that because the Earth's magnetic field is so weak (refrigerator magnets are stronger than Earth's magnetic field), any interactions of a molecule with the magnetic field

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will get swamped by the molecule's thermal effects.

The answer to the skeptics is timing. "If you manage to do the process fast, before the thermal effects take over, that thermal energy becomes irrelevant," says Schulten.

And then comes the task of proving biological relevance. In nonbiological molecules, quantum entanglement is known to happen. "But the entanglement doesn't give you anything extra," says Hore. The entanglement simply exists. The same may apply to radical pair spins in biological molecules; the quantum entanglement may not exert any effects.

Be skeptical, not dismissive

There are more ideas in quantum biology. Olfaction, the science of how we smell, has been linked to quantum effects. So has consciousness, with proposals that quantum processing of atomic spins may be at the core of consciousness or that voltage-gated ion channels may act as the centers for quantum effects. These areas are surrounded by more skepticism and controversy than the other areas of quantum biology.

Al-Khalili and McFadden are studying whether hydrogen tunneling can cause DNA mutations. The idea goes back to the Swedish physicist Per-Olov Lowdin, who proposed in 1963 that hydrogen tunneling occurs between the paired bases of A, T, G and C, creating tautomers of the nucleotides that then mismatch during DNA replication.

But the experiments, which McFadden's group is now planning, are difficult to interpret. The theoretical modeling by Al-Khalili's group so far has shown that the amount of hydrogen tunneling occurring in DNA is so rare that it's insignificant. Although Al-Khalili's group is going back to the

drawing board to try other theoretical frameworks, "if your results say hydrogen doesn't tunnel across DNA strands, then it doesn't," says Al-Khalili. "You have to live with it. You can't just make stuff up. That's where we are at the moment."

The one thing experts unanimously say is that they need new technologies and methods to delve deeply into the questions being asked about quantum effects in biology. Without having the experiments that unequivocally show that quantum effects are taking place in molecular biology, Olaya-Castro says the field will remain hung up on the question, "Are you sure you're seeing quantum effects?"

"We need to move this field forward to actually say for sure, 'Yes, here is the proof that it is quantum,' so we can move on now to address what is, I think, the most important question: 'What advantage does this bring to biology?'" she says.

But until that happens, the field will be hounded by skepticism. However, skepticism, which the experts welcome because they say it makes for better science, isn't the same thing as outright dismissal. Some experts say their ideas get rejected outright by biologists who have built entire careers without having to ponder the vagaries of the quantum world.

"Quantum mechanics is required to explain so much that underpins physics and chemistry. It's not beyond the bounds of possibility that it can underpin, in a very real and nontrivial way, certain mechanisms and phenomena in biology," says Al-Khalili. "But just because you've not had to learn quantum mechanics and have the headaches of figuring out how a particle can be in two places at once, it doesn't mean quantum mechanics doesn't happen in biology."



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COORDINATES

Those who wish to forge or advance careers in the biosciences frequently chase their dreams across the country and around the globe. The importance of where a student or scientist lands – temporarily or permanently – cannot be understated. The “**Coordinates**” series will consider the influence of place on professional and personal lives.

We welcome submissions of personal essays, short features, interviews, photos, artwork and poetry that:

- chronicle journeys of any length,
- celebrate the curiosities and delights of local people, haunts and fare,
- bring to life the two-body problem that dual-career couples often face (co-authorship is OK),
- examine how where you are or where you came from influences who you are or who you will become, and
- provide practical advice regarding travel and relocation.

Added challenge: Given the significance of coordinates to the study of structural biology, we will give special consideration to submissions that artfully connect the dots between molecular structure and personal coordinates.



TRANSITION STATES

While physical location will anchor the “**Coordinates**” series, the “**Transition States**” series will examine instances when scientists made (or decided to make) career changes. Scientists switch gears every day: They move into or out of academia or industry, abandon bench science, become managers and administrators, gain independence and responsibilities, begin and grow their families, start businesses, create or join nonprofits, enter government service and take on a variety of other roles. This series will scrutinize the many feelings, processes and influences associated with such transitions.

We welcome submissions of personal essays, short features, interviews, photos, artwork and poetry that achieve one or more of the following:

- offer a glimpse the period before, during and/or after a career change,
- counsel those considering career changes,
- describe the emotions and thought processes leading up to and resulting from changes,
- acknowledge unexpected outcomes of upheaval,
- reflect on the role of family when things were in flux, and
- take into account logistical and financial considerations of particular importance.

Guidelines: Written work and art must be unpublished, between **300** and **1,000** words and submitted through asbmbtoday.submittable.com/submit by **Jan. 31, 2016**. Please include a brief cover letter with the title of your piece, complete contact information, a headshot, and an author bio of no more than **100** words.



Exiting the hobbit hole

By Bree Yanagisawa

I'm a pretty big "Lord of the Rings" fan. I read the books for the first time when I was in high school and can still remember sitting in a bedroom in my parents' house, looking out across the front yard, and imagining a vast landscape of trees, mountains and hobbits to rescue.

What I really saw out that bedroom window was the same thing that unfolded every day: my neighbors' house across the street, their trampoline springing as the kids bounced around. I saw my health teacher running down the street and barely registered the all-too-familiar warning barks of my dog as she passed by our front door. Indeed, it would be hard to picture any life more removed from the tumultuous scenes playing out in the pages of those fantastical books than mine.

I grew up in rural Minnesota. The friends and family that were important to me were all within driving distance, and I easily got from my home to town without needing to know a single street name. Nearly all of my life had been spent within a two- or three-hour radius of my parents' house. At the time, I felt little need to venture farther.

My hometown was comfortable. It was safe. It was all I knew. It was my hobbit hole.

And then came my senior year of high school. There were no colleges in the immediate area, but I applied to the schools that were closest, never even bothering to look outside the state. I ended up at a small private college in Minneapolis, about an hour



The author and her husband, David Yanagisawa, in Baltimore.

away from home. As I packed my things and shopped for decorations for my new place, I felt excited. I was finally about to step out my front door and embark on an adventure of my own.

I remember my family moving me into my dorm. My younger sister helping to cart the boxes of belongings from the only home we'd ever known to this new, foreign place. My mom meticulously helping me organize my desk while my dad hung my pictures on my new wall. Everyone gathered before my door to say their goodbyes. Rolling my eyes at the tears running down my mom's face, I assured them all I'd be fine, hugged them and sent them on their way.

But once my classes started my feelings of excitement began giving way to doubt. Some of the people I was meeting disagreed with what I thought, and I found myself having to offer reasons for my beliefs — something, it turns out, I did very badly. I had never before had my beliefs challenged and was at a loss as to how to defend them. I began to question myself deeply. Did I even have reasons for what I thought?

Over the next three months, I spent most of my time isolated in my dorm room. When I was in class, I would scan the hundreds of unfamiliar faces and feel my heart sink. I didn't like the school. No, I hated it. I cherished Fridays, when my dad

would pick me up to go home for the weekend. This place wasn't my home, and it would never be my home.

I was miserable. I wanted nothing more than to pack up my belongings and go back to the place where everything was how I expected and every shared idea aligned with my way of thinking.

But I didn't do it. Somehow, I made it through that first semester. And then you know what? It got better. I made new friends and went to their rooms after classes instead of locking myself in my own. I chose to stay in Minneapolis on weekends instead of returning to my parents' house. I met people from various backgrounds who actually forced me to think about things in a different light. I began to stop seeing different opinions as threats. I slowly came to understand the type of truth these interactions could provide.

I lived in Minneapolis for two years after I graduated, and I loved it. The diversity of people, ideas and options no longer felt like a threat to me. But even as I grew more comfortable in this new life, I knew I wanted to do something other than the technician job that I'd landed. I applied and was accepted into graduate school at Johns Hopkins. I packed up all my belongings again — this time one husband, one dog and one cat heavier — and



The author back in her hometown on her grandparents' lawn with mother Deb Woelfel, father Bob Woelfel, and sister Jenna Woelfel.

drove across the country to my new home of Baltimore.

But when I arrived, I felt myself fall into that all-too-familiar mindset. This place was so different from anything I had experienced. The people thought and acted differently, and the academic environment differed from that of my small college. I thought I had made such progress in Minneapolis, but I panicked again. I felt myself retracing my steps, backing away into the comfort of my hobbit hole.

The panic turned out to be lighter this time and my discomfort more

transient. Instead of hiding away, I felt myself undergoing another personal transformation. These new differences weren't a threat to me; they were an opportunity. Another chance to push myself and challenge my beliefs and shape myself into a more informed person. An opportunity to respond, not with defensiveness and anger, but with empathy and a desire to understand.

Over my past three years in Baltimore, I have learned so many important things about the people around me and, in doing so, about myself. And it's all because I engaged in the very anxiety-inducing interactions that once were so threatening to me.

Differences can be scary. They threaten what we think we know. But learning from others who think differently from you is not only a useful path to take; it's a necessary one. Too often we are allowed to remain safe in our own hobbit hole, surrounded only by our own beliefs. My advice? Break out of that place, step out your front door onto a new path and don't ever stop walking. Maybe I'll see you out there.



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Research spotlight

A Q&A with Vimbai Chikwana of Dow AgroSciences

By Andrew Macintyre

Tell us about your current career position.

I have been working as a research biochemist since August 2014 at Dow AgroSciences, a company that discovers, develops and brings to market crop protection and plant biotechnology solutions for the growing world. I am part of a team that is dedicated to increasing crop yield through targeted pest management control.

What are the key experiences and decisions that have enabled you to reach your current position?

I never considered pursuing a research career, because there were no role models for me when I was thinking of what I might do with my life. For my undergraduate degree, I only joined a research lab because it was a requirement to graduate with honors. I chose to join a lab that worked on drug metabolism at the University of Zimbabwe under the supervision of Stanley Mukanganyama. I was completely transformed by the end of my final year performing research; I not only thoroughly enjoyed learning how to plan and design experiments but also realized that the discovery process was extremely fulfilling.

I was admitted to Portland State University for graduate school, where I joined a biochemistry lab focused on unveiling the enzymatic mechanisms involved in tRNA modification under the supervision of Dirk Iwata-Reuyl. In graduate school, I grew

significantly as a scientist through the numerous challenges I encountered. Toward the end of my graduate school work, in collaboration with Manal Swairjo's lab at Western University of Health Sciences, we solved the crystal structure for one of the proteins I was working on. I enjoyed probing the protein structure–function relationship so much that I looked for a structural biology lab for my postdoctoral work. As a postdoctoral fellow under the mentorship of Tom Hurley at Indiana University School of Medicine, I was able to pursue mechanistic enzymology and some structural biology.

My current research utilizes technical skills and training acquired in these three labs.

What skills did you learn during your scientific training that prepared you for your current role?

The broad-based scientific knowledge I acquired during my training via coursework, mentoring and performing research was critical for me to get hired into my current position. Having an analytical approach to outlining scientific questions, designing impactful experiments, and being able to objectively interpret and analyze data are also important skills. Teamwork is important, as most scientific projects require multidisciplinary approaches to support or disprove testable hypotheses. Last but not least, keeping up with scientific literature — critically evaluating it as well as keeping up with new, emerg-

ing techniques that can shed light on previously inaccessible information — is critical to stay ahead in science.

What is the biggest challenge that you have faced in pursuing your career? What have you done to overcome it?

The biggest challenge that I am still faced with is accepting that experiments fail more often than I want them to and that this is simply a fact of pursuing scientific research. It's important to remember that nobody knows the outcome of an experiment; if the result is 100 percent certain, then there is a chance the experiment has already been performed; repeating it is generally not as challenging or intellectually satisfying. Working in discovery-based science is exciting because we work at the edge of knowledge, and recognizing that most of the reward comes from the journey of discovery is an important element of research.

What advice would you give to young people who want to pursue a career similar to yours?

Be flexible and always be willing to learn. Research projects will come and go, but the techniques and what you learn along the way will stay with you. No person is an island. Projects that are impactful tend to be large and require a number of people with diverse skill sets to move them

forward, so try to collaborate as much as possible because science is quite social in this regard. Be nice to people not only because this is the right thing to do but also because you never know when someone will have something that you want or need. Try to always remember the bigger picture and let that guide you in your experimental design. Set goals, as these will help to keep you on track. Aim to design experiments that will advance the project regardless of whether the outcome is positive or negative. Never stop asking questions: Why is this experiment important? Who cares about the result? Is it of any benefit? While you might not have all the answers, it's still important to keep asking questions. Lastly, and possibly most importantly, enjoy your work, because when you love what you do it never feels like you are working.

What can young scientists do to learn more about careers in your field?

I think it is important for aspiring young scientists to seek opportunities to perform research from an early age. There are a lot of opportunities in colleges and universities for research, and they need to take the time to seek these and learn about the numerous fields that await them. For those already involved in research, I cannot over-emphasize the importance of networking and attending conferences. Get a mentor, someone who wants you to succeed in the competitive field of science who will push you to reach your full potential.

What are your hobbies?

I love to ride my bike and jog. I enjoy the solitude I get from both activities. It gives me time to organize



Vimbai Chikwana

my thoughts and plan ahead without distractions. I also enjoy hiking, travelling and gardening.

What was the last book you read?

"Please Understand Me: Character & Temperament Types" by David Keirsey and Marilyn M. Bates.

Do you have any heroes, heroines, mentors or role models? If so, describe how they have influenced you.

My research supervisors all taught me something valuable that has shaped me into the scientist that I am today, in addition to the technical skills. If I had to name some attributes from each one, this is what stands out for me: Mukanganyama inspired me by his excitement and passion for science; he set the path for my career. Iwata-Reuyl — I learned perseverance in his lab; there is always a way to find answers to challenging questions. I also learned to be very critical of not

only my work but of my peers too. Dr. Hurley — patience; in a crystallography lab, there is no such thing as instant gratification.

Lastly, Grete Waitz, the Norwegian school teacher who won more New York City Marathons than anyone else — her humility and athleticism made her a role model for young runners and women. She was a pioneer; at the time of her first New York victory in 1978, just 10.5 percent of entrants were women. In 2010, 36 percent of entrants were women. Waitz taught me that the road less travelled is a difficult one but that no obstacle is too great if one perseveres.

What is it that keeps you motivated?

I am part of a company that is working toward making agricultural practices more sustainable. Through increasing crop yield, we can enable farmers to better feed the ever-growing world population, projected to grow up to 9 billion by 2050. As land resources become ever more limited, there is a greater need to increase food production on the viable agricultural land that is available. In economics they call it supply and demand — if we do not increase food production as demand goes up, then food is going to become very expensive. Not all countries have the resources to continue making enough affordable food for their people using traditional farming practices. I am in a position to make a positive impact and find solutions to the food problem, which keeps me motivated.



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Continuity and expansion for minority affairs

By Marion Sewer

In 2015, the American Society for Biochemistry and Molecular Biology's Minority Affairs Committee continued its work to diversify the scientific workforce and spearhead new initiatives that promote inclusivity, engage and expand membership, and offer career development and outreach opportunities.



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MAC members Marion Sewer and Takita Sumter, with Ruth Kirchstein Diversity Award winner JoAnn Trejo at the 2015 ASBMB annual meeting.

2015

At the 2015 ASBMB annual meeting, the MAC sponsored sessions that targeted constituents at various stages of career development. We held symposia linking the gut microbiome to health disparities; spotlighted the FASEB Minority Access to Research Careers graduate student travel award winners at the MAC networking reception; and offered professor rounds, a mentoring program that paired the travel award winners with mentors offering career advice and guidance on navigating the meeting.

Also at the meeting, JoAnn Trejo, a professor of pharmacology at the University of California, San Diego, received the 2015 Ruth Kirschstein Diversity Award, which recognized

her efforts to increase diversity of the professoriate.

The MAC's Grant Writing and Mentoring Workshop continued to be a valuable opportunity for junior faculty members and postdocs who are seeking extramural funding for independent research. The 2015 workshop featured peer mentoring by previous workshop attendees, presentations by representatives from the National Institutes of Health and the National Science Foundation, and discussions by an experienced group of ASBMB members committed to mentoring and offering constructive feedback on applications.

During the year, the MAC established the Distinguished Undergraduate Scholarship, which supports

students who are interested in biochemistry and molecular biology and in diversifying STEM disciplines. Five students from universities across the country were awarded \$2,000 each to help defray the continually mounting costs of their education.

The MAC and the ASBMB's Student Chapters Steering Committee also aligned in 2015 to help existing ASBMB Student Chapters partner with minority-serving institutions and bolster participation in the society. The MAC joined forces with the Public Outreach and Education and Professional Development Committees to run ASBMB's Hands-on Opportunities to Promote Engagement in Science program, a platform for immersing budding K – 12 scien-

tists in research through neighboring universities.

2016

Looking forward to 2016, the MAC will continue its collaborations with the ASBMB's Student Chapters and Public Outreach committees with an eye to expanding initiatives. We also are excited in particular about developing a workshop that will target graduate students and postdoctoral scientists interested in careers that are not research intensive. Coined "Beyond the Bench," this initiative grew out of the realization that most trainees matriculate into careers outside the realm of faculty positions at large research institutions. These

careers include teaching, science policy, science communication and outreach. The workshop will help participants develop and refine individual development plans tailored to their career goals, get real-time feedback on key job application components and establish a network of mentors who are more closely aligned with their desired future positions.

The MAC will hold its Grant Writing and Mentoring Workshop in the summer of 2016 and continue to extend the one-on-one mentoring begun during the workshop throughout each participant's grant-writing and submission processes. A Web-based forum also is being developed so workshop participants can continue to exchange best practices for proposal

preparation, strategies for training and mentoring students and postdocs, and career development advice.

Finally, a series of MAC-sponsored symposia at the 2016 ASBMB Annual Meeting will provide an update on novel research being carried out on nonalcoholic fatty liver disease and explore why minorities disproportionately opt out of academic careers.

Keep an eye on the ASBMB website and ASBMB Today for more about all of the MAC's exciting 2016 initiatives. We welcome your participation and support for these efforts!



Marion Sewer (msewer@ucsd.edu) is a professor at the Skaggs School of Pharmacy and Pharmaceutical Sciences at the University of California, San Diego.



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Why should you be an ASBMB Student Chapters adviser?

By Ann Aguanno & Andrea Anastasio

Initiated in 2000 by J. Ellis Bell, who is at the University of San Diego and the University of Richmond, the American Society for Biochemistry and Molecular Biology Student Chapters program now boasts 110 chapters and 2,000 student members. Formerly known as the ASBMB Undergraduate Affiliate Network, the Student Chapters program is an ever-growing community dedicated to supporting undergraduate BMB research, education and outreach. It also provides an active network for its 200 associated faculty advisers.

Who are the ASBMB Student Chapters advisers?

Student Chapters faculty advisers work at more than 100 different colleges and universities across the U.S. and Puerto Rico. They are faculty members at small private colleges and large research universities. Their student clubs are independently established or built around existing clubs and range from BMB-focused groups to amalgams of biology and chemistry clubs. Although many advisers are junior faculty, a large number are tenured, senior faculty.

What do the chapters do?

Chapters meet regularly, giving students a chance to support each other's academic progress and work on chapter events. Each chapter elects leaders, and the ASBMB offers an

array of resources for chapters and their leaders, including support for travel to the annual meeting and help organizing regional conferences, conducting outreach and participating in science fairs. The society also presents an Outstanding Chapter award each year and inducts exceptional chapter members in Chi Omega Lambda, the ASBMB Honor Society.

Guiding tomorrow's scientists

The primary role of faculty chapter advisers is to guide the club members. Clubs vary in size from just a few members to 50 students or more, and, although each club is coordinated by the elected officers, the faculty adviser mentors the club in a variety of ways. Advisers may help plan events, recommend outreach activities, or consult on submissions of abstracts and the assembly of posters. They also mentor students on job and graduate school applications, interviews and the ASBMB accreditation exams.

Jeff Boles is an adviser for the club at Tennessee Tech in Cookeville, Tenn. He says the role is an opportunity to help students "become excellent leaders and explore new opportunities such as research." Boles adds, "I don't run their club — they run their club and I truly advise. If they get into trouble, I bail them out. That's happened a time or two over the years. That's active learning, for sure ... I enjoy being their adviser as I get to watch them grow in more ways than factual knowledge."

Serving the students, college and profession

Co-curricular activities teach students in many ways, and a student chapter is no exception.

John Tansey, chapter adviser at Otterbein University in Westerville, Ohio, says, "Being a chapter adviser gives me a closer interaction with the students in the major who are not in my classes or research lab ... (and it) gives us a structure through which we can conduct cocurricular activities that address many learning outcomes that may not otherwise fit into the curriculum such as outreach, teamwork and leadership."

Student chapters also strive to meet the mission of the ASBMB Student Chapters organization by supporting the research and educational efforts of chapter members, the institution at large and the scientific community. Outreach activities also extend this mission beyond the institution, raising awareness about science to the general public.

Professional development and networking

As a member of the ASBMB Student Chapters, the faculty adviser has access to networking and professional development opportunities. A reception for advisers is held each year at the ASBMB annual meeting, where faculty from across the Student Chapters organization meet, exchange ideas and develop relationships. Fund-



ACTIONFOTO CONVENTION PHOTOGRAPHY

Otterbein University Student Chapter faculty adviser John Tansey, far right, and his students at the 2014 ASBMB Annual Meeting. The Otterbein chapter won the ASBMB's Outstanding Chapter award in 2014.

ing and guided support for regional undergraduate research conferences helps advisers learn how to organize symposia, hone their mentorship skills and build collaborations with other faculty members. Participation in the varied educational and professional-development initiatives supported by the ASBMB (e.g., regional educational conferences, special symposia and grant-writing workshops) provides additional venues for faculty members to interact and opportunities for them to grow.

The role of chapter adviser itself fosters faculty development. Guiding students in educational and outreach activities and in the process of science

builds mentorship skills; hones time management, organizational and communication abilities; and provides an intellectual challenge.

Kirsten Fertuck, chapter adviser at Northeastern University, says, "One of the things that I really appreciate about the chapter structure is that it provides clear steps and deadlines associated with professional-development opportunities for both the adviser and the students. We all greatly benefit from having defined periods within the academic calendar in which we are actively discussing outreach projects, regional meetings, the honor society, and the certification exam — it keeps us organized and working toward

common goals!"

Learn more about the ASBMB Student Chapters program. Visit www.asbmb.org/studentchapters and join us at the 2016 ASBMB Annual Meeting Student Chapters informational session on Apr. 4 (www.asbmb.org/meetings/AM2016/undergrads).



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Working at a PUI

Faculty at primarily undergraduate institutions on the demands and rewards of their jobs

By Andrea Anastasio

Primerly undergraduate institutions are often smaller than large research universities, can be private or public, and offer varying levels of resources for students and faculty. Many faculty at PUIs run labs while maintaining significant teaching loads and regular contact with students. We spoke with PUI faculty about how to prepare for a career at a PUI and what to expect once you're in.

Understand the daily expectations



FURGE

Laura Lowe Furge is the Roger F. and Harriet G. Varney Professor of Chemistry at Kalamazoo College, a private

liberal arts college of about 1,400 students in Kalamazoo, Mich. Joining a PUI was the obvious choice for Furge, who is passionate about working with students. At Kalamazoo, Furge carries a full teaching load and runs a research lab, and her days are packed with answering emails, preparing for classes or the lab, meeting with students, completing departmental tasks, grading exams and planning ahead to the next work day. Because she is at a smaller school, Furge also finds herself teaching classes that are not always in her typical comfort zone. In addition to her biochemistry lecture and labs, she has taught organic chemistry lecture and labs, general chemistry classes and even a writing-intensive

course on cancer for first-year students, which has become one of her favorite courses.

In addition to these responsibilities, Furge's work in the lab also comes with significant mentoring responsibilities. "The instructor, not the lab manager or senior lab technician, serves as the 'continuity of knowledge' from one generation of undergraduate in the lab to the next," Furge says.

In Furge's experience, part of teaching at PUIs is offering consistent, hands-on guidance. It is not enough just to pose a scientific question; PUI faculty also must be ready to guide undergraduates in many aspects of answering the question. Each new group will need to learn how to keep a lab notebook, handle reagents, clean up, analyze data and use equipment. This requires patience from instructors and a desire to see students embrace the entire research process.

Find balance



CHASE

Mich., with a student-to-faculty ratio of 13 to 1. For Chase, teaching and managing a research lab are interconnected. After being in the job for 15 years, she says any balance between teaching and research is a "moving target." Chase says the work requires a talent for triaging, like having to

prioritize the development of a new course that is going to take time away from a basket of other duties.

According to Chase, PUI faculty must be adaptable to change. Each semester will bring new teaching schedules, research responsibilities and departmental duties that also must be balanced with a personal schedule. The challenge of finding enough time for everything can be stressful, and Chase recommends picking a different goal to focus on each semester. She says this helps to stave off feeling overwhelmed. "(Balance) may look different from semester to semester," Chase says. "If I approach my job with that attitude, I am inherently happier and less stressed about making sure that I am spending enough time in each role."

Become a mentor

PUI faculty play a strong mentoring role in students' lives, and it is often the direct interaction with undergraduates that has driven faculty to choose and keep careers at PUIs. "(Students') excitement and enthusiasm is refreshing," Furge says, when asked to describe her favorite part of the job. "It's a fun change after struggling with issues like where to put the electrical outlets in the chemistry laboratory remodel!"

Mentoring PUI students means providing guidance on questions ranging from how to finish homework to which career path to pursue. It also requires a grounding in topics other than science. Students engage with

more than just the science department while on campus, and PUI faculty need to provide them with opportunities and networking outside of science. There will be some students who decide the sciences are not for them, and part of mentoring will become helping them find courses or majors better suited to their wants and skills. All of this means engaging across departments and supporting students in balancing all of their academic responsibilities.

Faculty need mentors too



BAIRD

Teaster Baird Jr. is an associate professor in the chemistry and biochemistry department at San Francisco State University, a large public university of around 30,000 students. He advises those interested in becoming PUI faculty members proactively to seek out mentors who can guide them through the process. "A lot of the skills and knowledge that a faculty member needs are not taught in graduate school or at the postdoc level," says Baird. "These skills include managing people and personalities; determining what 'urgent' things can actually wait; navigating the politics of the department, college and university; and how to establish relationships with funding agencies."

For more information about interviewing or preparing for a job at a PUI, check out Joseph Provost's article series from the ASBMB's Student Chapters blog, *The Substrate*: <http://bit.ly/1NLU2cg>

Think like an undergraduate

Baird says it is also important that PUI faculty understand their audience so they can develop relevant and appropriate teaching methods. "After spending so much time in research-intensive environments, it can be easy to forget what it's like to be an undergraduate," he says.

Preparing to teach at a PUI can mean contacting a local community college and becoming an adjunct faculty member to gain teaching experience. Or it can mean taking those teaching assistant positions while still in school and searching for professional development sessions at conferences like the American Society for Biochemistry and Molecular Biology annual meeting.

Know your environment

PUIs vary in terms of funding, resources and academic requirements. Faculty need to be sure that undergraduates can be active participants

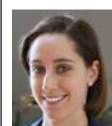
in any research programs they might develop. Programs requiring specific, well-developed areas of knowledge may not be feasible at PUIs, and expensive equipment may be beyond the budgets of many PUIs. Unlike larger schools, some PUIs may also not have lab animals. Faculty need to be resourceful when planning research and sometimes find they must rely on collaborations with other institutions and faculty.

Get excited



PROVOST

PUI faculty members stand a good chance of making a difference in the lives of students. It is a demanding, deeply rewarding job for those who are passionate about teaching. "I never go home bored or wishing I could do something different," says Joseph Provost, a professor in the chemistry and biochemistry department at the University of San Diego. "Every day is different. Every day. And that is exciting."

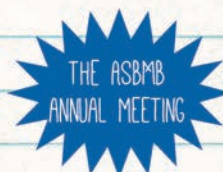


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