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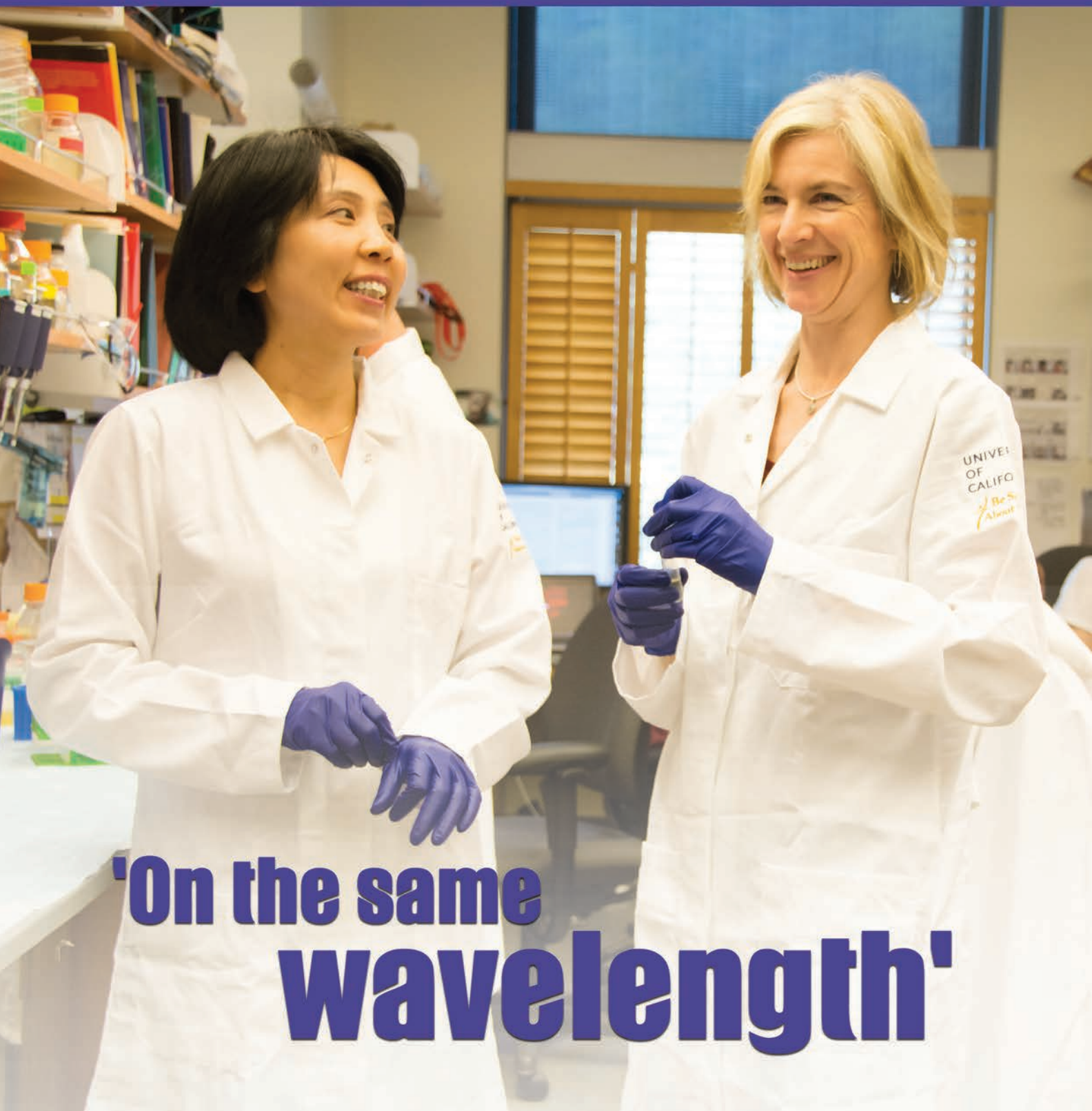
ASBMB TODAY

THE MEMBER MAGAZINE OF THE AMERICAN SOCIETY FOR BIOCHEMISTRY AND MOLECULAR BIOLOGY



'On the same wavelength'

2015 CALLS FOR SUBMISSIONS

HOBBIES

We know that a life in science can be grueling. We also know that some of you have very interesting or unusual ways of blowing off steam or finding your Zen. We would like to feature your essays, poems, artwork or multimedia reflecting on scientists' pastimes. We welcome all creative interpretations of the theme. You could send us a photo of you shooting hoops or jumping out of an airplane. You could send us a video of you jamming with your band. You could send us a poem about a childhood hobby or otherwise abandoned escapes. You could write about a hobby enjoyed by someone else — perhaps a figure in science history or one of your mentors. And you could send us a rant about how you don't have time for such frivolity.

GENERATIONS

This collection of essays, poems and artwork will explore generations in a very loosely defined way. You might have come from a family of scientists. You might have insights about parenting while doing science. You might have something to say about generations of cell lines or scientific lines of inquiry. You might have a story to tell about a line of researchers mentored by one scientist. Interpret the theme as you will. It is not a boundary but rather a springboard for the making of meaning.

DEADLINES FOR HOBBIES AND GENERATIONS: Dec. 31, 2014.

FORMAT: We'll print some; others, we will post online. Some might appear both in print and online.

SUBMISSIONS: Email (to asbmbtoday@asbmb.org) your manuscripts as Word documents, static images as JPEG or TIFF files (the higher the resolution the better), audio as mp3 or mp4 files, and videos in something like QuickTime, Vimeo or YouTube. Please indicate to which series you are submitting in your email subject line.

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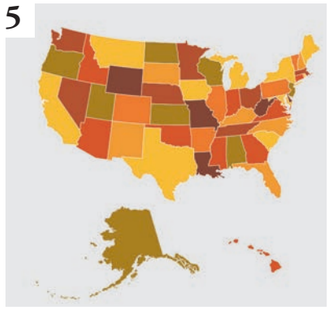

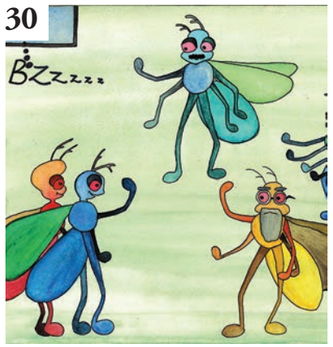

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Science writer Rajendrani Mukhopadhyay writes about Jennifer Doudna's work on CRISPR and her partnership with her lab manager, Kaihong Zhou.

Image courtesy of Cailey Cotner/University of California, Berkeley.

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Down but not out

By Steven McKnight

My colleague George DeMartino at the University of Texas Southwestern Medical Center at Dallas told me a humorous story that indicates the devolved state of our beloved field of biochemistry. George uses biochemical approaches to study the proteasome, including standard methods of protein purification. While interviewing a prospective postdoctoral candidate, George explained how he routinely purifies the proteasome, starting with bovine blood obtained from a local slaughterhouse. As the interview progressed, the applicant lauded George on his ability to study the purified macromolecular machine and stumbled into the telling question of the interview: "That's really cool, but how did you get the His tag into the cow?"

It is the unfortunate case that few of our trainees have any clue about ammonium sulfate cuts, differential centrifugation or column chromatography. Young scientists instead think affinity-precipitation of a tagged, overexpressed protein constitutes "biochemistry."

Few would dispute that our field is out of fashion. What is the in-vogue science that obscures biochemistry like a full eclipse of the sun? Topping the list is the big data science evolving from genomics.

The ever-expanding iterations of -omics research offer limitless access to data. The challenge of gathering fresh data used to be difficult; now it's a piece of cake. I venture to guess that the amount of data gathered and published by the ENCODE consortium last year might, in aggregate, constitute a larger amount of data than what has been accumulated in the entire history of the field of biochemistry.

There are two wonderful things about the gathering of huge data sets. First, it is can't-fail science. If I tell a trainee to immunopurify fragmented chromatin with an antibody to one of our transcription factors and then have our genomics core sequence the precipitated DNA, the experiment will work every time. What a deal it is to carry out fail-safe experiments! Second, the top-tier journals eat this sort of research up as if it were $1,000-per-ounce caviar. Those of us who have stuck with difficult and uncertain biochemical research are viewed as village idiots — how could we be so stupid not to see the light?

My friend Deepak Nijhawan offered a visual correlative of big data science. When we take our kids to a venue offering a variety of arcade games, they gravitate to the game that consists of a claw that can be moved in X, Y and Z dimensions by a joystick. Below the claw lies a carpet of stuffed toys, perhaps including frogs, bunnies, crocodiles and bears. It is so incredibly easy!

Our kids put their quarters in, maneuver the claw and drop it into place to retrieve the exact stuffed animals of their desires. Over time, they learn the hard way that this never works. Indeed, I have never seen it work a single time in my entire life. What a racket — an infinite number of quarters for nothing. Even if the claw wins once in a thousand attempts, the reward is a stuffed animal that may have cost less to produce than the 25-cent price of admission! Just as our kids mindlessly feed the claw, the National Institutes of Health feeds big data science. Time will tell if the investment will pay off.

Here is the idea on big science. Once we gather enough of it, really smart people will be able to extract all of the diamonds of biology. Magically, for example, they will be able to use big data to predict correctly that cells have an enzyme that senses intracellular DNA and then triggers the production of cyclic GAMP, which then activates the STING enzyme to mount an innate immune response. When this happens, we won't need the biochemical skills of James Chen, who painstakingly discovered the aforementioned pathway.

Had we had access to big data science 30 years ago, we would not have needed Tom Cech's chemical and biochemical acumen to discover catalytic RNA. Geez, would life have been simpler! The magic claw of big data science could have seen all of the discoveries of significance and simply plucked them out of the pile of massive data sets.

OK, enough foolishness. There is a place for everything, including big data science. The point I seek to make in this inaugural essay is the simple prediction that, as we peer into the looking glass of the future, Chen- and Cech-like discoveries abound. Not being a gambler, I will not short the stock of big data in anticipation of the bursting of its bubble. On the other hand, given that the market cap of mechanistic biochemistry may be at an all-time low, I could not be more bullish on our stock.

COURTESY OF WIKIMEDIA COMMONS USER NLAN86

A claw crane game in Trouville, France, promises plush unicorns.

Time will tell whether big data science is just a Ponzi scheme or will instead dazzle us with magnificent discoveries. If it does, the reductionist, mechanistic approaches now out of fashion may fade into extinction. I trust that readers will see where my money is: We biochemists are down but not out.

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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PLENARY LECTURER
FRITZ LIPMANN LECTURESHIP
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J. Ellis Bell, *University of Richmond*

ASBMB YOUNG INVESTIGATOR AWARD
Erica Ollmann Saphire,
The Scripps Research Institute

AVANTI AWARD IN LIPIDS
Karen Reue, *David Geffen School of Medicine, University of California, Los Angeles*

MILDRED COHN AWARD IN BIOLOGICAL CHEMISTRY
Judith P. Klinman,
University of California, Berkeley

DELANO AWARD FOR COMPUTATIONAL BIOSCIENCES
Vijay Pande, *Stanford University*

RUTH KIRSCHSTEIN DIVERSITY IN SCIENCE AWARD
JoAnn Trejo,
University of California, San Diego

WILLIAM C. ROSE AWARD
Kathleen Matthews, *Rice University*

WALTER A. SHAW YOUNG INVESTIGATOR AWARD IN LIPID RESEARCH
Britta Brügger, *Heidelberg University*

HERBERT TABOR RESEARCH AWARD
Joan A. Steitz, *Howard Hughes Medical Institute, Yale University*

EARL AND THRESSA STADTMAN DISTINGUISHED SCIENTIST AWARD
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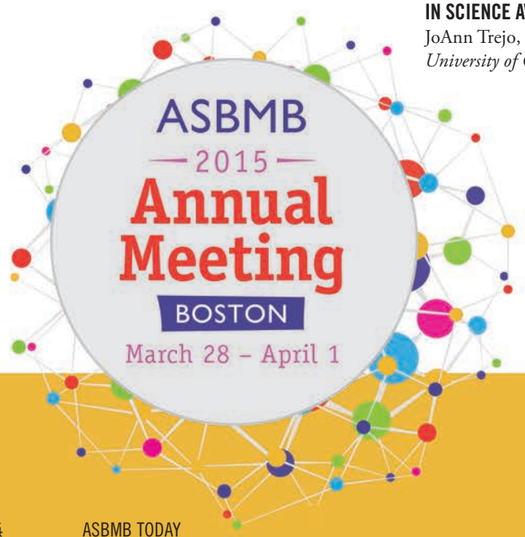
David Eisenberg, *University of California, Los Angeles, Department of Energy*

ALICE AND C.C. WANG AWARD IN MOLECULAR PARASITOLOGY
Alan F. Cowman,
University of Melbourne



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ASBMB
American Society for Biochemistry and Molecular Biology

Water, water everywhere — and not a drop to drink

By Benjamin Corb

In years past, there has been a healthy line of strong voices supporting the research community, and those backers have followed up their talk with action by increasing funding at agencies like the National Institutes of Health.

Take, for instance, Newt Gingrich, the former speaker of the U.S. House of Representatives, and U.S. Rep. John Porter, both Republicans who played essential roles in orchestrating the doubling of the NIH budget in the early 2000s. And then there was U.S. Sen. Arlen Specter, the Republican-turned-Democrat who single-handedly fought for $10 billion in federal stimulus funds for the NIH in 2009. These members of Congress valued federal investment in the research enterprise and provided tangible results that shaped the research community into what it is today.

More recently, however, the bench of real champions for research has grown rather thin.

U.S. Rep. Rosa DeLauro, an outspoken Democrat from Connecticut and a cancer survivor, is among the loudest and strongest NIH supporters on Capitol Hill. Sadly, DeLauro works in the House of Representatives, which has reached a point of near uselessness, as partisan politics and unwillingness to compromise rule the day. Republican U.S. Sen. Jerry Moran from Kansas also has shown sincere interest in supporting funding for the NIH and even has proposed funding increases (heresy to many in his party) but has yet to reach a position of authority to follow his well-intended proposals with results.

The 535 members of Congress represent Americans from all walks of life, and I spend much of my professional life talking with these lawmakers and their staff members about the importance of supporting and funding biomedical research. The more time I spend talking with them, the more I become convinced that biomedical research is just not a priority for them. Certainly, you'd be hard-pressed to find a member of Congress who is against biomedical research or against increasing the NIH budget, but it's a lot harder to find someone actually willing to fight for either. And the reason is simple. They're not hearing from their constituents that research and research funding are important issues worth fighting for.

These observations underscore the need for scientists to build stronger relationships with their elected officials. Why am I putting the onus on scientists? Because you are the constituents! You have the ears of your elected representatives. Whether your representative is giving speeches about immigration reform, fiscal responsibility or anything else, it's because that person's constituents have conveyed the message that those topics are important. And as much as I'd like for members of Congress to follow through on their talk by funding research, it's the scientist-constituents who have to pressure elected representatives into putting their money where their mouths are.

Scientists must help lawmakers understand the importance of funding research not just for America's status in the world but for the health and well-being of their own family members and neighbors. Scientists can no longer be a silent constituency without the time or interest to get involved. Furthermore, science proponents need to be savvier and hold elected officials accountable when their words and actions don't match. If current trends continue, many scientists will have more time on their hands than they know what to do with.

If you want to turn the tide, the American Society for Biochemistry and Molecular Biology can help by informing you of what's happening in Washington or setting up a meeting for you with your elected officials as part of the ASBMB 50-State Challenge. Isn't it time we all move beyond lip service?

How to participate

Do you want to meet with your member of Congress and his or her staff during the summer recess (Aug. 1–Sep. 5)? Register now for the ASBMB 50-State Challenge. More information at www.asbmb.org/50state

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

George Carman of Rutgers University, left, in June gave a Journal of Lipid Research-sponsored lecture at a research conference held by the Federation of American Societies for Experimental Biology. The conference focused on phospholipid cell signaling and metabolism in inflammation and cancer. Carman's lecture was titled "Phosphatidate phosphatase in lipid signaling." JLR co-Editor-in-Chief Edward Dennis, right, presented a plaque to Carman in recognition of the prestigious lectureship.

Plant biologists Siedow and Guilfoyle recognized

SIEDOW

GUILFOYLE

The American Society of Plant Biologists named two members of the American Society for Biochemistry and Molecular Biology as recipients of its 2014 awards, honoring excellence in research, education, outreach and service.

James N. Siedow of Duke University won the Charles Reid Barnes Life Membership Award. The Barnes award is the ASPB's oldest award and was established in 1925 to honor lifelong service in plant biology. Siedow will be recognized and honored for both his stellar research in plant biochemistry and his service to the plant biology community. Siedow has made a large impact in the field of mitochondrial bioenergetics and has been a strong advocate for plant biology research.

Thomas J. Guilfoyle of the University of Missouri won the Lawrence Bogorad Award for Excellence in Plant Biology Research in recognition of his many contributions to plant biology. His work has illuminated new paths of research in plant hormone signaling and has propelled discoveries in plant transcriptional regulation, viral replication and auxin biology. In addition, his dedication and generosity have inspired many plant biologists and students.

Rader named chair of University of Pennsylvania medical school

RADER

Daniel J. Rader, a leader in human genetics of lipoprotein biology and cardiovascular disease, was named the new chair of the Perelman School of Medicine's genetics department at the University of Pennsylvania. He has been at Penn for 20 years and holds multiple leadership roles there. In addition to heading the Division of Translational Medicine and Human Genetics, Rader serves as associate director of the Institute for Translational Medicine and Therapeutics and co-directs the new Penn Medicine BioBank. Rader has had a long interest in Mendelian disorders of lipoprotein metabolism and has a strong translational interest in development of novel therapies for these disorders. Along with numerous awards as a physician-scientist, he has received recognition for his outstanding teaching.

Berkeley Lab's Arkin wins Lawrence Award

ARKIN

Biologist Adam Arkin, director of Berkeley Lab's Physical Biosciences Division, is one of six recipients of the 2013 Ernest Orlando Lawrence Award presented by U.S. Energy Secretary Ernest Moniz. He is recognized as a leading authority on the evolutionary design principles of cellular networks and populations and their application to systems and synthetic biology. The thrust of Arkin's research has focused on developing physical theory, computational tools and experimental approaches for understanding the cellular processes that are critical to life. The goal is to provide a framework that will facilitate the design and engineering of new functions and behaviors in cells through synthetic and systems biology. The Department of Energy's E.O. Lawrence Awards were established in 1959 to honor Ernest Lawrence, the Nobel Prize-winning inventor of the particle accelerator known as the cyclotron. Moniz said that the recipients made significant contributions to the national, economic and energy security of the United States, strengthening U.S. leadership in discovery and innovation. Each recipient will receive a medal and a $20,000 honorarium at a ceremony in Washington, D.C., later this year. *Image courtesy of Peg Skorpinski.*

Neet appointed to FASEB finance committee

NEET

Kenneth Neet recently was appointed to the finance committee of the Federation of American Societies for Experimental Biology. Neet is a professor and the associate dean of research at the Rosalind Franklin University of Medicine and Science in Illinois. Neet, who studies neurobiology, has served on the editorial boards of many science journals and as a member of study sections for the National Institutes of Health and the National Science Foundation. In addition, he served many years as an associate editor for the ASBMB's Journal of Biological Chemistry.

Varshavsky wins Albany Medical Center prize

VARSHAVSKY

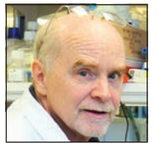
Alexander Varshavsky is the 2014 recipient of the Albany Medical Center Prize in Medicine. The $500,000 award, given annually since 2001, is one of the largest prizes in medicine and science in the United States. Varshavsky is a professor of cell biology at the California Institute of Technology. The focus of his research is the ubiquitin system. He received this award for his landmark discoveries that have transformed our understanding of how cell behavior affects diseases, including cancer, autoimmune disorders and other illnesses.

Lanier made VP for research at Wayne State

LANIER

Stephen M. Lanier has been appointed Wayne State University's vice president for research. Lanier had been the associate provost for research and a professor of cell and molecular pharmacology and experimental therapeutics at the Medical University of South Carolina. Lanier has served on multiple review panels for the National Institutes of Health and has developed a number of collaborative initiatives across departments and colleges. The president of Wayne State, M. Roy Wilson, stated, "We are delighted to welcome Dr. Lanier to Wayne State. He brings a wealth of talent and experience to this position, including extensive experience in technology transfer." Lanier expressed his eagerness to join the institution, saying, "Wayne State University has a number of outstanding, internationally recognized research programs and is playing a critical role in the development of the local and regional community."

O'Shea to receive Ross Prize in Molecular Medicine



O'SHEA

John J. O'Shea, scientific director at the National Institute of Arthritis and Musculoskeletal and Skin Diseases, has been named the 2014 recipient of the Ross Prize in Molecular Medicine. The award, which includes a $50,000 prize from Feinstein Institute board members Robin and Jack Ross, was given on June 9 at the New York Academy of Sciences in Manhattan. The award is given to an active investigator who has produced innovative, paradigm-shifting research that is worthy of significant and broad attention in the field of molecular medicine. O'Shea has been a physician and immunologist at the NIH for 33 years and has made fundamental discoveries related to the signaling of cytokines. His research has focused on the molecular cause of primary immunodeficiencies, inherited conditions in which the immune function is impaired and the genetic basis of autoinflammatory disorders. O'Shea has received numerous awards and is a fellow of the American Association for the Advancement of Science.

IN MEMORIAM: Ivana Weygan–Durasevic

WEYGAN-DURASEVIC

Ivana Weygan–Durasevic passed away April 7 in Zagreb, Republic of Croatia. Born in 1952, Weygan–Durasevic studied chemistry and molecular biology at the University of Zagreb. She joined the university as a faculty member in 1975 and was an internationally recognized expert in the field of tRNA and aminoacyl-tRNA synthases, molecules involved in protein biosynthesis. During her career, she authored more than 70 papers and four book chapters, and in 2005 she received the highly prestigious Croatian National Science Award. Her excellent scientific and teaching career earned her election into the Croatian Academy of Sciences and Arts in 2012. Weygan–Durasevic is remembered by colleagues as a dedicated teacher, supportive mentor, and collaborator for renowned and internationally recognized scientists.

Written by Nicole Parker

‘Nature’s escape artists’

Thematic series explores the various functions and applications of intein-mediated protein splicing

By Jenna Hendershot

Post-translational protein splicing occurs when intervening intein polypeptides excise themselves from larger precursor proteins and ligate their surrounding polypeptides, known as exteins. This is accomplished by a multistep enzymatic reaction mediated by the intein. Sometimes called “nature’s escape artists,” inteins are proteins that have been found in microorganisms from all domains of life.

Even though the first intein sequence was published 25 years ago, details of the splicing mechanism are just beginning to be elucidated. Inteins have fascinated scientists for years, and they have been shown to have a wide variety of applications in protein engineering and drug discovery. A new thematic miniseries on intein-mediated protein splicing appeared in a recent issue of **The Journal of Biological Chemistry**.

In the first minireview, Olga Novikova, Natalya Topilina and Marlene Belfort discuss the overall function of inteins and the sporadic distribution of inteins among closely related species. Overall, there is a bias for inteins to insert into proteins involved in DNA metabolism, such as polymerases, helicases and topoisomerases. In addition, inteins normally are located at protein active sites or in key ligand-binding surfaces. While the rationale for intein localization is still a matter of debate, the authors mention the importance of intein retention. Improper removal of an intein within a conserved protein motif would be deleterious and therefore ensures retention of an active intein for viability of the host. Understanding the evolution and distribution of inteins will shed light on the possibility that inteins function as unique regulatory elements.

In the second minireview, Kenneth V. Mills, Margaret A. Johnson and Francine B. Perler focus on the wide variety of splicing mechanisms. Inteins have evolved to regulate tightly the steps of splicing; however, inteins don’t use a universal mechanism. This review discusses the general strategies for catalysis and the roles of various amino acids during splicing. While the basic steps in protein splicing have been known since the 1990s, how the reactions are coordinated is still unknown. Detailed kinetic and structural studies are needed of multiple inteins to determine whether catalytic strategies are universal or specific to a subset of inteins.

Ertan Eryilmaz, Neel Shah, Tom Muir and David Cowburn explore in the third minireview the structural features of inteins and the variability in splicing mechanisms. While all inteins share the same fold and have highly conserved sequence motifs, inteins have surprisingly different splicing efficiencies. This review describes the structural basis of protein splicing, intein dependence on exteins for protein splicing and distal mutations that affect protein splicing. Allosteric networks, the authors conclude, may play a larger role in determining intein activity than previously thought, because mutations distal from the active site can modulate intein activity.

In the final minireview, David W. Wood and Julio A. Camarero share advances in the applications of inteins. Early engineered inteins were used in protein purification, but now optimized trans-splicing and trans-cleaving inteins have enabled a wide variety of applications in protein labeling, metabolic engineering, biomaterials construction, intein-based biosensors, gene delivery and protein cyclization. These new techniques allow specific control over biological functions of proteins in living cells, plants and whole animals. Future applications will build on these techniques and promise to reveal new classes of therapeutic proteins.

The four minireviews in this series help to broaden our thinking about protein splicing. In an editorial commentary, Perler and Norma M. Allewell conclude that significant progress has been made to better understand intein mechanisms; however, there are still many unanswered questions. While evolutionary biologists question whether inteins are selfish elements and biochemists seek to understand how inteins work, intein-mediated protein splicing creates opportunities in many scientific areas. The numerous intein applications have huge potential for modifying, synthesizing and controlling protein function in the future.

Jenna Hendershot (hendeje@umich.edu) earned a B.S. in cellular and molecular biology from Grand Valley State University and is completing her Ph.D. in biological chemistry at the University of Michigan.

The intricacies of the calcium ion-binding motif in the βγ-crystallin domain

By Emily Tsai

What do a bacterial spore coat and a human eye lens have in common? For one, the presence of βγ-crystallins. The βγ-crystallins are a superfamily of Ca^{2+}-binding proteins, grouped on the basis of their characteristic Greek key topology, that share a calcium-binding motif. Because the Ca^{2+}-binding motif is evolutionarily conserved, learning more about it in bacteria could improve our understanding of it in other domains of life. In the **Journal of Biological Chemistry**, biophysicist Yogendra Sharma and his group at the Centre for Cellular and Molecular Biology in India review the intricacies of the Ca^{2+}-binding motif in the βγ-crystallin domain. The authors cover the architecture of the Ca^{2+}-binding motif and Ca^{2+} coordination, paying special attention to Ca^{2+} coordination by the signature sequence residues of the Ca^{2+}-binding site.

In the crystal structure of a typical βγ-crystallin, such as Clostrillin from the bacterium Clostridium beijerinckii, two Greek key motifs together form the Ca^{2+}-binding sites. The partnering Greek key motifs share one β-strand (out of four). On top of the domain lie two (N/D)-(N/D)-(X)-(X)-(T/S)-(S) sequence stretches that connect the third and fourth strands from their respective Greek key motifs. Each calcium ion is coordinated by residues from both sequence stretches and the β-hairpin loop between the first and second β-strand.

In a βγ-crystallin domain, the Ca^{2+}-binding site generally has a coordination number of seven, including four protein ligands and three water molecules, and forms a pentagonal bipyramidal geometry. Ca^{2+}-coordination is mediated via second, third and fifth residues of the (N/D)-(N/D)-(X)-(X)-(T/S)-(S) stretch, along with one residue of the β-hairpin, while the first residue of the (N/D)-(N/D)-(X)-(X)-(T/S)-(S) stretch may play a role in stabilizing the pocket through hydrogen bonding. Meanwhile, the fourth residue of the stretch is involved in forming a hydrophobic core. Ca^{2+} binding is important for stabilizing the βγ-crystallin domain, and the extent of gain in stability varies from domain to domain.

“The Ca^{2+}-binding motif of βγ-crystallins is spectacular not only in its composition of a nonlinear sequence of amino acids but also in that it acts as a thread to connect an extensively diverse and chronologically vast array of proteins,” says Sharma. “Evolution of this motif displays the footprint of adaptations that the βγ-crystallin superfamily has undergone.”

While the Ca^{2+} coordination pattern has been well studied, very little is known regarding the functions of many βγ-crystallins. Current data suggest that many of these Ca^{2+}-binding βγ-crystallins are relevant with stress, virulency or adhesion. As more members of this group are being identified, further research is needed to explore the Ca^{2+}-dependent functions of βγ-crystallins.

Emily Tsai (emilyee@gmail.com) recently completed postdoctoral research studies at the Johns Hopkins University School of Medicine department of radiation oncology and molecular radiation sciences.

Unfolded protein response signaling and metabolic diseases

By Teodora Donisan

The ever-rising worldwide incidence of metabolic diseases, such as obesity and type 2 diabetes, has made them an important target for researchers. The therapeutic options available so far are rather scarce. Endoplasmic reticulum, or ER, stress, the focus of studies for two decades already, appears to be intimately involved, making it a good candidate for pharmacologic interventions.

In a minireview recently published in the **Journal of Biological Chemistry**, researchers Jaemin Lee and Umut Ozcan at Boston Children’s Hospital detail the correlation between ER stress and metabolic changes, highlighting some plausible therapeutic solutions.

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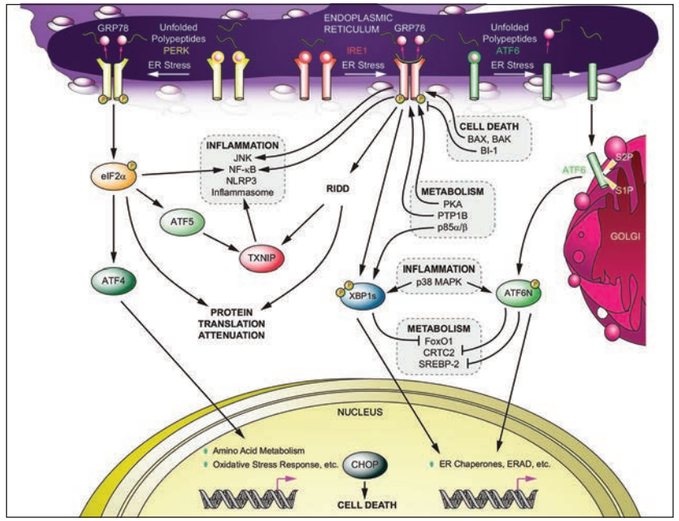
The ER is an essential organelle for protein biosynthesis. It processes newly synthesized proteins, modifying and folding them according to rigorous quality standards. This process is dynamically adjusted depending on the physiological status of cells. ER stress appears when the workload exceeds the folding possibilities of the ER, activating a compensatory system called the unfolded protein response, or UPR. The UPR tries to increase the resources that the ER needs to fold more proteins and to reduce the protein load in the ER, but if the ER fails to do so for prolonged periods of time, UPR signaling initiates cell death.

The UPR has three branches mediated by three ER transmembrane proteins: IRE1, or inositol-requiring protein-1; PERK, or protein kinase RNA-like ER-kinase; and ATF6, or activating transcription factor-6 (see figure). In their minireview, Lee and Ozcan summarize the current understanding of how IRE1, PERK and ATF6 pathways work and how they interact with other signaling networks.

ER stress can be induced in major metabolic disorders like leptin and insulin resistance, nonalcoholic fatty liver disease, and atherosclerosis. ER stress is caused in these conditions by increased levels of reactive oxygen species and ER calcium depletion by sarco/endoplasmic reticulum calcium ATPase, or SERCA, dysfunction; cholestasis and high levels of circulating homocysteine; and by fatty acids, oxidized lipids, cholesterol and hyperhomocysteinemia. While the causes of ER stress vary, all mechanisms that induce ER stress involve IRE1, PERK and ATF6.



UPR signaling and its cross-talk mediated by IRE1, PERK and ATF6

The minireview notes that not only have various studies elucidated the mechanisms responsible for some of the pathophysiological changes, but they've also shown that chemical chaperones reducing ER stress (e.g., 4-phenylbutyric acid and tauroursodeoxycholic acid) restore leptin responsivity, improve insulin sensitivity and glucose homeostasis, and reduce hepatic lipogenesis.

Also, attempts have been made to modulate specific components of the UPR as potential treatments for metabolic disorders and multiple myeloma (IRE1 modulators) and for inhibiting tumor growth and neurodegeneration (PERK inhibitors). Lee and Ozcan emphasize the need for more pharmacologic endeavors focused on UPR components.

Teodora Donisan (teodora.donisan@gmail.com) is a medical student at Carol Davila University in Bucharest, Romania.

Pyruvate dehydrogenase complex

From energy generation to novel drug target

By Alok Upadhyay

Energy generation in prokaryotic and eukaryotic organisms is a highly efficient, multistep and tightly regulated process. Normally, glucose is metabolized initially via the glycolytic pathway, generating pyruvate and small amounts of ATP. To harness the full energy content of glucose, pyruvate undergoes further oxidation in the Krebs cycle, generating large amounts of ATP required for cellular functions. The key enzyme complex bridging these two processes is known as the pyruvate dehydrogenase complex, or PDC, and is the subject of a minireview published in the **Journal of Biological Chemistry** recently.

In this review, Mulchand S. Patel and colleagues have compiled the latest developments in PDC research, compared PDC structural and regulatory mechanisms in bacteria and in humans, and considered their implications on human health. Patel, a distinguished professor and associate dean at the State University of New York at Buffalo, and Frank Jordan, a professor at Rutgers University, Newark, have collaborated for several years to understand the evolutionary changes leading to the functioning of these multienzyme complexes, have used novel methods to identify different steps in the catalytic reactions, and have elucidated high-resolution structures of several PDC component proteins.

PDC is composed of three distinct catalytic enzymes, namely pyruvate dehydrogenase, dihydrolipoamide acetyltransferase and dihydrolipoamide dehydrogenase, which work in tandem to convert pyruvate in to acetyl-CoA, CO_2 and NADH (H^+). Acetyl-CoA is then used as a substrate in the Krebs cycle to generate ATP or used for biosynthetic processes, such as lipid formation. The unique interactions among these components in the complex ensure efficiency as well as regulation of the aforementioned metabolic process. The downside of the human complex is that even a minor change in the complex can have a profound impact on health conditions ranging from neurodegenerative disorders to obesity, type-2 diabetes, and some types of cancer.

In contrast with E. coli PDC, mammalian PDCs have an additional structural component (a binding protein) and specific kinases and phosphatases for stringent regulation. The activity of human PDC is tightly regulated by tissue-specific kinases and phosphatases, which respond to different nutritional and disease states. For example, some cancer cells have activated levels of the kinase1, resulting in inhibition of PDC, which is not favorable for normal cells but is suitable for cancer-cell survival and growth. By studying structural and compositional aspects of the human PDC and its regulation, one can exploit mechanistic differences for therapeutic advantages to combat cancer and other human diseases.

Alok Upadhyay (alok7930@gmail.com) is a postdoctoral associate at Fox Chase Cancer Center. His major research area is Notch signaling regulation during cell fate decisions and neural crest stem cell development. Follow him on Twitter at www.twitter.com/alok7667.

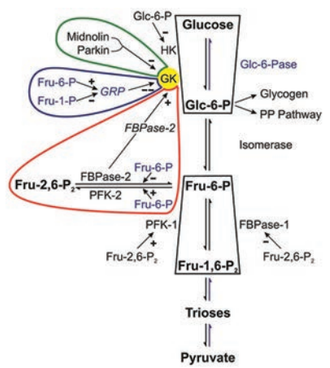
The many levels of glycolytic flux regulation

By Kathleen McCann

Glycolysis is a fundamental metabolic pathway that is critical for the production of energy. Glycolytic flux, or the rate at which molecules proceed through the glycolytic pathway, is tightly regulated in response to the cellular environment. In a recent minireview in the **Journal of Biological Chemistry**, Sigurd Lenzen of the Hannover Medical School in Germany describes the complex regulatory mechanisms underlying glycolytic flux.

Glycolytic flux is regulated during the initial steps of glycolysis, including glucose uptake and phosphorylation. Phosphorylation of glucose is carried out by hexokinases. While all cells express at least one hexokinase with extremely high affinity for glucose, select cell types, including liver and pancreatic β cells, also express glucokinase, which has a much lower affinity for glucose. The unique kinetic properties of glucokinase allow it to act as a glucose sensor and translate changes in blood-glucose levels into changes in glycolytic flux.

It long has been thought that glucokinase function is weakly regulated. However, in the past few decades, a number of studies have begun to demonstrate that glucokinase activity is not only regulated, but it is regulated differently in different cell types. For example, in the liver, glucokinase is inhibited by GRP, a nuclear protein that selectively binds and inactivates glucokinase during starvation. Glucokinase also is inhibited in β cells, although that is done by ubiquitin and ubiquitin-binding proteins, as



The regulatory unit of the glycolytic pathway composed of the fructose steps at the interface between the initial step of glucose trapping in the cell through phosphorylation and the conditioning of the glucose molecule for catabolism.

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GRP is not expressed in those cells.

While glucokinase activity is important for initiating flux, the most crucial steps in glycolytic-flux regulation are the two fructose steps. These steps, which are carried out by phosphofructokinase/fructobisphosphatase isoenzymes to produce fructose ester products, form a regulatory unit. Both the enzymes that participate in these steps and the products that are formed influence glycolytic flux at multiple levels. For example, the activity of PFK1 is responsible for establishing the glycolytic oscillations that drive insulin secretion. Additionally, the fructose ester products are allosteric regulators of glycolysis, as they can inhibit the FBPases and promote glucose catabolism.

As research in the past 30 years has continued to demonstrate, the mechanisms of regulation of glycolysis are more complex than initially thought. Significantly, movement through the glycolytic pathway is regulated on multiple levels by the enzymes that function in the pathway and by the glycolytic intermediates as well as by regulatory proteins.

Kathleen McCann (Kathleen.mccann@yale.edu) is a graduate student in the genetics department at Yale University.

Use your bean (and grain)

Substituting legumes and whole grains for rice can decrease activity of enzyme promoting atherosclerosis

By Mary L. Chang

A new study detailed in the August 2014 issue of the **Journal of Lipid Research** suggests substituting whole grains and legumes in place of processed, refined rice can reduce the activity of an enzyme implicated in atherosclerosis while also improving control over blood-sugar levels.

In a study conducted at Yonsei University in Seoul, South Korea, researchers randomly split into two groups of patients with impaired fasting glucose or who had been diagnosed recently with type 2 diabetes. Participants in one group were allowed to consume their usual diet dominated by refined rice, while participants in the other group were instructed to replace rice in their diet with a mixture of black soybeans, barley and brown rice for three meals a day for 12 weeks.

Researchers observed significant decreases in fasting glucose, insulin and other diabetic markers in the modified diet group compared to the control group, indicating that those participants had improved control over blood-sugar levels. Lower levels of plasma malondialdehyde, a marker for oxidative stress, also were found in the modified diet group; it has been suggested that increases in oxidative stress and damage caused by free radicals not kept in check may be linked to diabetes.

Also, while no differences were observed between the two groups when it came to general measures, such as body mass index and the energy levels that the participants reported, levels of the proinflammatory cytokine interleukin-6 were significantly lower in the modified diet group.

Probably the most important result of this study? The activity of lipoprotein-associated phospholipase A2, called Lp-PLA2 for short, was decreased in the modified diet group. This would explain the increase in IL-6 in the control group: Increased levels of this enzyme are associated with increasing levels of several inflammatory cytokines. Lp-PLA2 is an enzyme produced by inflammatory cells that breaks down oxidized phospholipids in low-density lipoprotein. Lp-PLA2 also is used as a marker in diagnosing cardiac disease.

It is still unclear how Lp-PLA2 activity and substantial improvement in glucose and insulin metabolism are linked to diet. However, the paper's authors point to two possibilities. They suggest decreased Lp-PLA2 activity could be linked to the increased protein in the modified diet. Also, because whole grains and legumes contain many antioxidants, the rate of oxidation of molecules that might ordinarily get broken down in the presence of a normal diet might be slowed.

The authors conclude that "grains should be consumed in a minimally refined form, and frequent consumption of vegetables and legumes should be recommended to reduce cardiovascular risk factors."

Mary L. Chang (mchang@asbmb.org) is publications manager for ASBMB.

The makings of a honeybee

By Rajendrani Mukhopadhyay

IMAGE COURTESY OF MUHAMMAD MAHDI KARIM, A WIKIMEDIA COMMONS USER

Honeybees give us our honey, royal jelly, propolis and beeswax and support the ecological structure of the environment by transferring pollen between plants. Despite their ecological and economic importance, very little is known about how honeybee workers develop from embryos to adults at the molecular level. In a paper in the journal **Molecular & Cellular Proteomics**, researchers tackled a proteomic analysis of honeybee worker embryos.

They found that while there is a central set of proteins involved in common biological pathways that drive development, "embryos at different developmental stages have their own specific proteome and pathway signatures," says Jianke Li of the Chinese Academy of Agricultural Science in Beijing. "These findings provide a vital resource as a starting point for further functional analysis and genetic manipulation for both the honeybee embryos" and other eusocial insects, such as wasps, ants and termites.

The investigators studied worker bees, which are responsible for building the honeycomb, cleaning it, defending the colony, foraging for nectar and feeding the larvae. The worker bees, all sterile females, rise out of fertilized eggs in four stages. The first stage is the egg, during which the body plan of the insect is established. Li and colleagues used liquid chromatography combined with mass spectrometry as well as bioinformatics to see which proteins were present and how expression changed in embryos during their 72-hour development period.

The investigators found that the core proteome of all stages of embryonic development consisted of proteins involved in protein synthesis, metabolic energy generation and consumption, development, and molecular transport. But each embryonic stage had specific sets of proteins turn up on top of the core proteome.

Embryos younger than 24 hours had more proteins involved in nutrient storage and nucleic acid metabolism, which could correlate with the cell proliferation that happens at the early stage. Embryos during the 24-to-48-hour span expressed proteins responsible for cell-cycle control, transport, antioxidant activity and the cytoskeleton. These proteins may be present to support early formation of organs. The late-stage embryos, during the 48-to-72-hour time frame, produced proteins implicated in fatty acid metabolism and morphogenesis. These proteins could be responsible for the final formation of organs.

As you can see, the study gives researchers an idea of the processes happening at the different stages of embryonic development. Scientists now can use the data to see if particular processes lend themselves well to creating genetically modified honeybees, an active area of research.

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Issue features research aided by PRIME-XS infrastructure program for proteomics in Europe

By Angela Hopp

The August issue of the journal **Molecular & Cellular Proteomics** features a substantial collection of articles describing recent research findings from investigators supported by the European Union-funded proteomics consortium known as PRIME-XS.

For the uninitiated, the acronym PRIME-XS is short for "Proteomics Research Infrastructure Maximising knowledge EXchange and access." The consortium's 12 partner institutions offer the critical infrastructure – specialized instrumentation, expertise and training — for proteomics researchers in Europe who otherwise lack access to such resources.

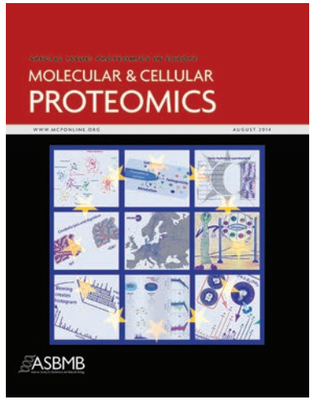
The prologue to the MCP special issue was written by Albert Heck of Utrecht University, Jesper Olsen of the University of Copenhagen and Ruedi Aebersold of the ETH Zurich (all PRIME-XS principal investigators), along with Reinout Raijmakers of Utrecht University (who manages the PRIME-XS project office).

"Prior to the founding of PRIME-XS, proteomics in Europe was already well-established, with several top-notch research laboratories and several proteomics facilities operating at the local and national levels. However, the European proteomics community was not well-organized," the prologue authors explain.

The EU's primary funding mechanisms for research and development are known as "framework programmes." After funding for PRIME-XS was secured under the seventh framework's infrastructure umbrella, "a major effort was made to organize the community and to establish a coordinated program to provide the European life-science research community with access to top-of-the line (proteomics) facilities."

Long story short: PRIME-XS put out its first call for proposals in July 2011 and since then has invited 104 investigators from 21 countries to carry out work at the consortium's six access sites in the Netherlands, Belgium, Switzerland, Spain, the U.K. and France.

"Sometimes guest researchers stay (at an access site) for a single day; others are embedded at a site for weeks or months," Heck et al. write. "Some users are proteomics novices; others are experienced researchers who want training and access to novel or specialized technologies that are unavailable locally."



The ongoing and completed work at the PRIME-XS access sites has yielded more than 100 publications so far. The 19 new publications in the special issue of MCP describe "a wide variety of proteomics applications in biology and medicine," Heck says, including antibiotic resistance, plant pathogens, brain malfunctioning, circadian rhythms and quality-control metrics.

Heck says submissions for the MCP special issue were sought openly from "people working in the PRIME-XS joint-research activity programs and researchers from all over Europe who requested access to the proteomics infrastructures."

PRIME-XS access site at Utrecht University

PHOTO BY BAS VAN BREUKELEN

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

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Report highlights nonacademic careers of STEM Ph.D. holders

Earlier this year, the American Institutes for Research issued a report titled "The nonacademic careers of STEM Ph.D. holders." AIR derived the data from the 2010 Survey of Doctorate Recipients by the National Science Foundation and the National Center for Science and Engineering Statistics. We have reprinted AIR's key findings with its permission in this issue.

As a preface to its analysis, AIR noted previous research showing that more than half of STEM Ph.D. holders work outside of academe and do so for many reasons, not the least of which is the increased competition for a declining number of jobs in academe.

AIR's report noted the following:

• The majority of Asian women and men and the majority of white men reported holding nonacademic positions. The other demographic groups surveyed (black women, Hispanic women, white women, black men and Hispanic men) were about evenly split between academic and nonacademic careers.

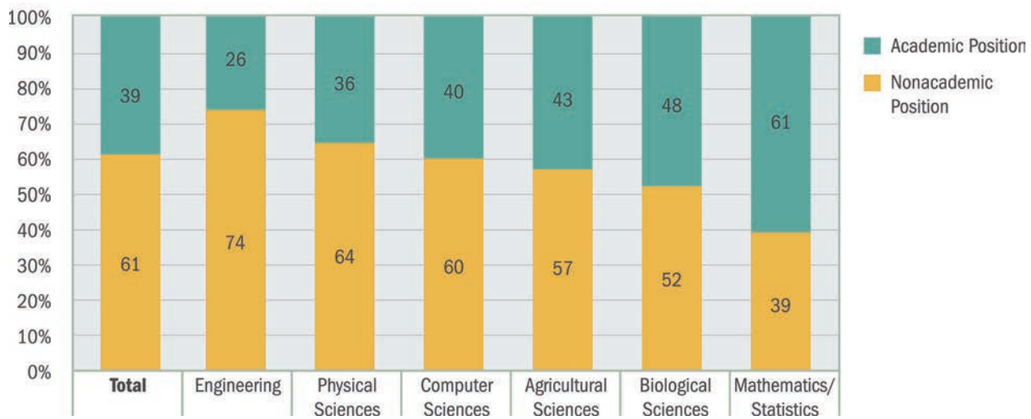
• Most of those in nonacademic careers worked for private, for-profit organizations or for government. Black women, Hispanic women and white women reported working for government at the highest rates.

• About half of those in nonacademic careers worked in research and development. Black women, Hispanic women and white women reported working in R&D at the lowest rates.

• About 20 percent of those in nonacademic careers worked in non-STEM fields. Black women, Hispanic women and white women reported working outside of STEM at the highest rates.

To read the complete AIR report, visit http://bit.ly/1jKL6rt.

Percentage Distribution of Employed STEM PhD Holders, by Career Type and by STEM Field



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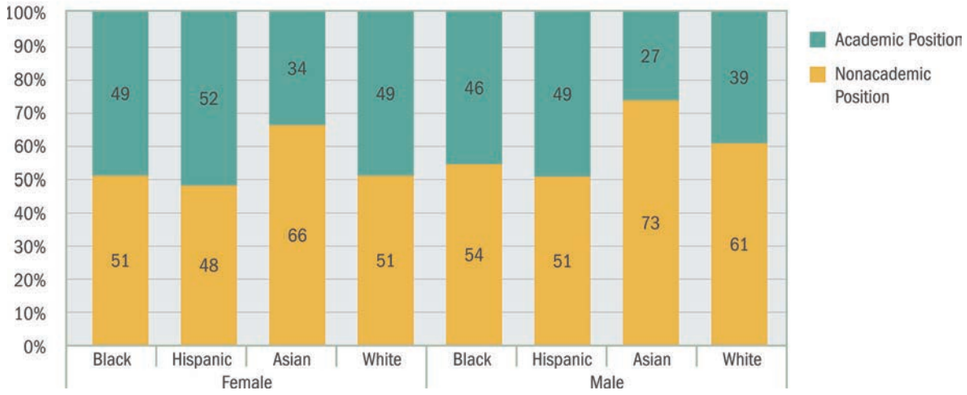
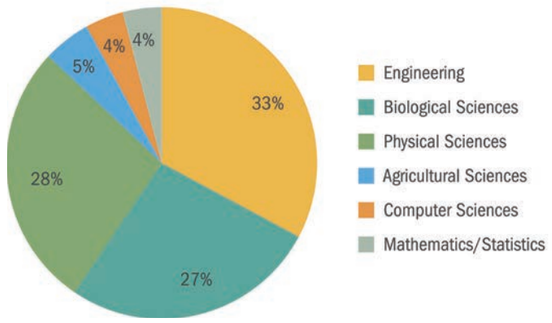
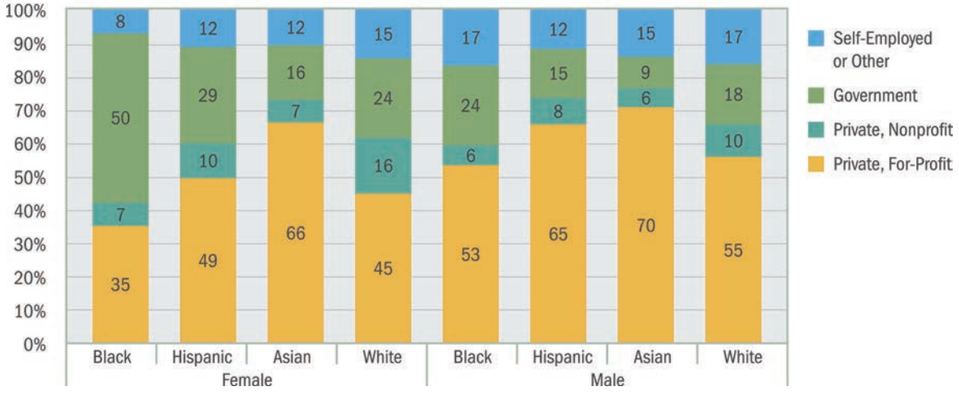
Percentage Distribution of Employed STEM PhD Holders, by Career Type and by Gender and Racial/Ethnic Group



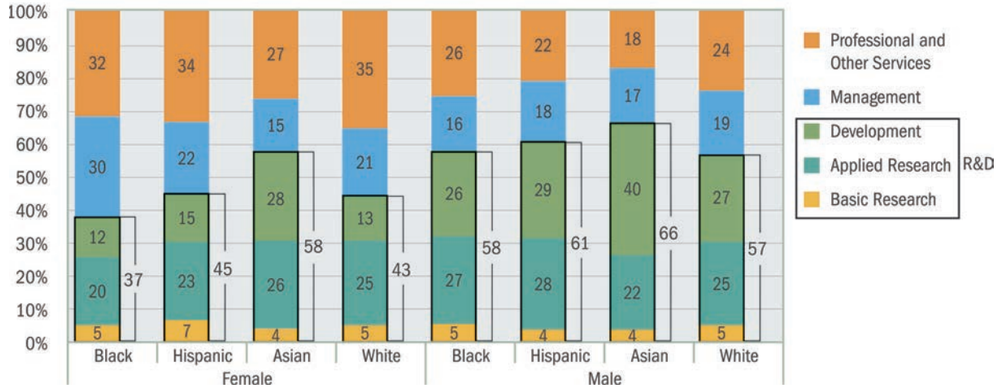
Percentage Distribution of Employed STEM PhD Holders Who Worked in Nonacademic Careers, by PhD Field



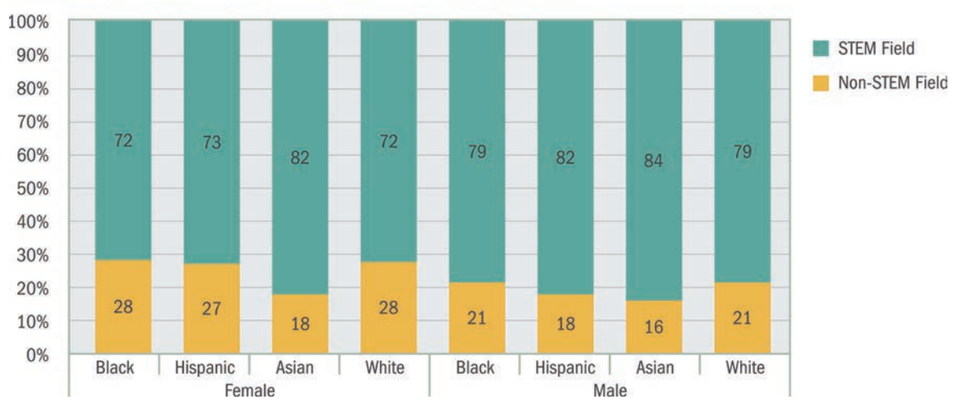
Percentage Distribution of STEM PhD Holders in Nonacademic Positions, by Career Sector and by Gender and Racial/Ethnic Group



Percentage Distribution of STEM PhD Holders in Nonacademic Positions, by Primary Work Activity and by Gender and Racial/Ethnic Group



Percentage Distribution of STEM PhD Holders in Nonacademic Positions, by Employment Outside of STEM and by Gender and Racial/Ethnic Group



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NIH launches a public website for bioscientific 3-D printing

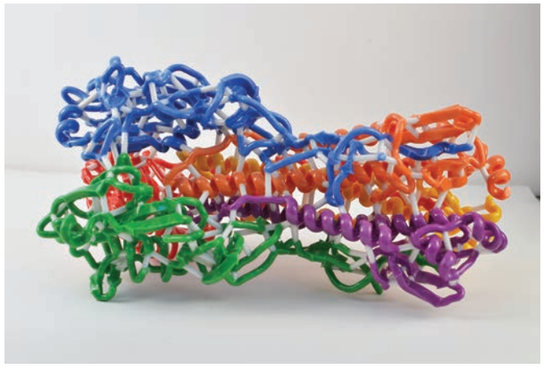
By Indumathi Sridharan

The National Institutes of Health's National Institute of Allergy and Infectious Diseases in June launched a free, public online library of 3-D printable files called the NIH 3D Print Exchange (or simply the Exchange). It is the first government-sponsored website dedicated to 3-D printing of scientific and medical models, such as those of bacteria, proteins and anatomical parts.

Visualization of scientific data is a driver of discovery. Typically, converting a digital model into a 3-D printable format is technically demanding and time-consuming, sometimes taking hours even for those who are experienced with it. The Exchange aims to leverage the potential of 3-D printing by saving time, money and labor.

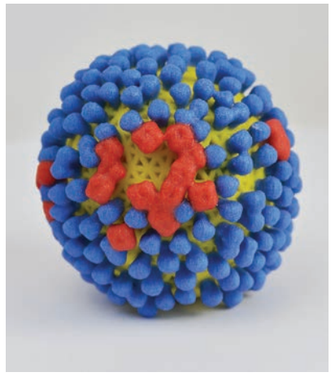
The Exchange allows users to create, upload, download and share printable files of their data. "We created this website as kind of a way to have a YouTube-like experience, but instead of exchanging and sharing and commenting on and remixing videos … we are doing all of those same things with 3D-print files," explains Darrel Hurt, a researcher at the NIAID who helped develop the Exchange, in a video about the new site (1).

The repository has a wide range of print-ready files, including an influenza virus, an insulin molecule and even a common lab microscope. Users of any skill level can obtain ready-to-print files within minutes either by uploading a digital 3-D model file or, in the case of proteins and macromolecules, by entering the Protein Data Bank or the Electron Microscopy Data Bank code. Users also can share files derived from other open-source modeling software, such as Blender, FreeCAD and the like.



A 3-D model of influenza virus.

IMAGES COURTESY OF THE NIH/NIAID.



A 3-D model of influenza hemagglutinin.

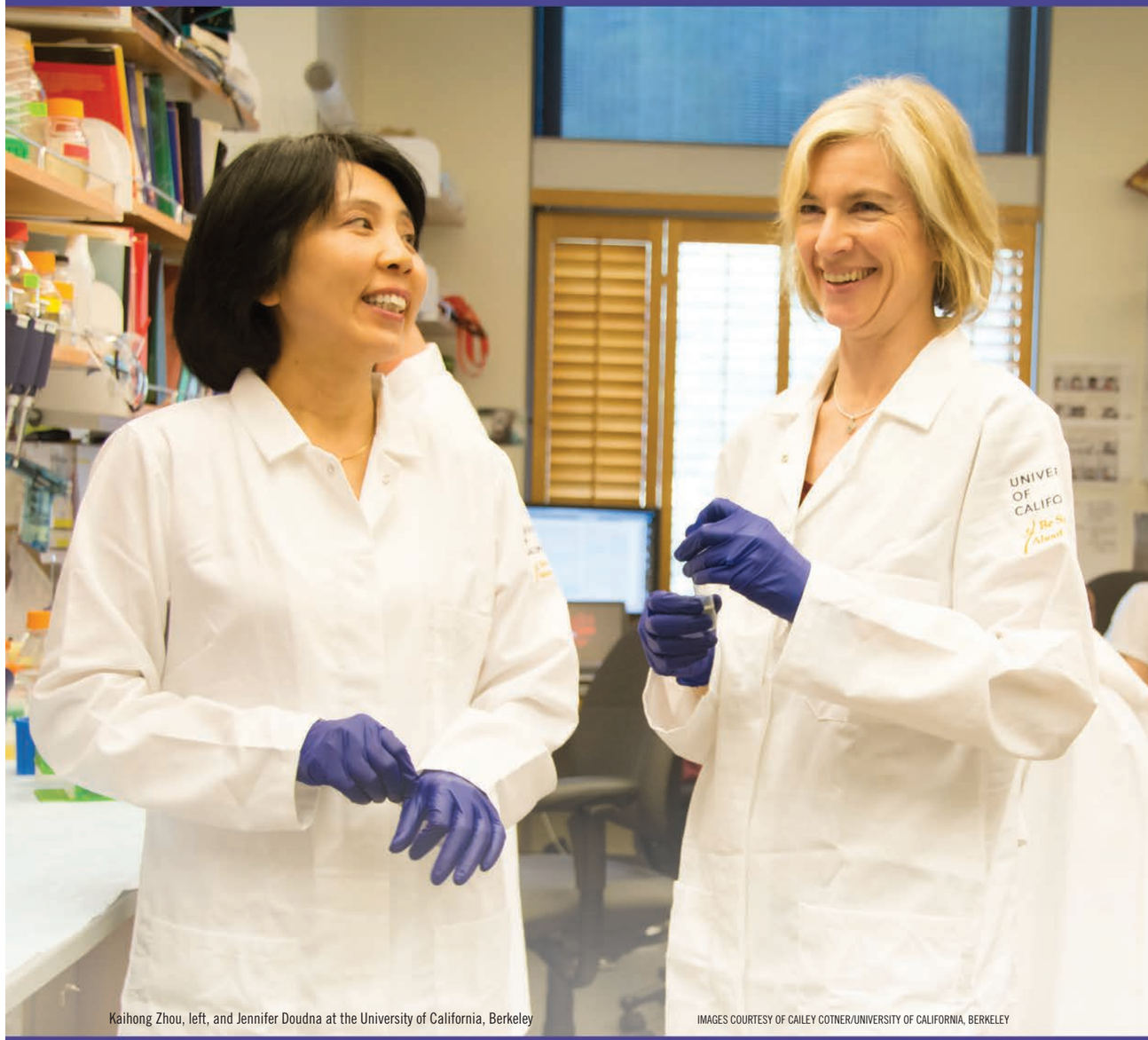
Additionally, modeling tutorials, illustrated workflows and other educational materials are available to help novice users build custom 3-D prints. The Exchange also will host online forums for sharing tips and tricks, and users will be invited to upload files of models that can be used for teaching.

This initiative was directed by the NIAID in collaboration with the Eunice Kennedy Shriver National Institute for Child Health and Human Development and the National Library of Medicine. More information about the Exchange can be found at http://3dprint.nih.gov/.

Indumathi Sridharan (sridharan.indumathi@gmail.com) earned her bachelor's degree in bioinformatics in India. She holds a Ph.D. in molecular biochemistry from Illinois Institute of Technology, Chicago. She did her postdoctoral work in bionanotechnology at Northwestern University and is now an intern at the Office of Technology Transfer at the National Institutes of Health.

REFERENCE

1. https://www.youtube.com/watch?v=w3z4BEEUT2s



Kaihong Zhou, left, and Jennifer Doudna at the University of California, Berkeley

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'On the same wavelength'

If you had asked Jennifer Doudna a few years ago about the gene-editing tool CRISPR, she would have described the research as "a pretty small effort in my lab, just a few people having fun checking it out."

That was before a lightbulb went off, before Doudna and her postdoctoral fellow realized that the bacterial defense system could be exploited to fix faulty genes or bestow new functions on existing genes in all kinds of cells. The small effort in Doudna's lab at the University of California, Berkeley, has since exploded into an international one, with laboratories in several continents furiously working on the gene-manipulation possibilities presented by the system. The method has received much attention in the mainstream press, including the New York Times, which described the adoption of CRISPR by researchers as a "scientific frenzy."

Doudna, who is also an investigator with the Howard Hughes Medical Institute, has found herself to be repeatedly sought after as a speaker and has received numerous accolades. Already a member of the National Academy of Sciences and an American Academy of Arts and Sciences fellow, Doudna won the inaugural Mildred Cohn Award in Biological Chemistry from the American Society for Biochemistry and Molecular Biology last year (for work she accomplished prior to the CRISPR craze). This year, she received the Lurie Prize in Biomedical Sciences from the Foundation for the National Institutes of Health. The annual prize recognizes outstanding work by a scientist age 52 or younger; Doudna won recognition for the work on CRISPR.

What is CRISPR?

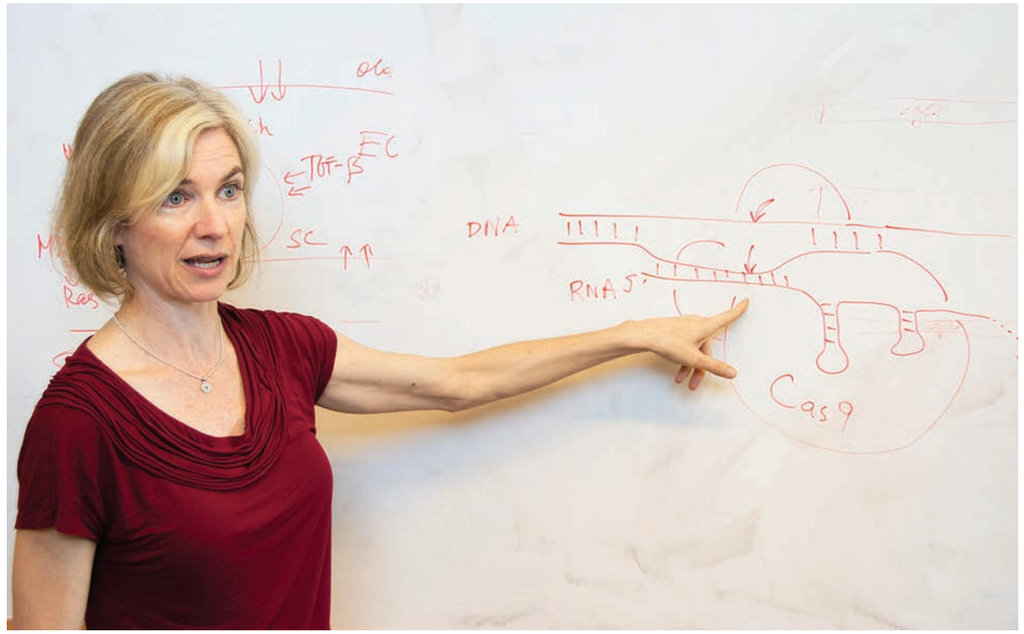
It stands for: clustered regularly interspaced short palindromic repeats.

Partnership

It is the morning after the Lurie Prize banquet, a mild spring day in Washington, D.C., with a chance of rain showers, when Doudna and I sit on an outdoor patio at the Ritz Carlton in Georgetown. Doudna's husband, Jamie Cate, and her preteen son are upstairs in their hotel room packing to fly back to California while Doudna speaks with me. Friendly and warm, Doudna exudes quiet, deep-rooted confidence. Dressed in crisp jeans and a light gray cardigan, she speaks thoughtfully, occasionally using her hands against the tabletop to make her points in measured sentences. Aware that she has a highly successful research portfolio that covers CRISPR, RNA interference and translational control, I ask how she manages to maintain such a prolific environment in her laboratory of 30 scientists. But Doudna is quick to reveal her secret – her laboratory manager, Kaihong Zhou. "She is the type of person who will do whatever it will take to make the lab successful," says Doudna. "I owe her a tremendous amount for what we've been able to do."

Fresh out of a postdoctoral fellowship with Tom Cech at the University of Colorado, Boulder, in 1994, Doudna was starting as an assistant professor at Yale University. Zhou also was new to New Haven; she had accompanied her husband for his postdoctoral position at Yale. She was searching for a job at the medical school, fully acknowledging that at that time she didn't know much about biology. Eschewing the human resources department, Zhou went door to door in the medical school asking faculty members if anyone would be willing to hire her. One faculty member said he just had filled his open position for a technician but recalled that a new faculty member was searching for one. He called Doudna to confirm and sent over Zhou's résumé.

Doudna failed to see any common scientific ground in Zhou's résumé but decided to give her a call anyway. Within 15 minutes of getting the call, Zhou was in Doudna's office. "She had these big neon-green glasses on and a very bright dress," remembers Doudna. "She was full of energy. She had no idea what my research was about, but she was eager to learn. She said, 'If you hire me, I will be in your office tomorrow at 8 o'clock unpacking boxes.' I thought, 'Wow, this person is just amazing.' I gave her a chance."



Jennifer Doudna's laboratory was one of the first to work on the CRISPR/Cas9 gene-editing system.

"I want the lab to be a place where people feel like they are all batting for the same team … As I've chosen people to join my group over the years, I've always tried to pick those who would foster that kind of environment."

– JENNIFER DOUDNA, UNIVERSITY OF CALIFORNIA, BERKELEY

Zhou showed up the next day even though her paperwork still had to be sorted out in Yale's human resources department and she couldn't get paid for another month. Zhou describes herself as restless: "I can't sit anywhere for more than 20 minutes."

The two women hold each other's scientific prowess in high regard. "She has great vision and foresight for science," says Zhou of Doudna; Doudna calls Zhou "a spectacular scientist." Neither is a procrastinator. If a good idea comes up, the two prefer to set the idea into action immediately. Doudna, describing Zhou and herself as "two peas in a pod," says, "We confer on all sorts of things, everything from who to hire into the laboratory, how to spend our funds, the kinds of science projects we're doing and key experiments that need to be done at a particular time."

An ambitious but supportive environment that's based on teamwork is important to Doudna. "I want the lab to be a place where people feel like they are all batting for the same team." The sports analogy comes to Doudna easily – her lab has a softball team and makes regular trips to Major League Baseball games

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(although Doudna is fonder of the social aspects of baseball than the actual sport). "As I've chosen people to join my group over the years, I've always tried to pick those who would foster that kind of environment," she says. "For the more senior members of the lab, they need to understand that part of their role in the lab is to provide mentorship to younger students."

And here is where Doudna says Zhou's presence is important: "She has maintained the kind of environment where students are pushed to do their very best but are also encouraged to seek help when they need it, to understand that they have the support of people in the laboratory when they run into technical challenges or anything else."

In 2001, UC Berkeley offered faculty positions to Doudna and Cate, who was at the Massachusetts Institute of Technology at the time. The offer was tantalizing: Doudna would have a joint appointment to the departments of molecular and cell biology and chemistry. Plus, Berkeley is just a five-minute drive from Lawrence Berkeley Livermore National Laboratory, a place indispensible for a structural biology laboratory like Doudna's. Furthermore, Doudna's mother was in Hawaii, so California would bring Doudna closer to her. They accepted.

Zhou decided to go with Doudna to the West Coast. Doudna's research into RNA appealed to her, but Zhou says that their relationship was the key factor. Still, it wasn't an easy decision for Zhou, because she had her husband's career to consider. They decided the move was worth the effort. Zhou was the only person from Yale to move with Doudna.

Doudna wholeheartedly gives credit to Zhou as an equal partner for making the laboratory successful. And life has taught Doudna that having a true partnership in her personal life also is hugely important. She speaks of Cate: "I didn't understand when I was younger the importance of having the right partner in life. I only realized it later. I now feel I do have the right partner in life, and I'm very, very, very grateful for that."

She emphasizes that choosing the right life companion is especially important for female scientists. "It's very important to have a partner who can understand your passion," she says. "We're a little bit crazed. We're driven by what we find exciting in science. I think it's so important for a partner to understand that level of passion. To make it work between career and family, it's really critical to have a partner who gets it and is willing to share the burdens."

CRISPR: "Small effort" goes big

Doudna always has been interested in RNA. Her research, starting with work she did with her graduate adviser, Jack Szostak at Harvard University, and continued with Cech, has shown over the years that large RNA molecules aren't a mess of spaghetti-like strings. Instead, they are more like proteins with defined, organized structures. Doudna solved the first crystal structure of a large domain of the protozoan Tetrahymena ribozyme. Her group got the first detailed structure of the P4-P6 RNA fragment of the group I intron, which showed the RNA to be packed tightly into a proteinlike globular fold. In 1998, her laboratory solved the crystal structure of the hepatitis delta virus ribozyme, work that demonstrated how the virus was capable of hijacking its host cell's machinery to replicate itself.

When CRISPR came onto Doudna's radar in the mid-2000s, her group was working on gene regulation by small RNA molecules in human cells and RNA interference pathways. Doudna became interested in CRISPR, an acronym for clustered

Kaihong Zhou has been Jennifer Doudna's lab manager for two decades. Doudna credits her for keeping the lab at the cutting edge of research.

regularly interspaced short palindromic repeats, because she realized it was a way for her lab to see how bacteria use small RNA molecules in a pathway perhaps similar to RNA interference. She and her colleagues then could search for any evolutionary relationships between bacterial and mammalian systems in using RNA to control genetic information.

Bacteria have three different systems involved in the RNA-mediated destruction of invading bacteriophage genomes by endonucleases. The endonucleases are called CRISPR-associated systems, or Cas. Doudna's laboratory got involved in studying the type II system when Emmanuelle Charpentier, then at Umeå University in Sweden but now at the Helmholtz Centre for Infection Research in Germany, approached her at a conference. "She wondered if it would be of interest to us to work together to figure out what the function of Cas9 was," says Doudna. Type I and III CRISPR/Cas systems use a variety of endonucleases; type II is different in that it relies solely on the Cas9 endonuclease.

In a 2012 Science paper, the collaborators described how Cas9 attacked bacteriophage DNA. Two pieces of RNA generated from the CRISPR sequences form a structure that Cas9 uses to find the complementary sequence in DNA. Once it finds the complementary sequence, the enzyme introduces double-stranded breaks.

That's what happens inside a bacterium. But one day, while Doudna and her postdoctoral fellow Martin Jinek were discussing some data, they both wondered out loud if they could engineer the two pieces of CRISPR-derived RNA as a single RNA chimera. This chimera could still guide Cas9 to DNA and get the enzyme to cut the DNA as a way of gene manipulation. "We looked at each other and said, 'If we link these two RNAs together into a single RNA, we will have a very simple two-component system that if we could get it to work in other cells, it would be a very useful tool," she recalls. "That was the turning point."

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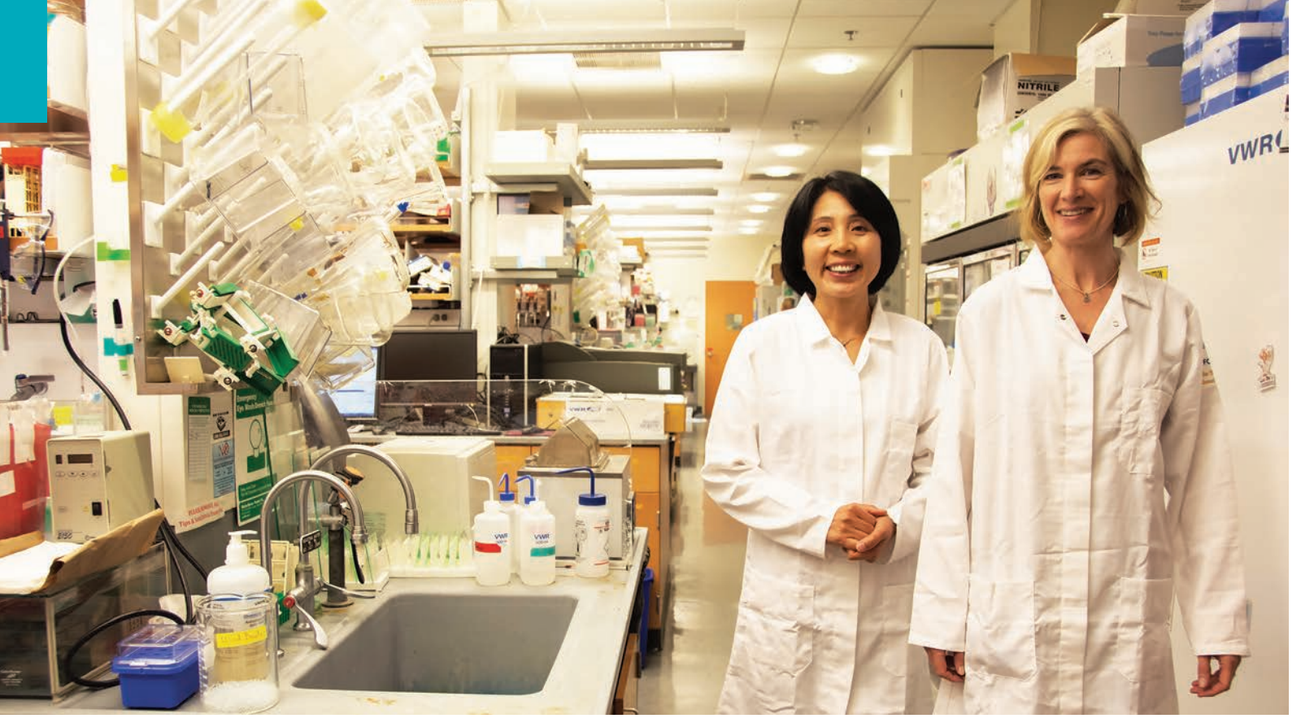

Jennifer Doudna, right, says that she and her lab manager, Kaihong Zhou, are "two peas in a pod."

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The investigators demonstrated a proof of concept in the Science paper using in vitro systems. In the paper, they presciently noted, "Rational design of chimeric RNAs is robust and could, in principle, enable targeting of any DNA sequence of interest with few constraints."

CRISPR isn't the first gene-editing tool, but its appeal is in its simplicity. All that is technically needed is the Cas9 endonuclease tagged with an RNA strand, which is simple to make in a nucleic-acid synthesizer using synthetic chemistry or enzymes. "Researchers have enthusiastically adopted this system because of the relative ease with which you can manipulate complex genomes compared to other similar technologies, such as zinc finger nucleases, transcription activator-like effector nucleases, and other more traditional methods," explains genomics expert Joel Gottesfeld at The Scripps Research Institute. To date, scientists have used CRISPR to edit genes in almost anything they can get their hands on: human cells, zebrafish, fruit flies, mice, worms and rhesus monkeys.

CRISPR gives Doudna a chance to do science with clinical applications. Her hepatitis virus work had a clinical aspect, but the research was far removed from medical applications. Not so with CRISPR. Through an academic collaboration with Hoffmann–La Roche, Doudna's group is looking to see if the CRISPR/Cas9 system can be used to correct known genetic defects in neurological diseases, such as Huntington's. "We've understood the genetic cause for a long time, but up until now, there hasn't been a good tool for how you might actually fix that mutation," says Doudna. "To me, that's very exciting, because it helps us to not only work toward having a direct impact on human health, but I think that when we understand better what the potential limitations are with the current system it will help us as mechanistic biologists to improve the tool further."

CRISPR is also the foundation for the Innovative Genomics Initiative, jointly supported by UC Berkeley and the University of California, San Francisco, and funded by the Li Ka Shing Foundation. The initiative aims to develop genomic analysis to understand disease processes and come up with novel therapeutics. Doudna, who also received a chaired professorship from IGI, is the initiative's executive director, with UCSF's Jonathan Weissman serving as a co-director. Although Doudna sees a great future for CRISPR, she says her heart breaks every time she receives an email from someone who has a loved one suffering from a terrible disease or illness asking if CRISPR can help. It's too early to tell, says Doudna, but the hope is there. Researchers still have to work out the fine-print details, which include figuring out how to target the gene-editing entities into certain cells and not others in a whole organism.

Zhou says that if the pace of Doudna's work was brisk before CRISPR came along, she can only describe it now as hectic. She says the laboratory used to hold an annual potluck, but Doudna's workload and travel schedule have been so relentless that they had to skip the potluck last year. "She's super busy," says Zhou. "She's become a celebrity!"

Passion and perseverance

The possibility of becoming a scientific celebrity isn't what drove Doudna to science. Biology infused her childhood, which she describes as "a big adventure." Her father got his Ph.D. in English literature from the University of Michigan, Ann Arbor. When Doudna was 7 years old, her father completed his thesis and moved his wife and three daughters from Michigan to take up a faculty position at the University of Hawaii. Doudna's mother, a stay-at-home parent in Ann Arbor who held a master's degree in education, went back to school to get another master's degree at Hawaii, this time in Asian history, and began to lecture in the subject at the university.

The environmental beauty and excitement of the islands, which included erupting volcanoes, instilled a sense of wonder about the natural world in Doudna. "There were so many fascinating bugs, plants – the natural environment there was so interesting. I was really curious about what makes a plant look the way it does. I always felt very drawn to the underlying mechanisms that work in biology." At school, Doudna was drawn to mathematics and science. The sense of discovery awed her. She recalls always wanting "to be the first person to know something. That, somehow, inherently was attractive to me."

Her father was a huge influence. "My dad always fostered a sense of curiosity in the house," says Doudna. Her father loved to read about science, filling the house with books about science geared for nonscientists; when Doudna was in sixth grade, her father presented her with a copy of James Watson's "The Double Helix."

Her high-school chemistry teacher was also an influence. Doudna, who paid homage to Miss Wong in her Lurie Prize speech, remembers her being "very encouraging and taught kids about the joy of having a question about how does something work and setting up an experiment to test it." But it was in 11th grade that Doudna discovered what she was meant to do. "The state sponsored a lectureship for people who worked at the cancer center in Honolulu on Oahu to travel around the state and go to high schools and tell the kids what they were doing," says Doudna. "We had this wonderful woman – I wish I knew her name – who came from the cancer center in Honolulu to my high school. She talked about her work on cancer biology and trying to understand what goes wrong in cells that are cancerous compared to normal cells. That just blew me away. I thought that was so interesting. I

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absolutely wanted to do that kind of work."

Doudna searched for undergraduate biochemistry programs. "This was in the early 1980s, so there were not that many undergraduate colleges that had biochemistry majors. But Pomona College in Clairmont, California, did, so I ended up going there and starting my work in that direction," she says. Doudna is the only scientist in the family – one sister is a teacher who is working on federally funded geography projects, and the other sister is an actress.

"When we are sleeping, Jennifer is working."
– KAIHONG ZHOU, DOUDNA'S LAB MANAGER

Even though she was inspired to study biochemistry, Doudna remembers having doubts while a sophomore in college taking general chemistry. "It was hard for me, and I was trying to understand why balancing equations was going to be relevant to my future life," she recalls. At the same time, she was taking a French class and really enjoying it. She approached her French teacher and told her that she probably wasn't cut out to do science and would be better off majoring in French. Her teacher wouldn't hear of it. "She said, 'I can see you're passionate about it. I know it's a struggle right now. But you should stick with it. That's going to be a great career path for you.' She was right."

The importance of being passionate about the work was reinforced by Szostak during Doudna's graduate training. Szostak "has a mild, quiet manner to him, but gosh, he could get so excited about science," says Doudna, adding that his enthusiasm for even the most simple result was infectious.

Zhou says Doudna embodies the same upbeat spirit as Szostak. She's never seen Doudna belittle anyone for experiments gone awry. "Even if something fails, she'll say, 'Wow, from this failed experiment, I've seen something really great. Let's try something else from here,'" says Zhou. "She never ever once freaked out because something didn't work."

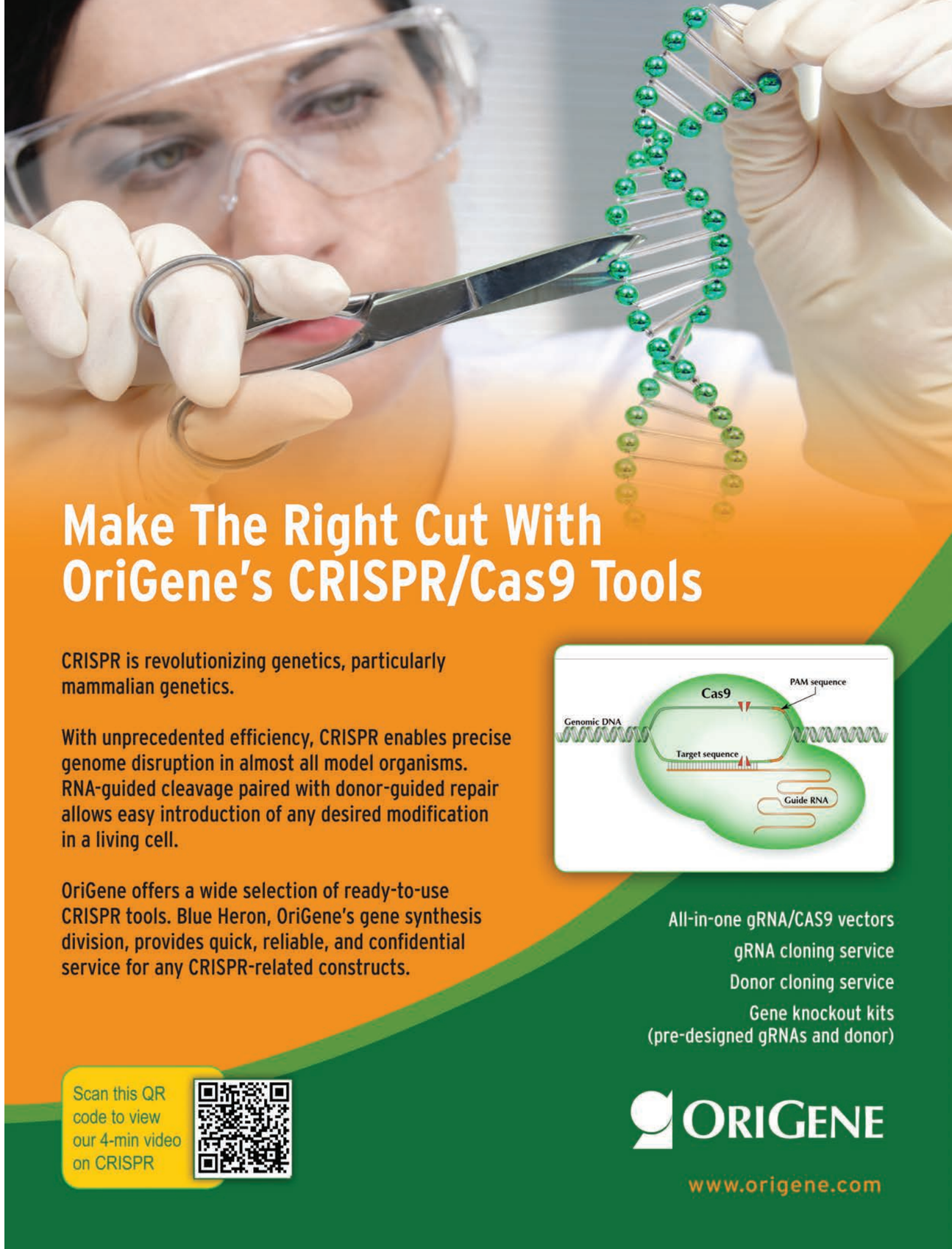
Szostak influenced Doudna in another important way. "He would also tell us students in the lab, 'Follow your passion. Don't worry about your next career move, because if you follow your passion and do excellent science all of those career decisions will become easy to make, because you'll know what you want to do and what's right for you.' That was so true," says Doudna. "It's really guided me in many moments in my career when I've had to make a decision."

She respects someone's enthusiasm for a particular research avenue, because she knows the enthusiasm will help the person persevere. "I think people do their best work when they are very motivated, very excited and passionate about a project," she says. It's true for her: Zhou describes Doudna as extremely hardworking, capable of chipping away at work at all hours. "When we are sleeping, Jennifer is working," says Zhou. "It's not surprising to get an email from her at 5 a.m."

Doudna is grateful that serendipity also has showed up a number of times in her career. One of those serendipitous moments was meeting Zhou. She emphasizes more than once how similar they are. "We think on the same wavelength," she says. "Our goals have always been aligned."

Passion and excitement for science is something Zhou says she shares with Doudna. But she adds there is something more fundamental to their relationship – trust and mutual respect. "This is why we've lasted for 20 years. We never ever say anything unhappy to each other. It's amazing. People don't believe it," says Zhou. "We've been happy together for 20 years!"

Rajendrani Mukhopadhyay (rmukhopadhyay@asbmb.org) is the senior science writer and blogger for ASBMB. Follow her on Twitter at www.twitter.com/rajmukhop.



A tale of friendly fruit flies in a jam

Author of new children's book hopes cute and curious cast of characters will ignite appreciation for model organisms

By Emily Huff

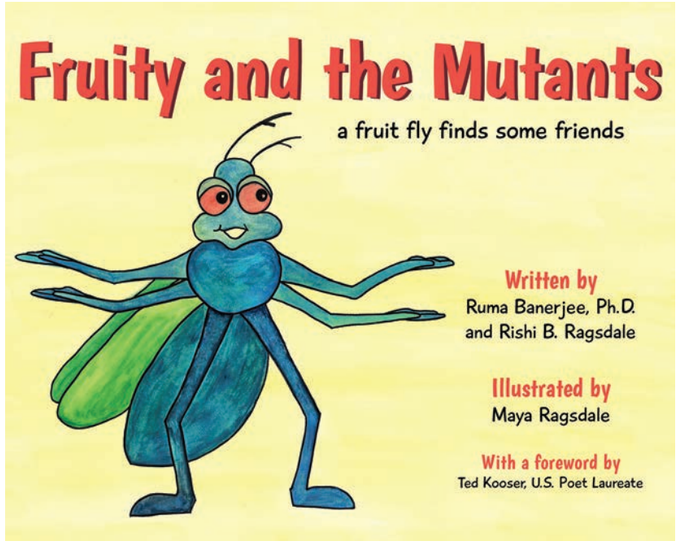
Eight years ago in a cozy coffee shop in Nebraska, biochemist Ruma Banerjee struck upon creative inspiration in a rather unlikely subject: Drosophila melanogaster.

It happened during a lengthy discussion in the Lincoln coffee shop with her longtime friend Ted Kooser, a Pulitzer-winning poet and former U.S. poet laureate who recently had completed his first children's storybook. The two discussed the powerful use of animal protagonists in works for children, which got Banerjee thinking about the storied history of the fruit fly.

"When Ted suggested having an animal as the main character (in a children's book), my mind immediately went to the idea of a model animal," Banerjee says.

Various factors, including the approaching 100th anniversary of the opening of what is known worldwide as the Fly Room at Columbia University, contributed to Banerjee's decision to make the fruit fly the central character in a children's book of her own. That book, "Fruity and the Mutants," was published by the American Society for Biochemistry and Molecular Biology earlier this year.

"Fruity and the Mutants" is the story of a wayward fruit fly, Fruity the wild type, who escapes the clutches of a vicious yellow jacket and finds her way into a band of misfit mutant flies – all named for their various genetic mutations. Their peace is short-lived, however, as that same nasty yellow jacket discovers the flies and chases them down. Then Fruity and her new group of friends must find a way out of the yellow jacket's clutches or perish.



Making the book

Though Banerjee does not work on fruit flies herself, soon after her talk with Kooser she spent several months reading about them and their uses in genetic research. In 2007, Banerjee left her faculty position at the University of Nebraska and moved to the University of Michigan. For several years, the idea for the book simmered on the back burner.

She says the book was begun in earnest during a vacation to Dharamshala, India, in 2012 with her children, Rishi and Maya Ragsdale. "We spent our evenings weaving this story and sharing laughs as we played with the fruit fly names and concocted roles for them in the plot," she recalls.

They selected a group of mutants with names that seemed like they would work in a story for younger audiences, deliberately omitting a few choices. (For example, "Slow-poke," with its mating defect, did not seem appropriate for a children's book.)

In the months that followed, Banerjee and her son, Rishi, drafted a manuscript while Maya, an artist since childhood, painted sample scene illustrations in watercolor.

"Our struggles were those that you might expect for novices – using language that was pitched for the elementary/middle school child and illustrating the book well," Banerjee says. "At the end, my daughter did a great job with bringing the book to life with her drawings, but her first attempt had the flies looking too true to their insect selves, and Ted recommended that she humanize them."

Before painting each scene, Maya used thumbnails and sketches to plan the composition and designs. The characters went through at least a few iterations before she found the style she wanted to stick with.

Getting it published

Once the manuscript and illustration samples were complete, Banerjee approached the ASBMB to discuss the prospect of having the society publish the book. "ASBMB has a serious science outreach mission, and publishing a children's book with a scientific theme is a different way of reaching into the community," Banerjee says, noting that she had contacted another society about the book but was not met with the same enthusiasm.

"Fruity and the Mutants" debuted at the ASBMB's annual meeting this spring in San Diego, where Banerjee held a book signing. She also presented the book at an international children's festival in Michigan in early May.

She says it's her hope that the book, as Kooser writes in the foreword, "teaches us a little something about our world."

More information on "Fruity and the Mutants" can be found at http://asbmbchildrensbooks.org/. The book also is available on Amazon.com.

Emily Huff (ehuff@asbmb.org) is the project coordinator for publications at ASBMB. She oversaw the publication of "Fruity and the Mutants."

Book contributors

Ruma Banerjee, a professor and associate chair at the University of Michigan Medical School, studies the chemical biology of mammalian sulfur metabolism, the structural enzymology of human B12 trafficking proteins and enzymes involved in H2S biogenesis and catabolism and redox signaling in immune and neuroimmune function. She earned her Ph.D. at Rensselaer Polytechnic Institute and completed postdoctoral research at the University of Michigan. She is an associate editor of the Journal of Biological Chemistry.

Rishi Ragsdale, son of Banerjee, is an undergraduate at the University of Wisconsin-Madison who intends to major in both physics and mathematics.

Maya Ragsdale, daughter of Banerjee, graduated from the University of Michigan with a degree in international relations and intends to one day hold political office.

The amazing green fluorescent protein

Events leading to the cloning and expression of its gene and reflections on its impact

By Milton J. Cormier and Richard O. McCann

Only Mother Nature could construct a molecule whose fluorescence quantum yield approaches 100 percent when dissolved in water (1). This characteristic of green fluorescent protein is the reason its gene has revolutionized cell biology. The use of the GFP gene is responsible for advancing our knowledge of mechanisms in many areas of cell biology, such as gene expression, cell division, cytoskeletal organization, vesicle trafficking and neurotransmission. Moreover, only during a time when a project was supported, as a matter of course, because it asked an interesting, fundamental question about the natural world (in this case, "How do marine invertebrates emit light?") would GFP have been discovered.

Many of the details leading to the cloning of the GFP gene from the laboratory led by Milt Cormier (one of the authors) never have been reported. Because of the importance of the GFP gene, we feel that these details may be of interest to the scientific community.

From enzymology to molecular biology

Cormier began his graduate work at the University of Texas at Austin under the guidance of Lester Reed and obtained his Ph.D. at the Oak Ridge National Laboratory in Tennessee as a fellow of the Oak Ridge Institute of Nuclear Studies. While at Oak Ridge, Cormier and Bernard Strehler discovered two of the components required for light emission in luminous bacteria (2, 3). During his stay at Oak Ridge, Cormier had the pleasure of meeting many well-known scientists from various parts of the world as a result of the famous Gatlinburg Conferences held each year during this time.

Starting in the late 1950s, the goal of the research program in the Cormier lab at the University of Georgia was to understand the biochemistry and biophysics of light emission in bioluminescent marine invertebrates, with the major focus initially on the sea pansy Renilla reniformis, which is an anthozoan soft coral common along the Georgia coast.

During the 1970s, Bill Ward was a postdoc in the lab. He is now a professor at Rutgers University in New Jersey. Harry Charbonneau was a graduate student at the time and is now a professor at Purdue University in Indiana. Rick McCann (also an author) was a technician in the lab and is now a professor at Mercer University School of Medicine in Georgia.

Over several summers, the three of them went to the University of Washington Marine Laboratory in Friday Harbor to collect the bioluminescent jellyfish Aequorea victoria. In that period, thousands of jellyfish were collected and processed, and the extracts were frozen on dry ice for transportation back to the laboratory in Georgia.

After moving to Rutgers, Ward, who continued to collect Aequorea at Friday Harbor alongside the Cormier group, focused his research on the structure and function of Aequorea GFP after characterizing Renilla GFP at the University of Georgia (4). Charbonneau, who was by then a postdoctoral fellow with Tom Vanaman at Duke University, was determining the amino acid sequence of the Ca^{2+}-activated photoprotein aequorin (5) using protein purified by McCann at UGA.

By the late 1970s, members of the Cormier laboratory had isolated and characterized the three major proteins involved in bioluminescence in Renilla reniformis: luciferase (6), luciferin-binding protein (7) and GFP (4). It became apparent that we would never be able to isolate sufficient amounts of these Renilla proteins in order to study their structure–function relationships required for bioluminescence. We had to take a different approach.

There were by then two examples of the cloning of genes in higher organisms. One was the cloning of the gene coding for human insulin. So Cormier decided to change his lab from an enzymology lab to a molecular biology lab. Since Charbonneau had made significant progress in determining the amino-acid sequence of aequorin, an attempt to clone the aequorin gene seemed logical.

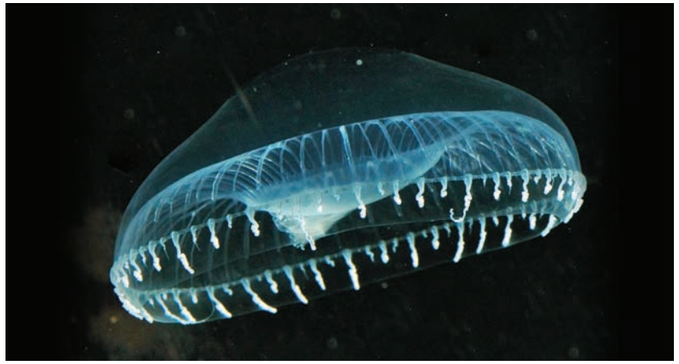
This was before the facile cloning of your favorite gene was a routine procedure in every lab: no polymerase chain reaction; no automated DNA sequencers; no commercially available plasmids with multiple cloning sites; no cloning kits; no BLAST, or basic local alignment search tool. From the partial amino-acid sequence of aequorin, we were able to derive oligonucleotide probes that were used subsequently to identify putative aequorin clones.

At about this time, the National Science Foundation grant that supported the Cormier lab was up for renewal, so Cormier submitted a new grant proposal to support the cloning work. For the first time in 25 years, his funding request was denied. Fortunately, Cormier had a contact at a major pharmaceutical firm who seemed interested in the project. After he presented a seminar to the company, it offered generous support for the cloning work.

At that point, Cormier began looking for a molecular biologist who could help clone the aequorin gene. Doug Prasher, then a postdoc in the UGA genetics department, was interested and agreed to join the Cormier lab in the early 1980s. By the time Prasher arrived, everything was in place for molecular biology, including some frozen Aequorea tissue. That summer Prasher and McCann went to Friday Harbor to collect more jellyfish and, ultimately, construct an Aequorea cDNA library.

By the autumn of 1984, Prasher felt that he had isolated the aequorin gene based on the hybridization of the aequorin-specific oligonucleotides to several clonal isolates, but he could not verify this, because he was having difficulty in expressing the gene. We had a conversation about this problem.

McCann suggested Prasher might be expressing aequorin at a low level



Aequorea victoria. IMAGE COURTESY OF SIERRA BLAKELY - WIKIMEDIA COMMONS

even from pBR322, which was an early cloning vector in which inserts were cloned into either amp^R or tet^R genes but not an expression plasmid, and that this could be measured in E. coli extracts, given that it is possible to detect sub-attomole (10^{-18} mole) levels of aequorin.

We suggested Prasher look for expression using a bioluminescence assay used routinely in the lab. The very first try produced so much light that the luminometer became saturated. There was jubilation in the lab. We knew then that we had expression of aequorin. That paper was published in 1985 (8).

Cloning of the GFP gene

Upon completion of our work on aequorin, Cormier suggested that Prasher try to clone the GFP gene, since we already had a cDNA library from Aequorea. Furthermore, Ward was willing to furnish us with partial amino-acid sequence data. Prasher agreed and was successful in isolating a GFP clone. When the gene was sequenced, we realized that the clone represented 70 percent of the coding sequence.

Since Prasher could not identify the full-length gene in that cDNA library, it was obvious that additional collections of Aequorea were required. At this point, Prasher obtained a position at the Woods Hole Oceanographic Institution, but he and Cormier agreed to continue their collaboration on the cloning of GFP.

Cormier was running out of research funds again by then, so he applied to the NSF. Once again, the grant was turned down. This loss of funding forced the closure of his lab. Cormier subsequently retired but insisted that two assistant professors be hired to replace him. That was done. He also remained available while Prasher continued his work on GFP. Fortunately, Prasher obtained independent funding in 1989. An additional collection of Aequorea was made, and the full-length gene was isolated. That work was published in 1992 (9).

Based on the protein sequence of GFP, Frank Prendergast, a professor at the Mayo Medical School in Minnesota who earlier had published a paper on the characterization of Aequorea GFP (10), predicted the likely GFP chromophore structure.

Prasher then turned his attention to the expression of GFP.

After making a number of attempts to express the gene, he phoned Cormier about the difficulty he was having. Cormier assured Prasher that he would figure it out. However, Prasher's research position at WHOI was ending. (Had Cormier known

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this, he would have urged Prasher to return to Georgia to complete his work on the expression of GFP.)

Rather than let the project languish, Prasher gave the gene to Martin Chalfie and Roger Tsien in 1992 upon their request. The rest, as they say, is history. Chalfie's lab figured out how to express the GFP gene shortly after receiving it. They then used the GFP gene to study gene expression in living cells. This work was published in 1994 (11).

Tsien subsequently designed variants of GFP that fluoresce in the various colors we now use in virtually all of cell biology. The Nobel Prize committee credited Osamu Shimomura with the discovery of GFP in Aequorea and gave him, Chalfie and Tsien the Nobel in chemistry in 2008. The seminal contributions of Prasher to this work were not forgotten by Chalfie and Tsien, however, and that part of the story was covered in a long article in the magazine Discover in 2011 (12).

But there is a larger point about the work that led to the discovery of GFP and the ongoing revolution in cell biology that has been facilitated by this fascinating molecule. All of the foundational research in the Cormier laboratory and that of the others who worked on bioluminescence in coelenterates was supported by the NSF, the National Institutes of Health and a precursor to the Department of Energy largely because it addressed a fundamental question straight out of natural history: How do these organisms emit light?

The simple answer is that one protein with enzymatic activity (luciferase, aequorin) oxidizes a reduced substrate (luciferin, coelenterazine) to produce blue light. In the organism, however, the energy from the excited state of the substrate is transferred nonradiatively with high efficiency to GFP, which then emits the green light seen when living Renilla or Aequorea are stimulated. This is the same green color seen when the original Aequorea GFP, expressed as a recombinant protein, is excited by blue light in a fluorescence microscope.

Multiple applications in cell biology

Native aequorin was first injected into living cells and used as a calcium indicator by E.B. Ridgway and C.C. Ashley in 1967 (13). Today, aequorin-expression vectors are used to measure calcium transients in animal, plant and fungal cells.

Shortly after aequorin was cloned in the Cormier laboratory and following on the work of John Matthews (6), now a professor at the University of Mississippi, Walt Lorenz and McCann cloned and expressed Renilla luciferase (14). This luciferase, in tandem with firefly luciferase, which has a completely different substrate, is now used widely as a reporter for gene expression in cells of all types. The use of GFP in all its colors is limited only by the imagination of cell biologists. For example, fluorescence resonance energy transfer, known as FRET, between GFP variants of different colors can be used to measure the distance between molecules in living cells.

Although we outline here events that occurred in the Cormier lab, Frederick Tsuji also has written an informative article from his perspective regarding the history and cloning of the GFP gene (15). All investigators who took part in this exciting endeavor to clone and express the GFP gene and the other proteins responsible for coelenterate bioluminescence should take heart in knowing that they were part of the effort that resulted in a revolution in cell biology.

Moreover, as outlined recently by Joram Piatigorsky (16), those responsible for deciding which research gets funded, from policymakers to members of review panels, should remember that the answers to scientific questions cannot be known in advance and that these questions and answers often lead to advances in scientific knowledge and scientific practice that are as revolutionary as they are unimaginable and unpredictable.

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Uncovering the unexpected

By Andrew D. Hollenbach

I couldn't believe it was happening to me. I'd always worked hard and succeeded – not only succeeded but excelled. Now there I was: I had just finished my second year of graduate school, and I had been told that I had failed my qualifying exam. I was devastated.

Not only was this the first time I had worked hard and failed, but it also meant that I could be asked to leave the program, derailing my dream of becoming a scientist. The more I spoke with my committee members about why I had failed, the more I realized that my failure stemmed not from my intellectual ability but rather from my inability to cope.

I had thought that sleepless nights and paralyzing stress were normal for a graduate student. What soon became evident, though, was that they not only were not normal but were a serious problem called severe panic attacks; and if I didn't get the problem under control, my own psyche would derail my dreams.

'You must get this under control!'

Graduate school is a whole new stage in a scientist's development. Gone are the undergraduate days when you work hard to memorize facts so that you can regurgitate them for exams. Instead, you are expected to learn concepts and apply them to real-world problems. The ideas are no longer someone else's that you have to learn; the ideas are yours that you have to defend. Information comes fast and furious, and you are expected to balance class, laboratory work, journal clubs, presentations and, yes, life.

I learned that it was OK to admit that I had a problem and accept other people's help.

The increased expectations and workload can bring out problems that you might never have realized existed. Or if you realized these problems existed, maybe you were able to control them just enough to survive. For me, this new stage in my development attacked my self-confidence. I had always suffered from a lack of self-confidence (I still do, in fact, but I know how to manage it now); however, up to the point when I entered graduate school, I was able to deal with this problem, or so I thought. The new demands fueled this negative psychology, fed it like oxygen to a raging fire, ultimately leading to my debilitating and paralyzing panic attacks.

Fortunately, I had a stern yet understanding exam committee. To this day, I remember the wise words of the late John Scocca (a man who scared the heck out of me as a student but whom I remember now with extreme fondness and the utmost respect): "You will always be faced with pressures at every stage of your career. If you want to stay in this profession, you must get this under control!"

Taking these words to heart, I began therapy through the student health program, and over the next year I got my panic attacks under control, which allowed me to demonstrate to my examining committee my true capabilities.

'A transformative moment'

When I look back and read what I wrote for that exam with the eyes of experience, I see just how horrible that exam truly was. What I now realize is that it was a transformative moment in my life, a hard realization that made me reevaluate myself and rededicate myself to my dreams and goals. Through the ordeal, I learned about my shortcomings. I learned that it was OK to admit that I had a problem and accept other people's help. I learned how to lick my wounds and fight for my ambitions.

Many students look at me today and see a confident and secure faculty member. Little do they realize that I nearly failed out of graduate school and suffered a lot of pain (and a lot of therapy!) to get to this point in my life and career. Now my experience serves as an example for students — to let them know that they are not alone, that the hard times they are experiencing will help them realize something new about themselves and that from these experiences they can grow in unexpected ways to succeed in ultimately realizing their dreams.

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Curricular revision: embracing the journey

By Neil Osheroff

Few words strike as much fear in the hearts of medical-school faculty members as "curricular revision." It is a long, arduous and often unsettling process. However, curricular revision is a phrase that many, if not most, of us are hearing these days.

A large number of medical schools have revamped their preclerkship curricula over the past decade, and many are in the process of doing so now. It is a trend that is being driven at the national level. Commonly, new curricula are marked by a move from discipline-based to interdisciplinary courses, by decreased time devoted to the foundational sciences, by the devaluation of lectures and other traditional teaching methodologies, and by the inclusion of small-group sessions and other types of learner-centered teaching.

The Vanderbilt University School of Medicine has undergone two major curricular revisions since 2007. The first (now referred to in the local vernacular as Curriculum 1.0) seems relatively mild by today's standards; however, it seemed earth shattering at the time. That was when we moved from discipline-based courses to interdisciplinary blocks. After directing the medical biochemistry course for 17 years, I had to work with two faculty members from other departments to develop a new course that encompassed biochemistry, cell and tissue biology, and genetics.

Prior to Curriculum 1.0, the preclerkship science courses, which were run out of departmental offices, had little to do with one another. For many years, the only interaction that I had with the directors of the anatomy course (which ran simultaneously with biochemistry) was when they sent an annual message telling me when the anatomy exams would be and to make sure that I did not schedule the biochemistry exams too close to those dates. In those days, medical student courses were important to departmental missions, because they provided departments with an identity within the School of Medicine. Although it had become harder to define what a biochemist actually was, everyone knew a biochemistry course when they saw it. Discipline-based courses also gave course directors a certain level of status within their departments. Directors had a time-consuming and often thankless job, and most faculty members were grateful that the responsibility for the course rested in someone else's hands.

IMAGES COURTESY OF VANDERBILT UNIVERSITY AND MEDICAL CENTER

After the initial shock of our mandate for Curriculum 1.0 wore off (along with all of the now-familiar questions: Why are we doing this? What was wrong with the old curriculum?), we settled into our task.

Our first foray started with three coordinated semi-independent courses. We soon abandoned this idea and decided that it would be best to work together rather than as separate entities. After several months and many different approaches, we arrived on a mutually acceptable interdisciplinary schedule and christened our new course Molecular Foundations of Medicine. To help set up the block, I generated a color-coded spreadsheet

of the classes. I lined up the lecturers for biochemistry (blue) and my co-directors lined up the lecturers for cell and tissue biology (red) and genetics (green). Once we had everyone scheduled, I changed the color scheme to denote the type of class: Blue now stood for lectures, red for exams, green for patient sessions and so forth.

"That was the day that everything changed."

Although altering the color scheme seemed like a minor modification at the time, it turned out to be a pivotal point in the development of Molecular Foundations of Medicine and in my development as an educator. The block became more than the sum of the individual disciplines. We stopped caring, for instance, whether a lecture on membranes was cell biology or biochemistry and started caring more about how everything in the block fit together. After all was said and done, Molecular Foundations of Medicine was far better than any of the courses that it replaced; it allowed us to place important scientific information into a more logical, appropriate and meaningful cellular context.

The block turned out to be a startling success with the medical students, which was music to my ears after so many years of running biochemistry, "the course that all physicians loved to hate." I found it much more rewarding to teach as a member of a faculty team than to go it alone. Faculty members from other departments and administrators soon became my colleagues and valued friends. For the first time, I felt that I could translate the creativity I put into my research into my teaching. Although my value to the mission of my department had diminished, my value to the mission of the school had grown enormously.

In 2011, only five years into Curriculum 1.0, we learned that we would be moving to a new model, Curriculum 2.0, starting in autumn 2013. This time around, I had greater responsibilities. In addition to being a block director, I was one of four faculty members charged with developing, implementing and overseeing the entire preclerkship science curriculum. The task was daunting, especially in light of the far more radical (or cutting-edge) demands of Curriculum 2.0.

We had to decrease the preclerkship time for the foundational sciences from two academic years to one calendar year with a later reintroduction of the foundational sciences in the clinical years. Moreover, the individual science blocks were much

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more heavily integrated with one another than in the previous curriculum. My eight-week Molecular Foundations of Medicine block morphed into a six-week Human Blueprint and Architecture block that included several hours of pathology, anatomy and pharmacology in addition to its previous core elements. Furthermore, the blocks contained less time for lecture and a featured unifying thread of weekly small-group sessions that taught the sciences in the context of patient cases. These case-based learning sessions were critical to the success of Curriculum 2.0 and were allocated six hours a week of in-class time.

Despite the complexities of Curriculum 2.0, our experiences with Curriculum 1.0 prepared us for the interdisciplinary and collaborative approaches necessary to develop the science blocks in a model that was unique to Vanderbilt. In contrast with the curricula at many other medical schools, Vanderbilt's Curriculum 2.0 deftly incorporated a variety of teaching modalities and valued them all. Students, according to their block evaluations, greatly appreciate this approach.

We now have completed our first year of Curriculum 2.0. By all accounts, it has been very successful. Initial evidence suggests that students who have participated in the curriculum are scientifically inquisitive, display strong reasoning and teamwork skills, and can effectively apply these underlying scientific concepts to clinical scenarios.

The successful implementation of the curricular revisions at Vanderbilt required a strong working relationship between the faculty and the administration. Each group valued the other as an educational partner.

The successful implementation of the curricular revisions at Vanderbilt required a strong working relationship between the faculty and the administration. Each group valued the other as an educational partner. Although the administrators established the guardrails for and oversaw our curricular revisions, they did not micromanage the process. They trusted the faculty members to implement a creative and appropriate set of science blocks. This trust allowed the faculty members to take ownership of their blocks, which was a critical contributor to our success and serves as a model for how administration and faculty members can work together on critical projects.

I am looking forward to our next major curricular challenge: the insertion of the foundational sciences into the clinical curriculum. I am already certain regarding one aspect of the process: If we want our students to reinvest themselves in the biosciences while on the wards, we cannot separate the science from the clinical experience. We have to repackage the foundational sciences in terms of their patients' illnesses, symptoms, test results and treatments rather than in terms of the traditional disciplines that once defined our teaching. Pilots of such integrated courses show promising results.

Finally, although our two curricular revisions have had a profound effect on the way that we teach our medical students, in many respects they have had a more profound effect on me. By embracing the journey rather than fighting it, I have gone from being a teacher to an educator to an educational leader and have written a new chapter in my three-decade academic career.

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Need help with curricular revision?

If your department or institution requires assistance with curricular revision; the adoption of new teaching methods; or the development of learning objectives, assessment items or competencies, the Association of Biochemistry Course Directors can help.

Founded by the Association of Medical and Graduate Departments of Biochemistry in 2008, the ABCD is a membership organization of nearly 300 biochemistry (and related) faculty members from about 170 schools of medicine, dentistry and pharmacy. ABCD members are educational and curricular leaders who have tremendous experience and expertise in all aspects of curricular design and integration, learner-centered teaching modalities and educational scholarship.

If you are involved in teaching the molecular sciences to professional students, consider joining the ABCD. Faculty members at all levels of experience are encouraged to apply for membership. For more information, visit www.abcd.wildapricot.org.

Q&A with Pumtiwitt McCarthy

By Andrea Anastasio

Tell us about your current position.

MCCARTHY

I completed my postdoctoral fellowship at the Center for Biologics Evaluation and Research at the Food and Drug Administration on the National Institutes of Health campus in Bethesda, Md., last July. The following August, I started as an assistant professor of chemistry at Morgan State University in Baltimore. I am teaching courses, establishing a research program and serving on university and department committees. My research program is focused on gaining a better understanding of enzymes that produce capsular polysaccharides in the pathogen Neisseria meningitis, one of the leading causes of bacterial meningitis.

What are the key experiences and decisions you made that have helped you reach your current position?

I had great mentors as an undergraduate student, graduate student and postdoc. They were encouraging and supportive, which really helped me to gain more confidence in myself and my scientific ability. This confidence led me to seek out and go after opportunities that I otherwise would not have pursued. I also think developing my skills outside the lab, such as writing, serving on committees and giving presentations, has made me more well-rounded.

How did you first become interested in science?

I can remember being interested in the way things work even at a young age. I distinctly remember a time when I broke my parents' record player because I wanted to figure out how all its parts worked together. I really developed a love for science when I had the opportunity to do research as an undergraduate.

Were there times when you failed at something you felt was critical to your path?

The transition from high school to college was particularly difficult for me, and I had to take a step back and reassess what was working for me and what wasn't and make appropriate changes. This made me more determined not to be defined by my past failures but instead by what I have succeeded in. I think failures and disappointments are, of course, unwanted but necessary. It is through these disappointments that I can appreciate and be grateful for how far I have come.

What advice would you give to young persons from underrepresented backgrounds who want to pursue careers in science similar to yours?

I am honored and proud to be at Morgan State University, which is a historically black college or university, so that I can hopefully help make a difference in increasing the number of minorities entering science, technology, engineering and math fields. My advice is to seek out mentors who are in the position you want to be in and learn from them. I also would say work hard, never give up and always take the opportunity to learn from your mistakes.

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

My mother is my heroine. She immigrated to America from Liberia in the late 1970s. She had a very good job back home but essentially had to start all over in America. She was hard-working, humble and respectful to everyone she encountered. She always told me, "To whom much is given, much is expected." I try to remember that I have been blessed and give my all to whatever I do.

What is it that keeps you working hard and studying science every day?

I would say my desire to be a lifelong learner. I want to always keep growing and continually improve. My ultimate wish is to instill a love and understanding of biochemistry in my students so that they see it as a field that is accessible to them and one they can pursue.

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Looking beyond the lab

AAAS webinar highlights paths to nonacademic careers

By Shaila Kotadia

The new normal is that most Ph.D.s will have nonacademic positions. Nowadays, jobs in nonprofits, government, industry, patent law and many other areas employ newly minted Ph.D.s. But how does a budding young scientist transition to these careers? As I was searching for my next step, advice from those that had experienced the transition was priceless.

Earlier this year, when I was looking for my next professional position, I had the chance to view a webinar (now a members-only privilege) presented by the American Association for the Advancement of Science titled "Thinking outside the lab: finding a fulfilling nonresearch career." A panel of speakers with mixed experiences that led them to positions outside of the lab relayed their personal journeys and the necessary skills they developed along their paths. The webinar was full of gems that are crucial when navigating the career world away from the bench. Here, I recap some of the major points.

The panelists included Marcia McNutt, editor-in-chief of Science magazine; Lori Conlan, director at the National Institutes of Health Office for Postdoctoral Services; and Anish Goel, director of geopolitical affairs at The Boeing Company.

McNutt started on a traditional academic path, even obtaining tenure at the Massachusetts Institute of Technology, but decided to switch careers and accepted a position as a director of a small, not widely known oceanographic research lab.

She said that she had taken a personality test for a university study on women in science. The personalities had been organized into a triangle, with the points designated as the leader, the loner and the follower.

"This professor called me breathlessly to tell me that I was her Joan of Arc because I had fallen on the midway point between the leader and the loner," McNutt said. "Basically, she said I was the person who would lead the troops into battle, but if they wouldn't follow me, I would just do it myself."

Conlan described her path as "planned happenstance." She said, "Looking back on it, it looks very planned, but at the time it seemed like a random walk."

The constant in this walk was her effort to highlight careers outside of academia while she was in graduate school and during her postdoctoral training. This helped her obtain a position at the Science Alliance at the New York Academy of Sciences and her current job at the NIH.

Goel began by saying, "I like to tell people that I'm actually on my third career now." He said he began as a graduate student — delaying the process of facing the real world. He kept his eye out for opportunities even if they were outside his comfort zone and found the AAAS Science and Technology fellowship. After working for the government, he decided that he would switch to the private sector, landing eventually at Boeing.

The webinar continued to be a goldmine of advice for a scientist looking to transition to a nonacademic career. Below are several highlights from which anyone on the job search can benefit.

Educate yourself

One takeaway from the webinar is that when you're choosing a graduate school or postdoctoral position, you should seek out institutions with career-development offices or grants that allow Ph.D.s to intern at other organizations.

For those already stationed somewhere, Conlan suggested looking to neighboring institutions that offer programs if your current institution does not. In addition, she says that the myIDP resource provided by Science Careers is an excellent resource to match your skills, values and interests with possible career paths.

McNutt added that you should push for nonacademic career speakers for seminars.

Sell yourself

But what about that frustrating loop of needing experience to get a job but not being able to get a job due to lack of experience? Goel says that you have more experience and skills than you might think. Being able to think critically about issues is important for many careers. Think hard about how you are selling yourself.

Develop your skills

If you are already in a position meant to develop your skills, consider also gaining new experiences.

For instance, Goel said he would have practiced nonacademic writing and presenting to large groups of people by giving speeches. Conlan said that she would have developed office skills by volunteering at nonresearch offices at her home institutions. She said she also valued her service on various committees.

McNutt said that she would have honed her people skills – how to motivate people by recognizing their strengths and weaknesses, bringing them together to work as a team, and assigning tasks that they will excel at and be comfortable with.

If you do not feel ready after graduate school in these areas, consider taking a postdoctoral fellowship. As Conlan said, "A postdoc is a necessary career step for some people, not a holding pattern."

Transitioning to a new marketplace

Goel has made the jump to a new career twice and said he did his homework beforehand. It is important to seek out all of the options that exist and to be able to step out of your comfort zone. In the end, you need to find what best fits you at that time.

McNutt added that she approached every job as the job she would have for the rest of her career. With this strong work commitment, she moved forward in her career to many leadership positions.

Networking

The webinar speakers discussed networking at the most length, and I cannot stress its importance enough. "Networking is the foundation for making the right connections, building personal relationships with people, getting your name and work out there," McNutt said. Nowadays, with so many scientists and publications, networking is the best way for someone to connect you with your work.

Conlan talked about informational interviewing, which is a great way to build your network. When contacting individuals in fields of interest, be prepared to ask better questions by recognizing your skill sets and finding the jobs that best match those.

Prepare to cover four basics:

- the present – what the interviewee's current position entails
- the past – the path the person took and whom he or she spoke with on the journey
- the future – where the person is headed and where the field is going
- advice – who else you should talk to and career opportunities that might be available

If you are intimidated by networking, then try to think of it more as data gathering and an exchange of ideas like a research collaboration. Also, Goel notes that networking includes helping others out.

In the end, McNutt made an excellent point: "always build bridges along the way; never burn them." You never know where someone will end up or how he or she can help you, so always be respectful and courteous.

No matter what you do next, it is going to be "like jumping off a cliff," says Conlan, because you will not have any idea of what it is like until you are in the thick of it. If you keep your network open, you always can use that as an opportunity to transition back to a previous career or onto the next.

A career outside of the lab can be fulfilling and prestigious and can lead you on the road to a happy and successful life. Now is your chance to explore and find what job fits your best attributes!

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Moving into administration: Is it really that difficult?

By Mary Huff and Benjamin D. Caldwell

Editor's note: This is the second article in an occasional series about transitioning from the faculty ranks into university administration. In February, Benjamin D. Caldwell, dean of the Missouri Western State University Graduate School, wrote about the routes to administrative positions, how the transition affects relationships and duties, and other considerations. Here, Caldwell and Mary Huff, assistant dean of Bellarmine University's College of Arts and Sciences in Kentucky, explore shared experiences as administrators at regional institutions. Caldwell and Huff also act as regional directors for the American Society for Biochemistry and Molecular Biology's Undergraduate Affiliate Network.

At institutions like ours, the administrations tend to grow their own – developing faculty and promoting from within.

One good thing about this approach is that those who are selected for administrative positions know the institution, faculty members and students. When an institution fills administrative positions with external candidates, it can take some time for these new employees to learn the systems and culture of the institution before getting down to business.

On the other hand, one potential downfall to promoting from within is that it takes successful faculty members away from areas in which they have excelled, such as teaching and research. Also, newcomers could bring in fresh perspectives and ideas.

We both have been in our positions for about two years now, and we both split time between our administrative and faculty roles. We both love teaching at the undergraduate level. Sharing our passion for biochemistry and watching students become lifelong learners are just two of the highlights of being involved in undergraduate education.

So why'd we do it?

Honestly, the idea of moving to what many faculty members refer to as "the dark side" had never appealed to either of us. While we didn't really know what administrators did, we long had believed that they served to create more work that hindered faculty members like us from doing our jobs! Why would anyone want that type of position?

On the other hand, it was flattering to be offered positions with new responsibilities. And, having great respect for our own deans and administrators, we knew that working with them would be a good experience. So we decided that it was time to leave our comfort zones and see if there was a different way to make an impact at our universities.

The beauty of both of our offers is that they were not going to remove us from teaching. In fact, we both would continue teaching 10 to 12 credit hours per year while performing those mysterious administrative duties. We told ourselves that teaching and having daily interactions with department colleagues would make us different from the other administrators: We'd be faculty members with only one foot on the dark side, and we could save ourselves if we began to approach a point of no return.

Mary's story

My journey began two years ago. My students often tell me that they can tell that I am busy but that they have no idea what I'm doing. I am not sure that I can easily put into words what I do either!

One major focus is course scheduling. I review all of the schedules as they are developed and make sure that there is enough variety. I also work with the school registrar to maximize classroom space. When registration begins, I monitor the schedule to make certain that we have enough courses and cancel those with insufficient enrollment.

I also oversee textbook orders each semester, working with faculty members and the bookstore staffers.

Then there are the other duties, such as mentoring new faculty members, overseeing the faculty-development budget, approving student internship applications, reviewing student petitions and sometimes listening to student complaints.

Of course, there are endless meetings: meetings with the dean, meetings with the chairs, meetings with other academic leaders, meetings of subcommittees that I lead, meetings over lunch, meetings over breakfast, and more.

Ben's story

My situation is very similar to Mary's. I have just completed my second year as dean of the graduate school.

Like Mary, I attend a multitude of meetings. I serve on a number of standing committees that meet regularly (weekly, biweekly or monthly). This can create scheduling nightmares, and I worry about the time I have available for students in my classes and labs. Time management and organization have been essential and, at times, challenging! There are times when both students and faculty members have difficulty tracking me down. Am I in my faculty office or at the graduate-school office across campus? (I am getting more exercise going back and forth across campus!)

Like Mary, I'm responsible for monitoring student registration, course offerings and faculty-member assignments. However, I dedicate a lot of time to overseeing student complaints about grade assignments, requests for course substitutions or exceptions for hardships, and other similar student issues.

I also oversee admissions, recruiting and program advertising and marketing – areas in which most faculty members (other than those who specialize in these areas) have little experience.

In general, I do enjoy my role as dean, mostly because I get to interact with all kinds of people across our campus as we build new programs for our students and our community.

In conclusion

Over these past two years, we both have learned that, while the work that we do as administrators is very different from what we do in a classroom, it is not necessarily difficult. It takes organization, an eye for detail and a commitment to meeting deadlines, which can add a level of stress. It also requires patience, strong listening skills and the ability to work with all types of personalities.

Some of the work is routine; yet then there are projects that are at the heart of the position that are enjoyable. Our universities are both in a period of growth, and helping to implement the strategic plans is exciting. Analyzing course and program enrollments to see where we are experiencing growth in our schools, predicting where we need additional faculty members, creating additional office and lab space (sometimes out of utility closets), and looking for new ways to enhance programs is rewarding. It is nice to know and meet faculty members who show passion for their disciplines, and the enthusiasm they exude for their programs is inspiring.

We both have come to realize that administrators and faculty must work together to support the overarching goals of our universities and that we all value the success of our students. Helping to shape that vision, resolving problems that can hinder the university's success and knowing that we share a common goal has been a truly transformative experience.

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The Florida Biomedical Career Symposium

November 7, 2014

KEYNOTE SPEAKER:

Sir Harold W. Kroto

Co-recipient, 1996 Nobel Prize in Chemistry
Francis Eppes Professor
Department of Chemistry and Biochemistry
Florida State University

KEYNOTE LECTURE TITLE:

The Global Educational Outreach for Science, Engineering and Technology (GEOSET) Project Pioneered from Florida State University

Supported by The Scripps Research Institute, Florida and the American Society for Biochemistry and Molecular Biology Career Symposia Program

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The CAISE for informal science education

Open repository offers thousands of project and activity descriptions for use by scientists and students interested in engaging new audiences in their work

By Angela Hopp

The Association of Science and Technology Centers, a Washington, D.C.-based membership organization, is home to the Center for the Advancement of Informal Science Education, a National Foundation of Science–funded center that houses a repository of informal science-education projects and related professional resources. ASBMB Today's editor, Angela Hopp, talked to two CAISE staffers: James Bell, the project director and a principal investigator, and Kalie Sacco, the program and community manager. The American Society for Biochemistry and Molecular Biology's outreach coordinator, Geoff Hunt, also joined the discussion. This transcript has been edited for length, style and clarity.

Can you tell me about your backgrounds?

BELL

Bell: I've been in informal science education for almost 30 years. I started after having initially a music degree. When I finished my undergrad, I was volunteering at a place called the Exploratorium in San Francisco, a science center. And through my exposure there to a very different way of teaching and learning science, I (made) a career shift ... The way things were done there and how creative the enterprise was – (it was) an experience that I did not have as a student in K – 12. I just was not engaged: It might have been the teachers; it might have been me … It was through unique learning experiences and a relationship with an informal institution that I changed my career trajectory and began running programs and redirecting my education trajectory so that I could continue working in this field, which I've been doing since then.

SACCO

Sacco: I started getting interested in museum education specifically and working in museums when I was an undergrad in college too. I started at a children's museum and an anthropology museum in the Bay Area and then took a class up at the Lawrence Hall of Science, which is a science center in Berkeley. While I was there, I ended up getting involved in a whole bunch of different departments and programs.

I started working in the education department doing summer classes and after-school classes for kids of all different ages. And when I graduated, I started working there full time. I was half-time in the research department, doing research and evaluations of different STEM learning programs, both formal and informal, and then half-time as the manager for a national after-school organization called the Coalition for Science After School. I was explicitly interested in museum education – not necessarily science – but working at the (Lawrence Hall of Science) was fun.

I guess, like Jamie, I didn't have a lot of great experiences in formal science education growing up. I was in a small town. There was no real big science museum. So coming at it as a young adult was really exciting for me.

IMAGE COURTESY OF RISDON PHOTOGRAPHY

CAISE convenes informal STEM education professionals at the 2012 ISE PI Meeting to discuss and advance ideas for better learning designs, settings and research.

ASTC members are mostly from museums and science centers, right?

Bell: Correct. And, as they are an anchoring sector for the field, it's a perfect place for us to be. But (the CAISE) project is meant to serve as much of the broader informal STEM education field as we can in addition to those – so zoos and aquaria, nature centers, afterschool, media, citizen-science programs. Part of our cooperative agreement from the very beginning with NSF is that we must always strive to create resources for and connect all of the ISE sectors to cultivate and strengthen the sense of a professional field.

I understand that CAISE's website offers a searchable database of informal-education activities. Tell me why or how you think it might be useful to ASBMB members.

Bell: If scientists, directors and their students — and sometimes those people in the role of designing outreach or engagement experiences — are looking to develop activities to engage the public, or any audience, in the scientific content of their research, they have a lot of different options available to them. They can go to a school and try to do something with a (class) or teacher. They can go online and look for activities ... They can develop things out of their own heads, which they often do.

I guess the point we'd like to make … is there's this whole body of knowledge and a repository of … examples of ways to design those experiences based upon evaluation and research and years of experience of what works and what doesn't.

What we've found as we interact with these communities, like your own, is that often people just aren't aware that there is accumulated wisdom from the work that has been done over the past almost 50 years and funded by NSF for over 30 of those. (A) People don't know about it, and/or (B) they might not understand the term. "Informal science education," frankly, puts some people off, because they feel like it connotes less serious … And perhaps it's an unfortunate term, but really it's only meant to distinguish between in school and out of school.

HUNT

Hunt: I would add that these kinds of projects and activities are becoming more integrated into the scientific process. It's no longer something that's for a select few dedicated individuals who like doing it. But it's becoming a part of the NSF grant process, a part of the (National Institutes of Health) process … And this (repository) is a way to say, "Hey, don't worry. We've got this covered based upon all of these years of experience," which you guys are accumulating on the site.

Bell: Right. The broader-impacts criterion for the NSF-funded projects has been given a new focus … to re-elevate it to equal importance with intellectual merit. In order for scientific research to get funded, it has to have the support of society. This is the theory of action, right? To have the support of society, people have to understand why it's being done, what the benefits of it are, who it's for, and how rigorously and thoughtfully it's being conducted.

And so these broader-impacts criteria — which are projects like the ones we try to catalogue and make accessible — help people communicate, engage the public and other audiences through these variety of strategies — from exhibits to citizen-science projects to television to film to gaming.

Sacco: I'll also just add that, from the informal educators' side, we always hear that they're really eager to connect with scientists and to get access to cutting-edge research and resources that are coming out of people's education and outreach branches of their labs and university departments. So there's a two-way need there.

How are projects and activities organized in this repository? How should ASBMB members go about digging into it?

Sacco: Every record in our repository — and there are almost 9,000 of them now — is tagged with a set of metadata, and you can use that metadata to search and sort different records. The big bucket categories that records are sorted into are these:

- Funding source — Which federal agency or private foundation funded the project or piece of research or evaluation?
- Content — What is the science topic or discipline? Your members might go look for records that fall under the life science metadata tag.
- Audience — Who is the record for? And that's for both learners — elementary school children, adults, youth, etc. — as well as the professional audience — a scientist or an undergraduate or graduate student.
- Resource type — That tells you what you're looking at — whether it's an evaluation report, a peer-reviewed research paper, project description, presentation, etc.
- And the last thing is environment type. That's the learning setting in which the record you're looking at takes place … like after-school programs, broadcast media, conferences, exhibitions, etc.

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You have both mentioned the media. What are some examples?

Bell: It's projects at public media stations, for example, that were funded, say, by the NSF to achieve public engagement and learning goals via an innovative approach. One primary example … is the KQED (program called) "Quest" in San Francisco. There's a public media station, and they partner with 16 other organizations locally, some of which are science museums, science centers and children's museums, but others are actual labs that have outreach offices, all of whom contribute to multimedia stories that Quest produces on local science-related issues.

Sacco: You might be surprised to know that some relatively well-known science programming has been funded by the NSF ISE program. I know this isn't in the biology sphere, but Neil deGrasse Tyson's original radio show, "StarTalk Radio Show," was funded through the ISE program. NOVA has been funded by the ISE and AISL program at the NSF. A whole variety of other science shows on PBS have been funded by the NSF.

Is there anything else you feel ASBMB members should know about CAISE's online project repository or informal science education in general?

Bell: If they have any questions or want to contribute anything, caise@informalscience.org is an email address that both Kalie and I receive. And we are here every day. You can get a really quick response and help with figuring out how you can use the resource and/or contribute to it.

Sacco: Exactly – our willingness to help people navigate the website and our eagerness to help your readers connect with the ISE resources that we have and also to learn from what they're doing.

Hunt: In my eyes, CAISE is the premiere online resource for scientists looking to get involved with science outreach and informal education. It makes my job much easier!

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

An open letter to press officers who won't promote unembargoed research papers

By Angela Hopp

Author's note: While this letter is addressed to press officers who won't promote research papers that cannot be embargoed, it raises an important issue that scientists should understand. A news embargo ensures that certain information is not made public until an agreed upon time. Some scholarly publishers use embargoes to keep newly accepted research papers out of the public sphere until they are published, allowing only a handful of people (such as authors, press officers and journalists) to see the material in the interim. One often-cited aim is to facilitate thorough reporting of the research. But more and more publishers today post all accepted papers online immediately. Most press officers will still promote those papers to the media, even though the news cannot be embargoed. But others will not.

Dear press officer who won't promote unembargoed research papers,

I know we haven't met and it's upsetting when strangers wag their fingers, so let me begin with a bit about how much we have in common.

I wear multiple hats here at the American Society for Biochemistry and Molecular Biology. My primary job is as editor of this magazine. I also am the media contact for the ASBMB's three scientific journals and annual meeting. Before coming here, I was a press officer at a university on the science beat. Before that, I was a newspaper journalist. I've pitched stories, and I've been pitched stories.

You probably can see, then, that you and I have shared goals. We are committed to spreading the word about scientific discoveries that have been hard fought and may one day change or save lives. We have the courage to reveal our own wonder and ignorance to scientific experts with the hope that the answers to our questions will increase scientific literacy. We want to showcase the expertise and creativity of researchers, because it's what we're paid to do, scientists aren't very good at doing it themselves, we like helping people and we're good at it. Most importantly, we want to tell stories that others will share and remember.

I promise: I get you. I respect you. And that's why I have to tell you that you're disappointing me. Your refusal to promote research papers that cannot be embargoed is undermining the researchers you represent, devaluing their work and diminishing your profession.

Papers in press

ASBMB journals accept dozens of

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submissions every week, and each acceptance letter asks researchers to contact me if they're going to work with their institutional press office on a release. I get queries every day from press officers wondering about embargoes, and I explain to each the ASBMB in-press policy: All accepted papers are published online immediately, putting them in the public sphere and making them ineligible for embargo. I tell them, usually in these very words, "I know this makes your job more difficult, but it's good for science."

Some press officers get it, and sometimes I get a disappointing reply, like this one: "The press office will not consider a paper for a press release after it publishes."

While I cannot speak for all journals that immediately publish accepted papers online (and there are many of them), I can tell you that the ASBMB views its authors as its primary customers. Those customers are scientists at universities, federal agencies and research institutes. In other words, those authors are the people that you, as a press officer, represent.

The scientific community clamors for the rapid dissemination of research results. Put simply, the hope is to facilitate the quick production of more discoveries. The in-press policy clearly was fashioned in response to that din. Publishers are meeting your people's needs.

While researchers — both journal authors and those scientists reading their papers — are the primary beneficiaries of the in-press policy, the public benefits too. They also can access these hot-off-the-virtual-presses results right away. And that's great, because, after all, they paid for federally funded research with their taxes.

The problem for press officers

I can think of several reasons you might not want to write about an unembargoed paper. Among the most compelling:

• Reading a paper, interviewing the authors, composing, checking facts, rewriting, editing and collecting media takes time. Embargoes give you that time.

• You cannot promote every paper your scientists churn out, so you prioritize. Embargoed papers, as noted above, are relatively convenient.

• The reporters you pitch to might ignore an unembargoed news release. That means you'll have fewer media placements to report to your researcher and, importantly, your boss.

I concede all three points. Your job is more intellectually challenging and time consuming than most people, including scientists and journalists, realize. You are burning calories like crazy running around your campus, donning bunny suits to get into the clean rooms and glad-handing politicians visiting new research centers. Some (overworked or lazy) reporters will disregard your unembargoed press release. Yes, writing about an unembargoed paper puts you at a disadvantage.

But you can and, in many cases, should do it anyway.

It's the story that counts

Here are my recommendations:

• Don't operate under a false construct. The primary criterion for a press release is news value. That a paper has been put in the public sphere does not diminish its news value.

• Don't undermine your researchers. They've worked hard to figure out whatever it is that they've figured out. For all you know, they've worked on that project for decades. Passing on their story is hardly the reward they deserve for wanting the scientific community to know about their findings right away.

• Don't overestimate journalists. Trust me, most of them are not trolling journal websites to see which papers have just been accepted and published online. They're lucky to have you to do the digging.

• Don't underestimate the importance of your work. I don't have to tell you how influential press officers are to the news cycle, but it is worth emphasizing. You've seen (and not taken credit for) plenty of media reports that were conspicuously cribbed from your press releases.

• Don't become complacent. You're a storyteller. That's why you got into this business in the first place. Stretch yourself. You know that a great story trumps timeliness any day and that many times the real story isn't even the result of the study. Tell the story right, and nobody will care that the paper isn't under embargo.

I hope that you can acknowledge that I might have a point. All I ask is that the next time a researcher with a new unembargoed paper requests a press release you actually read the paper and ask a few questions. You never know. There might be a great story there.

Best,
Angela Hopp
Editor, ASBMB Today

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

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Bonnie Bassler, Princeton Univ.
Zhijian James Chen, UT Southwestern Med Ctr.
Rachel Klevit, Univ. of Washington
Ian Wilson, The Scripps Res. Inst.

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