ASBMB today

Vol. 12 No. 8 September 2013

Science Globetrotters

Why and how do researchers work in two parts of the world at the same time?

ALSO INSIDE THIS ISSUE:

DERAILED, DETERRED, GOT OVER IT
The next installment in our personal essay series

HOW TO COMPETE WITH A LAB DIVA

American Society for Biochemistry and Molecular Biology

OPEN LETTERS

An open letter to our readers who have something to say but need a place (and maybe even permission) to say it

Dear Reader,

This is your magazine. Seriously, it is. You support it when you renew your ASBMB dues, share its contents with your friends and colleagues, crack it open on the train and even when you use it as a coaster for your coffee mug. It's yours.

Over the past two years, we've worked hard to get more of *you* in these pages. We've asked for your science-inspired poems (thanks for humoring me), your unique perspectives (keep 'em coming) and, most recently, your inspiring stories of failure and triumph (the "Derailed but Undeterred" series). Your contributions have transformed this magazine into one with greater depth, unique storytelling and diversity of ideas.

For our next essay series, to be published in 2014, we want your letters. Now, yes, we always welcome your letters to the editor, but this time we're looking for open letters — ones addressed to someone or something (keep reading if "something" sounds odd) but intended for public dissemination.

Perhaps you, like our in-house science writer, Rajendrani Mukhopadhyay, once had a faculty member say just the right thing when you were having a nervous breakdown during your Ph.D. qualifying exams, and you want to thank that person publicly. Perhaps there's a technique or an instrument that's been the bane of your existence, and you need to vent your frustrations and tell it exactly what you think of it. You might even have sent a letter to someone years ago that now deserves wider distribution.

To have your open letter considered for publication, do the following:

- Send us your letter in a Word document or in the body of your email. Letters with fewer than 1,000 words are preferred, but longer letters won't be rejected outright.
- Include a brief author biography of 100 words or fewer.
- Send your letter to asbmbtoday@asbmb.org by Dec. 31, 2013.

I look forward to reading your epistolary masterpiece!

Sincerely,
Angela Hopp
Editor, ASBMB Today

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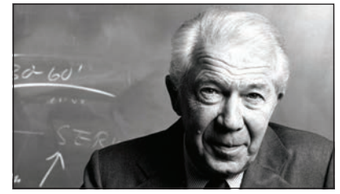

IMAGE COURTESY OF THE ROCKEFELLER UNIVERSITY

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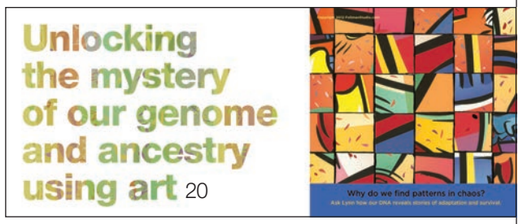

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president's message

Solving the insoluble (and watching them dance)

BY JEREMY BERG

I recently have started to work on the next edition of "Biochemistry," the textbook first written by Lubert Stryer. The initiation of the revision process is always a bit daunting, but it is a great occasion to take stock of progress across the entire field of biochemistry. In my survey, four facets stood out: newly appreciated roles for RNA; an increased interest in the importance of metabolism; the ever-growing knowledge of the vastness of the microbial world, including the human microbiome; and the structures and mechanisms of action of membrane proteins. I will focus on the last topic here.

Membrane proteins, of course, play hugely important roles in almost all aspects of biochemistry and molecular biology as receptors, ion channels, other transporters and enzymes that act on lipid substrates, among others. Furthermore, proteins found through genetic studies often can be identified as membrane proteins by virtue of characteristic stretches of relatively hydrophobic amino acids in their deduced primary structures. Progress toward understanding the structures and mechanisms of these proteins, despite their importance, has been relatively slow until recently for several reasons.

First, almost by definition, membrane proteins are insoluble in aqueous buffers. Purification techniques that are so effective for most soluble proteins need to be modified for membrane proteins. Membrane proteins must be solubilized through the use of detergents or other amphipathic molecules, and the micelles formed are the actual subjects of purification.

Second, most membrane proteins are quite conformationally flexible and dynamic. This is not simply a consequence of the fact that they must be removed from their natural lipid-based environments for purification. Many depend on substantial conformational changes for their function, as in inactive versus activated forms of a receptor or open and closed states of a channel. This makes the purification of a conformationally homogenous sample, not just a pure covalent polypeptide chain, additionally challenging.

Finally, many membrane proteins, particularly those from human beings and other eukaryotes, can be quite complex, with several domains or multiple subunits.

The structural biology of membrane proteins was launched with the low-resolution determination of the structure of bacteriorhodopsin in the mid-1970s by electron microscopy and the determination of the bacterial photosynthetic reaction center in the early 1980s. With the development of molecular biology techniques for protein expression and engineering and the cloning of the genes for many key membrane proteins, the possibilities seemed limitless. Yet advances came quite slowly. This was due partially to the challenges noted above. The availability of a range of highly purified detergents was required to examine empirically different purification and crystallization protocols to find the most effective ones. The use of appropriate ligands or antibody fragments facilitated locking membrane proteins into single conformational states in some cases. Finally, in some cases, prokaryotic sequences that represented simpler versions of eukaryotic proteins of interest could be identified.

Another problem emerged related to financial support for membrane-protein structural biology. Agencies in Europe and organizations including the Howard Hughes Medical Institute displayed long-term interest in the field. However, the conservative nature of grant-review panels presented barriers, as the purification and crystallization of membrane proteins is very challenging and can be quite expensive. Reviewers were confronted with the task of comparing applications describing structural studies of interesting soluble proteins for which purified material and crystals already were available with those applications proposing the purification and crystallization of membrane proteins. Almost invariably, the proposals with crystals in hand won out. The National Institutes of Health tried many approaches to address this issue, including program announcements clearly articulating its interest in facilitating membrane-protein structural biology but not setting aside funds specifically for this purpose.

This approach had only limited success, so the NIH set aside funds for membrane-protein structural biology as components of its Roadmap and the National Institute of General Medical Sciences' Protein Structure Initiative. Many outstanding proposals were submitted, and considerable progress was made both on general methods and on specific membrane-protein structures.

Another NIH investment also played an important role. During the agency's budget doubling, NIGMS and the National Cancer Institute committed to building new synchrotron beamlines at the Advanced Photon Source at Argonne National Laboratory. One of these is capable of producing a very intense beam with dimensions of less than 10 microns (1). This allows examination of crystals too small to be useful at other sources and the scanning of larger crystals to find small regions that are well-ordered for data collection.

What progress has been made through these investments? One of the most spectacular successes was the determination of the structures of G-protein–coupled receptors including the β2-adrenergic receptor that was the subject of my column in December (2). The research that led to this structure was supported by the NIH through a variety of mechanisms, including the Roadmap and Protein Structure Initiative programs, and some key data sets were collected on the microfocus beamline at Argonne. More general data about progress on membrane-protein structural biology is compiled at various databases, including the Membrane Proteins of Known 3D Structure (3), which tracks both the total number of membrane-protein coordinate sets and the number of unique membrane-protein structures – that is, those with truly distinct polypeptide composition (i.e., not separately counting structures with different ligands bound or simple mutations). The number of unique structures grew from one in 1985 to five in 1993 to 83 in 2003 and 415 in 2013 (to date). Included in the list are representatives from almost all major classes of membrane proteins, including receptors, ligand- and voltage-gated ion channels, ion pumps, transporters of various classes, and a range of membrane-bound enzymes. Membrane proteins represent approximately half of the targets of drugs, and the structures of many of these have been solved.

However, for most membrane proteins, a single structure does not tell the whole story because, as noted above, most membrane proteins undergo large conformational changes in the course of performing their functions. What is particularly exciting is the availability of structures for a given protein in a range of conformational states, often captured through the use of different bound ligands: receptors in their inactive and activated states, ion channels in several distinct closed and open forms, ion pumps in states throughout their pumping cycles, transporters open to either side of the membrane. Many of these structures reveal dramatic domain motions and other conformational changes. These structures can be integrated to construct complete approximations of full functional cycles either by interpolating between structures or by more sophisticated molecular dynamics calculations (4, 5). The depictions of these molecular dances are quite aesthetically appealing, imbuing the molecules with lifelike features as they twist and jiggle into new shapes. More importantly, these simulations can provide additional insights into mechanism and can suggest incisive experiments.

As I prepare myself for the beginning of a new textbook revision, I go back and reread to the first edition of Stryer's "Biochemistry," published in 1975. I first learned biochemistry from that wonderful book. I am always struck by how much progress has been made. Many of the topics that were hinted at but covered only briefly are now much more fully understood. For example, the first edition contains many pictures of crystals of proteins that had been grown but for which no structure was yet available.

These were clearly included as promises for things to come. Moreover, it feels as if Dr. Stryer had to work to find topics for which sufficient information was available for a reasonable discussion. This is very different from the experience of writing a biochemistry text today. My desk and computer drives are littered with papers to be considered for inclusion, but the pile of topics that are fascinating and important but for which there is insufficient space is much larger than the one for the topics that make it in. As is often the case, the more we know, the more we realize how much we don't know.

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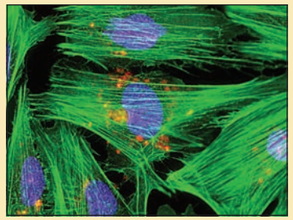
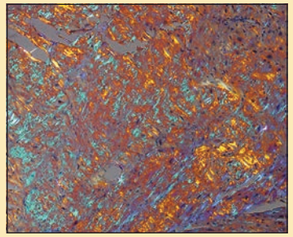
asbmb member update

The 2013 BioArt winners

Two members of the American Society for Biochemistry and Molecular Biology were named winners of the BioArt competition held by the Federation of American Societies for Experimental Biology this year. FASEB chose 10 winning still images and two winning videos. Find out more about the contest at http://bit.ly/12mgnZH.



This winning micrograph was from ASBMB member James D. McCully, along with his colleague Douglas B. Cowan, both of Harvard Medical School. It shows laboratory-grown heart muscle cells (cardiomyocytes) from a rat injected with fluorescently labeled mitochondria (red) isolated from the liver of another animal. Fluorescent labeling also was used to visualize the muscle cells' cytoskeleton (green) and nuclei (blue). The researchers found that injection of mitochondria from an unmatched donor in the heart decreases the amount of damage in a model of myocardial infarction, also known as a heart attack. This project aims to provide a clinically relevant treatment for humans and is supported by the National Institutes of Health's National Heart, Lung and Blood Institute.



This winning submission was from William Lewis of Emory University School of Medicine. Amyloidosis of the heart is a set of complex diseases caused by the accumulation of cellular proteins that forms an amyloid plaque. Although amyloidosis was described more than 100 years ago, the causative proteins were not identified until recent chemical analyses were conducted. This image shows an amyloid plaque stained with Congo red stain and viewed through a polarized lens. The optical properties of the amyloid-forming protein cause it to appear green, while other matrix materials within the plaque appear as orange and blue. Lewis' research is supported by the NIH National Institute on Drug Abuse.

IN MEMORIAM: John G. Bieri

BIERI

John G. "Jack" Bieri, a longtime biochemist at the National Institutes of Health, died in late July. He was 93. Bieri was born into a navy family in Norfolk, Va., and was the second in a brood of five boys. He attended Antioch College in Ohio for his undergraduate studies, Pennsylvania State University for his master's and the University of Minnesota for his doctorate. He served during World War II in the navy. He joined the faculty of the University of Texas Medical Branch in Galveston in 1949 and in 1955 joined the NIH. His accomplishments and accolades were many: He was a Fulbright Fellow with Henrik Dam in Denmark, a president of the American Society for Nutrition, a fellow of the American Association for the Advancement of Science and an editorial board member of the Journal of Nutrition. He, with George Briggs, developed the standard diet for lab rodents at the NIH. When he retired in 1983, he was head of the nutritional biochemistry section at the National Institute of Diabetes, Digestive and Kidney Diseases. He was an avid golfer, active church member, visiting lecturer and dedicated hospital volunteer. He is survived by Shirley Bloch Bieri, his wife of 70 years, three children, four grandchildren, two step-grandchildren and two great-grandchildren.

IN MEMORIAM: Anthony Pawson

PAWSON

Anthony "Tony" Pawson, the Canadian cell biologist whose team first reported in 1990 the process of signal transduction, died in early August. He was 60. Pawson was born in Maidstone, England, in 1952 and named after his father, a well-known cricketer and Olympian footballer who instilled in his sons a love for fly fishing. The younger Pawson completed his undergraduate studies at Winchester College, his master's at the University of Cambridge with Tim Hunt, his doctoral work at King's College London and postdoctoral work at the University of California, Berkeley, where he began working with tyrosine kinase, then poorly understood. In 1981, he opened his first lab at the University of British Columbia and worked there for four years before joining the University of Toronto and the Samuel Lunenfeld Research Institute of Mount Sinai Hospital in 1985. In 1986, his team published the first report of SH2 interaction domains. For his contributions to the field of signal transduction research over the following decades, Pawson won the Kyoto Prize in 2008. Many considered Pawson, one of the top 25 most-cited scientists in his field, to be a strong candidate for a Nobel Prize. He was preceded in death by his wife, Maggie, and is survived by two children and a stepson. *Image: Mount Sinai Hospital.*

Will this time be any different?

BY CHRIS PICKETT

> **"Sequestration — and its unrealistic and ill-conceived discretionary cuts — must be brought to an end."**
>
> – U.S. Rep. Hal Rogers, R-Ky., chairman of the U.S. House Appropriations Committee

Most Septembers and Octobers in Washington, D.C., for the past several years have been filled with angry rhetoric and finger pointing. This is because the government's fiscal year ends on Sept. 30, and Congress and the president need to agree to a spending plan for the next fiscal year or risk a government shutdown. Thus, this time of year brings about rancorous debate over the size of the federal budget and the government's spending priorities.

Despite all the tension, though, we often are left with spending bills that keep the budgets of most federal agencies unchanged. Most often, Congress passes continuing resolutions, which keep federal agencies funded at or near the levels in the previous fiscal year. While this prevents the government from shutting down, continuing resolutions take away Congress' ability to increase funding to beneficial programs, such as those for science research, and cut programs that are deemed wasteful. After years of the same tired arguments and heated rhetoric from both political parties, most scientists and the general public are asking very important questions: Will we see yet another continuing resolution? Will the outcome this year be any different?

A new wrinkle to this process is sequestration. Sequestration of the fiscal 2013 budget resulted in significant cuts to most federal agencies, and the maximal FY14 spending allowable by law is lower than that of FY13. The degree to which programs need to be cut to fit under the spending caps has made some lawmakers throw up their hands in frustration. It's this frustration that has given some political observers hope. Both the Democratic and Republican caucuses have fractured over the degree of government austerity and the indiscriminate nature of sequestration. These fractures offer an opportunity for lawmakers to have a serious discussion about making smart, targeted changes to the federal budget and avoiding across-the-board budget cuts.

One threat to this process, though, is a growing vocal caucus of Republicans who are opposed to funding the Patient Protection and Affordable Care Act. This group of senators and representatives has vowed to vote against bills that provide funding for the health care law, while President Obama has threatened to veto any spending bill that defunds this program. Such an impasse would result in a government shutdown. Shutting down the government would be devastating for scientists, as all science-funding agencies would cease to function. Grant applications would not be reviewed, and the funds already dedicated to grants would not be disbursed.

American Society for Biochemistry and Molecular Biology staffers and members have been conducting and will continue to conduct meetings with senators and representatives across the nation to urge them to come to an agreement that avoids a shutdown, overturns sequestration and improves funding for scientific research. The threat to shut down the government over funding the Affordable Care Act is a sideshow for now. But, if the debate shifts and centers on the health care law, then politicians will be fighting to simply find a way to keep the government operating, and there will be little hope for a new outcome to the budget debate. However, if the health care law remains a sideshow and the debate centers on making targeted cuts that eliminate government waste and increasing funds for beneficial programs, a grand bargain may emerge that eliminates sequestration and allows for the growth in the budgets of federal science-funding agencies. So will this year's budget debate be any different from those in the past? Stay tuned.

Chris Pickett (cpickett@asbmb.org) is the senior science policy fellow at the ASBMB.

The hyaluronan connection

From Type 1 diabetes to cutaneous melanoma

BY KAMALIKA SAHA

Nadine Nagy and Sanna Pasonen–Seppänen were named the joint winners of the Herbert Tabor Young Investigator awards at the 2013 International Hyaluronan Conference in June in Oklahoma City.

Nagy, a postdoctoral research fellow in the laboratory of Thomas N. Wight at the Benaroya Research Institute in Seattle, was recognized for her work investigating the role of hyaluronan and associated extracellular matrix molecules in the development and progression of Type 1 diabetes.

Her novel findings indicate that alterations in hyaluronan and hyaluronan-associated molecules accompany the invasion and destruction of pancreatic islet tissue by T cells and may create a permissive environment for autoimmune attacks. She aims to facilitate the use of hyaluronan-directed therapies as a potential means to prevent juvenile diabetes in the future.

NAGY

Nagy received her Ph.D. from the University of Duisburg–Essen in Germany, where she studied the role of hyaluronan in chronic atherosclerosis. She then completed a postdoctoral stint at the neighboring University of Dusseldorf.

"Hyaluronan is a fascinating molecule that functions as pro- or anti-inflammatory in a disease- and progression-specific context," explains Nagy. Type 1 diabetes "is an interesting and challenging disease to work on. The incidence and prevalence is rising annually. Currently, there is no effective therapy, and the triggering mechanism is still not known. The JBC Herb Tabor Young Investigator Award is an enormous honor and a great motivation to pursue my research."

Pasonen–Seppänen, an assistant professor at the University of Eastern Finland, was recognized for her work studying the role of stromal cells in the progression of cutaneous melanoma. Her research includes investigations into the role of hyaluronan in tumor and stromal cell interactions.

PASONEN–SEPPÄNEN

Pasonen–Seppänen received her Ph.D. from the University of Kuopio in Finland under the guidance of Raija Tammi and Markku Tammi. Her doctoral dissertation thesis, for which she received the university's Best Thesis Award in 2006, focused on the effect of epidermal growth factor and keratinocyte growth factor on metabolism of hyaluronan and keratinocyte differentiation.

Her current research focuses on the role of hyaluronan in the progression of cutaneous melanoma. Her studies have demonstrated that melanoma cells activate the phosphatidylinositol 3'-kinase(PI3K)-Akt signaling pathway in fibroblasts, resulting in hyaluronan synthase upregulation and enhanced hyaluronan production. This is accompanied with increased matrix metalloproteinase 9 production and increased invasion of the fibroblasts in the matrix. Additionally, her studies suggest that hyaluronan expression inversely correlates with melanoma aggressiveness. These findings indicate that hyaluronan may favor tumor progression in the early stage of melanoma, when melanoma cells lose their contacts to keratinocytes and start to invade.

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Retrospective

Christian de Duve (1917 – 2013)

BY JOHN EXTON

Christian de Duve, one of Belgium's greatest scientists and winner of the 1974 Nobel Prize for describing the structure and function of lysosomes and peroxisomes, died at his home on May 4. He was 95 and elected to die by euthanasia, which is legal in Belgium.

De Duve was born in 1917 in Thames–Ditton, England, where his parents had gone to escape the ravages of World War I. He was educated in Belgium at a Jesuit school, where the classes were taught in either French or Flemish.

He attended the medical school of the Catholic University of Louvain, earning an M.D. in 1941, and went on to conduct research on the action of insulin with Joseph Bouckaert as his mentor; Bouckaert was unusual as an avid reader of the Encyclopedia Britannica. They measured the amount of glucose infused to maintain the blood glucose at a constant level.

De Duve was a proponent of insulin action on the liver, but his findings were complicated by the presence of glucagon in most preparations of insulin at that time. He wrote up his work in a book titled "Glucose, Insuline et Diabète," with 400 pages and 1,200 references, which was submitted as the equivalent of a Ph.D. and published in 1945. He earned an M.S. in chemistry the next year.

He completed a short stint in the Belgian army during World War II and was held briefly in a prison camp, from which he managed to escape.

At the end of the war, he went to Stockholm to work with Hugo Theorell, an enzymologist who later won the Nobel Prize. He wondered why Theorell accepted him even though he had little knowledge of biochemistry. He attributed this to Theorell's great love of the French language. De Duve was fluent in four languages, which he attributed to his extensive travel throughout Europe and considered an asset in his scientific career.

De Duve then decided to go to the Cori laboratory at the Washington University School of Medicine in St. Louis, but Carl Cori at first was reluctant to take him, because the Cori group had found that insulin stimulated the breakdown of liver glycogen, whereas de Duve had evidence that insulin caused the uptake of glucose by the liver. The dilemma was solved when de Duve, working with Earl Sutherland in the Cori lab, showed that the glycogenolytic action of insulin was caused by a contaminant that was identified as glucagon. This observation later led to Sutherland's discovery of cyclic AMP, for which he won the Nobel Prize.

De Duve returned in 1947 to the Catholic University of Louvain to teach physiology and do research on glucose-6-phosphatase. He found that the enzyme seemed to be attached to an intracellular structure, which now is recognized as the endoplasmic reticulum. His group also monitored another enzyme termed acid phosphatase because it interfered with their results. They set about defining its nature using differential centrifugation. The fraction containing this phosphatase exhibited an interesting property: It exhibited low activity initially, but this markedly increased with storage. They also found that when particles in the fraction were disrupted, the enzyme was released, which indicated that its latency was due to its enclosure within vesicles.

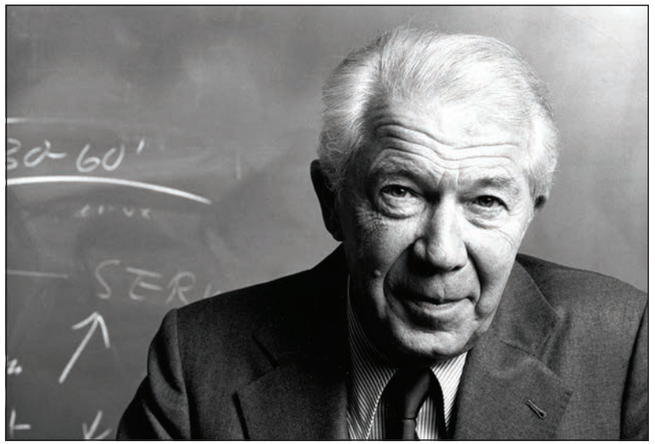

IMAGE COURTESY OF THE ROCKEFELLER UNIVERSITY

The next phase of the research was to define the nature of the subcellular particles. De Duve's group again used differential centrifugation and analyzed the various fractions for enzyme markers. A different procedure, namely isotonic sucrose, was used to prepare the starting homogenates, and gentler homogenization was used to preserve the structure of the particles.

De Duve was surprised to find that the enzyme was in both the mitochondrial and microsomal fractions, and he thought he was dealing with a new particle. He started varying the centrifugation protocol, and serendipity intervened when one of the centrifuges broke down and had to be used at a lower power.

This yielded enzyme-containing particles that sedimented midway between mitochondria and microsomes. The new particles were called lysosomes, a term that de Duve later regretted because of its possible confusion with the enzyme lysozyme. Interestingly, lysosomes had been discovered earlier by Russian zoologist and Nobel laureate Elie Metchnikoff as vacuoles involved in digestion in protozoa.

De Duve searched for other enzymes associated with lysosomes and found some acid hydrolases. Later, more than 50 hydrolytic enzymes were found to be contained within lysosomes, and these organelles were recognized as major sites for the digestion of intracellular macromolecules.

The medical importance of lysosomes emerged when a variety of diseases were traced to lysosomal enzyme deficiencies. Pompe's disease was recognized initially. It causes the accumulation of glycogen due to deficiency of an acid α-glucosidase. Later, other devastating diseases were ascribed to deficiencies of lysosomal enzymes leading to the accumulation of glucocerebrosides, glycolipids and sphingomyelin.

After his work on lysosomes, de Duve studied urate oxidase, which he found had very different properties to acid phosphatase. Work on this enzyme led to the identification of a new particle, which he called the peroxisome.

In 1962, de Duve began to tire of his duties at the Catholic University and took a position at what was then the Rockefeller Institute, now The Rockefeller University, in New York. He split his time between the two institutions, and when the Catholic University was divided, he commuted between New York and Brussels, where the new medical school was located.

To strengthen the new school, he conceived of the establishment of an international, multidisciplinary research institute. He founded it in the early 1970s on the basis of three principles: priority of basic research and freedom of investigators, special attention to medical benefits resulting from basic discoveries, and multidisciplinary collaboration within a critical mass of competency. It was called the International Institute of Cellular and Molecular Pathology. It began with only four research groups but grew to include 270 investigators, and its cumbersome name later was changed to the de Duve Institute.

De Duve received the Nobel Prize for physiology or medicine in 1974 along with Albert Claude and George E. Palade, both of Rockefeller, "for their discoveries concerning the structural and functional organization of the cell."

In 1985, de Duve became an emeritus professor at the Catholic University, and he retired as president of the institute in 1991.

In his retirement, he wrote several books. One of these was scientific, "A Guided Tour of the Living Cell," and one was more philosophical, "Genetics of Original Sin: The Impact of Natural Selection on the Future of Humanity."

Excerpt from "My Love Affair with Insulin"

"It all started with a chance encounter in the fall of 1935. As a second-year medical student at the Catholic University of Louvain (Belgium) with time on my hands, I conformed to the local tradition according to which 'good students' would 'do a laboratory,' which meant that they joined the laboratory of one of their professors and participated on a voluntary basis in whatever research was going on. This arrangement suited both parties. The professors got free manpower. The students kept out of mischief, gained experience, had fun, and (if they persevered long enough) could write up a dissertation and use it to compete for a traveling fellowship. Many a scientific career was launched in this way."

Read the rest of Christian de Duve's 2004 scientific memoir in the Journal of Biological Chemistry at http://www.jbc.org/content/279/21/21679.

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Jack of a few trades, Master of Science

BY AKSHAT SHARMA

Allow me to set the scene: A few months ago, I was at a big-deal school interviewing for a Ph.D. position with one of the asthma research gods of our time. As I waited for him to arrive, I struck up a conversation with another candidate. As we exchanged phatic nothings, I revealed that I was getting an M.S. in an immunology lab in the Midwest. The candidate scoffed, "Well, isn't that just a waste of time? I'm a senior right now, and I applied directly!"

Had the circumstances been different, I would have responded with something subtle yet piquant. But this was an academic institution and not a pivotal moment on the sets of "Mad Men," so I let it pass. Besides, perhaps it was nerves. What else could cause another person to call out so blatantly a relative stranger's choices? Anyway, it wasn't my first time at the Ph.D. rodeo. I'd done this before: I'd also interviewed right out of undergrad. "Why, then, the M.S?" you ask. I wanted to be sure.

"(I)t was experience that I lacked the first time I applied for Ph.D. programs.

As young experimental scientists, when we read papers in the likes of Cell, Science, Nature, et al., we get lulled into believing that the doing of elegant science is, well, elegant. None of those papers, as important and awe-inspiring as they are, gives even the slightest hint of how grueling the process of acquiring those results probably was. Excremental things happen: standards fail, proteins unravel, machines become temperamental, mice die … and then you start over. Rinse; repeat. I'm not saying that these papers should read along the lines of "Abstract, Introduction, Materials and Methods, Results, Discussion, and Thoughts, Feelings and Coping Mechanisms" – but that last section is a product of experience, and it was experience that I lacked the first time I applied for Ph.D. programs. As one of my interviewers in the spring of 2010 said to me, "I'd take you on, but you lack experience. A Ph.D. is a six-year commitment. What if you burn out halfway? Do you know if you have the stomach for this?"

And surely I was not alone in this. How many undergrads do you know who have been handed the reins of a project? While there is now a great push to bring undergraduates into a lab, how many of them know the Imposter Syndrome that plagues graduate students and those above them?

I posit that an M.S. program is an important rite of passage. It's a spiritual journey of sorts on which you find out if you care enough about a question that the adversity doesn't matter, that you'll come in the next day and want to start over, if need be. As I elected to pursue my M.S., I promised myself that if I burnt out in two years I'd not pursue a Ph.D. As it turns out, I didn't burn out. I ended up thirsting for more – more techniques, more questions, more independence on the bench. Today, in my Ph.D. lab, I know how to work smarter; how to keep a lab notebook; how to run routine assays; how to manage my time between teaching, learning and researching; and, most importantly, how to regroup and not fall apart when something fails. Sans the M.S. experience, I wouldn't be here, and I mean both at my dream school and in my more confident head space. In the Hess' cycle of achieving one's dreams, this is but one more pathway. I won't insist that this is the right one, but it certainly isn't a waste of time!

Akshat Sharma (asharma28@wisc.edu) received his M.S. in microbiology from North Dakota State University and is a Ph.D. student in the department of medical microbiology and immunology at the University of Wisconsin, Madison.

ASBMB Today always welcomes personal essays about school, work and doing science. Have an idea for an essay? Send your pitch to Editor Angela Hopp at asbmbtoday@asbmb.org.

NIH commits $24 million annually for big data centers of excellence

BY LESLEY WASSEF

Every day, numerous researchers produce an abundance of datasets. However, the scientific community lacks tools, accessibility and training in how to use these large, diverse datasets.

In response to these problems, the National Institutes of Health is launching the Big Data to Knowledge initiative, or BD2K, in December. The NIH will provide up to $24 million per year for four years to establish and support six to eight investigator-initiated BD2K Centers of Excellence.

The centers will focus on developing policies and practices for collaborative sharing of data and software; finding new ways of organizing, managing, processing and analyzing large data sets; and training students and investigators to use data science methods, such as informatics, biostatistics and computational biology.

The NIH's goal "is to help researchers translate data into knowledge that will advance discoveries and improve health, while reducing costs and redundancy," NIH Director Francis S. Collins said in a statement in late July.

The deadline for applications from those interested in establishing BD2K Centers of Excellence is Nov. 20. Applicants must identify a research topic and propose research in data science. Particularly, applicants must highlight approaches, methods, software and tools for data integration, analysis, database development and management, and visualization and modeling to address important research questions.

A webinar for prospective applicants will be held from 3 p.m. to 5 p.m. Eastern on Sept. 12. More details about this event and the BD2K initiative can be found at bd2k.nih.gov.

Lesley Wassef (lesleywassef@yahoo.com) is a research associate in the Food Science and Rutgers Center for Lipid Research at Rutgers University.

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DERAILED, DETERRED, GOT OVER IT

BY H. JANE DYSON

As an eldest child, and an eldest girl, I and my family always expected a great deal from me. I was a star student in my country high school but recognized that (of course) the kids from the big-city schools would outshine me by default at university. It came as somewhat of a surprise to find that I was among the best students in my class at the University of Sydney and that I enjoyed my courses and the whole science experience so much that it went without saying that I would go on to a higher degree. My path appeared seamless – after a degree in biochemistry, I switched to inorganic chemistry for a Ph.D. and thoroughly enjoyed myself, even though my experiments were difficult and the data were puzzling. At the end of my Ph.D., I put it all together in a most satisfying way, and I felt that a career in science was for me. For no better reason than that a postdoctoral position was offered to me, I changed fields again to work in a molecular biology lab.

I arrived at the Massachusetts Institute of Technology in Cambridge, Mass., in January 1977 to feet of snow, already a world away from the mild weather of Australia. The research involved a lot of wet-lab work, protein and tRNA preparation, which I found uncongenial. (If scientists are, as Robert Heinlein says, either "bottle washers or button sorters," I incline more to the button-sorting end.) Nevertheless, I was able to win a fellowship from the Damon Runyon–Walter Winchell Cancer Fund for this work.

As the months went by, the work became more and more frustrating. The problem was that my job was to repeat (and hopefully scale up) an observation made in the lab some time previously by someone else. The protocol was clearly established, I knew I was doing every step correctly, but I could not reproduce that result however hard I tried. There was no apparent reason why that result should not have been reproducible – so I blamed myself for missing something. I became depressed and frustrated, and about the only thing I was enjoying was a stint teaching classes as a teaching assistant, as the department at the time had a shortage of graduate students.

Finally, I decided that this scientific career just was not working. Not only was I all alone away from my family on the other side of the world, but nothing in my research was in any way interesting or rewarding or, it seemed, worth doing. I left my postdoctoral position, almost abruptly, and went back to Australia, intending to forget about a research career and focus on teaching. I was lucky enough to obtain exactly the position I wanted teaching freshman chemistry at the University of New South Wales in Sydney. Teaching occupied and rewarded me in a most satisfactory way for the next few years until finally I left to accompany my husband to California in 1984. Here, I have regenerated my research career completely, starting again as a postdoc and working my way up through the ranks to professor.

So what went wrong in the first postdoc? Primarily, I think I was low on confidence in myself. Moving from Australia to MIT was a bit like when I had moved from the country to university in Sydney: Big-time people and places must be better than me. Then, when the experiments didn't work as expected, I blamed myself instead of stepping back and wondering if, just maybe, the original result was not what it seemed. (That actually turned out to be the case.) In hindsight, I think my decision to leave MIT and return to Australia (with no job waiting when I arrived) was the right one. I was very fed up and miserable, but I knew I was good at teaching and that this alternative pathway would be a good one for me. As it turned out, the interlude in Sydney greatly boosted my confidence and gave me the satisfying feeling that I was giving something back to a system that had invested heavily in my education.

By the time we moved to California, I had matured sufficiently to be able to give research another chance, and I always will be grateful for the opportunities given to me along the way. Another important factor, in hindsight, was the nature of the research work I was doing day to day. The tasks did not excite me, and I could see no pathway toward more congenial tasks. As a result of this experience, I am always very careful to watch those working for me to make sure they enjoy the type of work they are doing, and if not, I try to find something that will be better for them. I think it is important to emphasize to students that they need to enjoy what they are doing, especially in science, when even if you enjoy the work it may not be successful.

Jane Dyson (dyson@scripps.edu) received a bachelor of science with honors and a Ph.D. from the University of Sydney and undertook a Damon Runyon–Walter Winchell postdoctoral fellowship at Massachusetts Institute of Technology. She was a faculty member in chemistry at the University of New South Wales from 1979 to 1984 before joining the Scripps Research Institute in 1984, where she is presently a professor. She received a Doctor of Science degree from the University of Sydney in 2009. Her research interests are in the conformation of peptides, protein folding and dynamics, and structure and functional studies of proteins, both folded and intrinsically disordered, using nuclear magnetic resonance and other spectroscopic techniques.

Science Globetrotters

Why and how do researchers work in two parts of the world at the same time?

BY RAJENDRANI MUKHOPADHYAY

This is a story without a single narrative – but rather tales of people who have maintained simultaneous scientific endeavors in two parts of the world, with one base in the U.S. Their motivations for doing so are all over the map.

HELPING THE HOME COUNTRY

Carlos Bustamante, University of California, Berkeley

"Twin labs" is what Carlos Bustamante calls his setup. An expert in single-molecule manipulation techniques, Bustamante runs laboratories both at the University of California, Berkeley, and Cayetano Heredia University in Lima, Peru.

In the 1980s, Bustamante intended to return to his home country of Peru after completing his Ph.D. at Berkeley. "But by the time I was finishing my Ph.D., it was impossible to go back," he says. "The country was in the midst of a revolution by the terrorist Maoist group called Shining Path."

Bustamante built his career in the U.S. developing optical and magnetic tweezers that researchers use to manipulate individual molecules, such as DNA and DNA polymerase, and to get a close-up view of molecular dynamics.

In 2005, officials at Cayetano Heredia University asked him to help invite American scientists to give lectures to students at the university. With the lecture series for three years, "I realized that even though I was not going to go back to Peru as a scientist, I still could do something to help my country to strengthen its science and technology," says Bustamante. "Eventually the idea came up of creating a twin laboratory in Lima that would be parallel to mine."

Bustamante corralled representatives of the major universities in Peru and made his pitch for mirror labs. The next day, officials at Cayetano Heredia University offered to host the laboratory. Bustamante explained the idea to officials at Berkeley and got their support.

The laboratory in Lima got off the ground in 2009 and today has six undergraduate and master's students. The students get to spend a summer in the Berkeley laboratory, and the flow of people goes the other way as well. "I think the experience of American students going to South America and having the sense of what it is like to live in a country not as rich as this one is a very sobering experience," notes Bustamante.

The experience is not just for students. Bustamante acknowledges that as an investigator of the Howard Hughes Medical Institute, "I'm not only doing well but I'm doing better than well in some respects. From that point of view, [the Lima laboratory] is very important, because it gives me a perspective and a context that is always good to keep in mind."

The Lima laboratory, like the Berkeley laboratory, does both fundamental and applied research, but with a local twist. "At my lab at Berkeley, we study transcription by RNA polymerase from yeast or E. coli," explains Bustamante. "In Peru, we are purifying and isolating the RNA polymerase from Mycobacterium tuberculosis, because tuberculosis continues to be the main cause of death in Peru. The RNA polymerase from mycobacterium is the main drug target for most of the frontline antibiotics that are used today."

The laboratories stay connected by Skype, but Bustamante goes to Lima three times a year. Bustamante says his family in Peru has been enthusiastic about the project because "for them, it was a good pretext to see me more often instead of once every two years!"

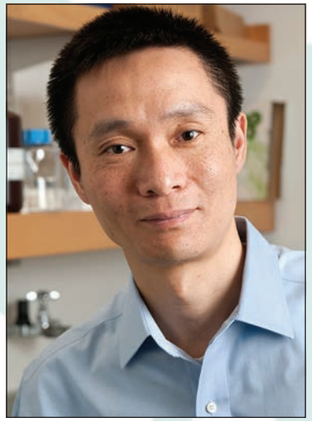
One concern in doing science in developing countries is lack of easy access to reagents and instrument parts. Bustamante has outfitted the Lima laboratory with mostly older instruments from his Berkeley laboratory. "Instead of sending instruments to landfills, we fix them a little bit or the university in Peru pays for fixing them," says Bustamante. On every trip, Bustamante and his students carry instrument parts and reagents in their luggage to bypass delays they would otherwise hit with mail-order service. "We want to avoid the kind of delays this sort of collaboration normally involves," says Bustamante.

The Lima laboratory has had a ripple effect not just within the university where it's located but also in

South America in general, says Bustamante. It's the only one in the region with an optical tweezers setup, so scientists from Chile and Argentina have requested collaborations because they want access to the instrument. "It's like a snowball rolling down a hill," says Bustamante. "The only concern that I have is that I don't want to be the only Peruvian scientist who does this. There are many Peruvian scientists in the U.S. I think if each one of them tried something like this, we could in a few years completely change the face of the science in Peru."

TAKING THE LONG VIEW

Chuan He, University of Chicago



In the late 2000s, Chuan He at the University of Chicago attracted the attention of officials at Peking University in China. His group was busy developing, among other things, chemical methods to study the epigenetic marker 5-hydroxymethylcytosine, which they recently had discovered along with potential RNA demethylation. The Chinese university officials had noted He's scientific contributions and asked if he'd be willing to help establish a chemical biology center at the university.

He was impressed by the fact that the Peking University officials were taking the long-term view. In his mind, the center would be defined by faculty members who would start their careers there and eventually become established and successful. "That was going to take 10 to 20 years," he explains. "It couldn't be done in three to five years. It would not be sustainable. They completely understood that."

He accepted Peking University's offer, and in the summer of 2011 the Synthetic and Functional Biomolecules Centre opened its doors. He found the provost and dean at the University of Chicago very supportive. "I think the university views this as a positive way of building more connections in China," he notes. The center will have five full-time tenure-track faculty members by the end of 2013, and there are already two assistant professors, who were recruited from the U.S.

He travels to China four or five times a year, making sure his trips to the center coincide with scientific conferences in the region. But He is honest when he says that the timing for this endeavor was not the best. "It happened right when I was transitioning to full professor and my science was beginning to take off," he says. "It's a lot of traveling. Occasionally, my family will go with me to China, but with the kids in school, it's not going to happen regularly." He has two children, ages 6 and 11.

Still, He says he couldn't have let the opportunity go. "How many times in a life do you get to build something new?" he asks. "My own science will probably not generate as much impact as this center will in the long run."

FORESEEING A SCIENTIFIC CHALLENGE

Akhilesh Pandey, Johns Hopkins University

A decade ago, Akhilesh Pandey, then a visiting scientist at the University of Southern Denmark, could see that the demand for bioinformatics was only going to increase. When Pandey landed a tenure-track position at Johns Hopkins University in 2002, he decided to devote his spare time to a bioinformatics institute. "My

parents are based in Bangalore. I convinced them to start helping me finance the institute," he explains. With his parents' financial backing and credit-card loans, Pandey established the nonprofit Institute for Bioinformatics in India. His parents are on the board of trustees, while Pandey focuses on the science.

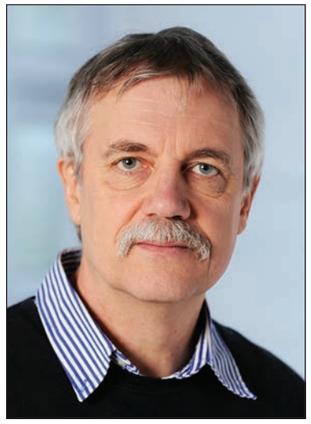
The Institute of Bioinformatics now has 56 employees, and more than 200 students have gone through its doors. It focuses on areas such as database development, computational genomics and proteomics. One of its goals is to create a freely available Human Protein Reference Database using open-source technology and to verify predicted human genes using molecular biology and proteomics-based methods.

Pandey, who visits the institute four or five times a year, acknowledges that funding has been an issue. "We've passionately been doing science and largely ignored the funding. Funding has always been a sore point, but somehow we have worked within huge constraints," he says. "We operate on a shoestring budget." He has applied for grants in India and is hopeful, because India has significantly increased its spending on biomedical and biotechnological research in the past two years.

Although he describes the institute as a grassroots effort, Pandey has a fierce vision and ambition for it. "The kinds of models I've set up for myself are places like the Broad Institute and [the European Molecular Biology Laboratory]," he says. "We have high aspirations."

MAKING A TRANSITION

Ruedi Aebersold, ETH Zurich



Ruedi Aebersold agreed to run two laboratories in two different countries only because he knew the situation was temporary. In the early 2000s, Aebersold was busy with the Institute for Systems Biology, which he had cofounded with Leroy Hood and Alan Aderem in Seattle. But ETH Zurich, the Swiss university for technology and natural sciences, approached Aebersold with an offer that was impossible to refuse.

At the time, Aebersold was three years into spearheading a large proteome center at ISB sponsored for seven years by the National Heart, Lung and Blood Institute. When the offer from ETH Zurich came down, Aebersold approached the NHLBI leadership to discuss his options. "They were extremely generous and accommodating," he says. "They said I could continue to run it, provided I spent 20 percent of my time on the center."

Running laboratories in Seattle and Zurich "wasn't something I was aspiring to, nor was it an easy thing to do," he says.

Firstly, logistics were difficult. Zurich and Seattle have a nine-hour time difference. "It took me a while to figure out how to do this best, because the worst was the one-week visit. You constantly are jetlagged and tired, and then you get back and it goes the other way around," he says. Aebersold eventually decided that fewer, but longer, visits to Seattle were better, and he used Skype and phone calls to fill in for the other times.

Then there was the human challenge. At the beginning, Aebersold knew everyone well. "It felt as if I was

away on a trip," he says. But over time it grew more difficult because there was turnover. As someone who thinks the small, personal touches are important in a team setting, Aebersold found the loss of face-to-face interaction difficult.

Aebersold's advice to anyone contemplating a dual-lab arrangement is to think about it carefully. "Is it an opportunity like I was offered that will lead to this long-term, relatively protracted transition? Or is it a permanent solution to some problem?" he asks. "Just doing it because someone offers lab space and instrumentation or some other form of support – I would carefully think if it's worthwhile."

AN OPPORTUNITY COMES ALONG

Patrick Casey, Duke University

Patrick Casey and Mei Wang.

For Patrick Casey at Duke University, the idea of moving to Singapore gradually crept up. In the early 2000s, the Singaporean government was looking to establish a new medical school and got into talks with Duke University administrators about a possible partnership. Casey got involved because he was building up interdisciplinary sciences at Duke, particularly around translational medicine. "By the spring of 2005, it all came together," he recalls. "That's when Duke asked me if I could go over to help get the school off the ground."

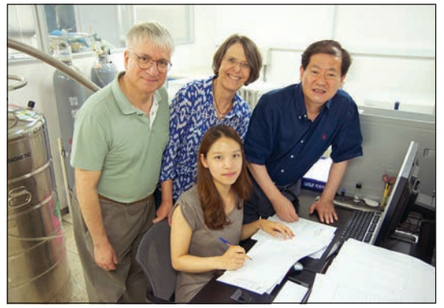
Casey was searching to do something new, and the idea of building a medical school and research institute from the ground up was appealing. "My wife is a clinician-scientist, and she was also looking for an opportunity," says Casey. From a personal standpoint, a stint in Asia made sense. Casey's wife, Mei Wang, is Chinese by birth, and her parents would be able to join them in Singapore and spend time with their grandchildren.

Casey and Wang considered the Singapore stint to be temporary, so Casey kept his research group going in North Carolina. "I would spend 10 weeks in Singapore and two weeks in Duke," explains Casey, describing the two weeks in North Carolina as intense. But Casey did not take on new graduate students and postdoctoral fellows at his Duke laboratory after his move, which "in hindsight, was the right thing to do," he notes.

As the years went on, each of Casey's graduate students and postdoctoral fellows completed their training. Their projects either went with them to their next stints or got moved to Singapore, where now both Wang and Casey have their own research groups. When he went back to Duke this summer, Casey turned his laboratory over to another faculty member. He is still active in Duke's administration but has decided to focus his research efforts in Singapore – knowing that he can always move back to the U.S. if he so desires — because he finds the science happening in Asia to be very exciting.

Casey gives an example: In conversation with a hematologist, one of his NUS-Duke colleagues, Tiong Ong, found out that there was a higher incidence of Asian patients who didn't respond to the cancer drug imatinib (also known as Gleevec; read the August 2013 issue of ASBMB Today to learn more about it). Hematologists in other Asian countries confirmed the observation. From a genomic-profiling study, Ong's group discovered "there is a gene variant that is only found in east Asians, in about 15 percent of the population, that not only explains their resistance to imatinib but provides a new target for therapeutics for this population."

So, much like real estate, science benefits from location. "Patient populations and demographics of disease can really inform a research program," says Casey. "I had not thought of that much when I was in Duke."



PHOTOGRAPHER: ATSUTOSHI YOKOYAMA

Andrew Clark (Valentine's husband), Joan Valentine, and Wonwoo Nam (standing, left to right) and Sumin Lee (seated), who is entering UC Berkeley as a Ph.D. candidate in the chemistry department this fall.

TIMING IS EVERYTHING

Joan Valentine, University of California, Los Angeles

A former graduate student of Joan Valentine's recruited her to the Ewha Womans University in South Korea. Wonwoo Nam had established himself as a chemistry professor at the university, one of South Korea's top institutions with an all-female student body. In the mid-2000s, Valentine, who is at the University of California, Los Angeles, got a call from Nam. He described a new initiative to be launched by the South Korean government called World Class University, in which researchers in science, technology, engineering, math and social science fields from around the world would be invited to spend part of every year at a South Korean institution and get funding to do research and teaching. On hearing the proposal, Valentine recalls telling Nam that "there was no way" UCLA would let her do that. "But Wonwoo, who is my dear friend, is very persistent."

Nam and Valentine spoke with the dean of physical sciences at UCLA, proposing the idea that her research would benefit from spending time abroad. The dean happened to be a physicist. "Physicists have to go to labs all over the place all the time because of specialized facilities," says Valentine. "The idea that I would be able to extend my research efforts and get more resources that would be published under UCLA as well as Ewha – that was normal to a physicist."

Since 2009, Valentine and her husband, who is an independent scholar of ancient Greek vases, have been going to South Korea every year for four months. "I'm sure I couldn't have done it if my husband had to stay behind," she says.

Valentine collaborates with Nam, who works on biomimetic and inorganic chemistry; Valentine's UCLA laboratory focuses on superoxide dismutase and its role in amyotrophic lateral sclerosis. The collaboration has been wonderful, says Valentine, because she gets to revisit an area of research she had to abandon. "I'm at a later stage in my career," she says. "Right from the beginning, I told Wonwoo that I didn't want another independent research lab."

The World Class University attracts scientists from all over, and Valentine has found the experience to be enriching. "I feel as though as I've had an opportunity to start talking science with people in a way that I haven't done since I was an assistant professor," she says.

Valentine also teaches master's students metal and oxygen chemistry and plays the role of cultural ambassador. The top students get their master's degrees at Ewha and head off to the U.S. to get their Ph.D.s. "These are wonderful, brilliant young women, but I've been talking to them about the requirement to be more assertive right from the beginning. They don't even want to make eye contact," says Valentine. "I've really challenged them with that. I've said to them, 'You've got to be willing to make eye contact!'"

When Valentine is back in the U.S., she stays in regular contact with Nam. But she doesn't directly interact with the Korean students, because "although they speak English, they are very shy to do so. It's a lot of effort for them to converse in English over Skype." While in South Korea, Valentine keeps up with her UCLA group by Skype and email.

To anyone considering a similar move, Valentine offers this advice: "If you're feeling a little restless in what you're doing now and this opportunity comes along, you should certainly explore it. If you're totally satisfied and busy with what you're doing, it's probably not for you, because it takes too much of your attention away from your primary goal." And then Valentine offers a practical tip: "You should like the food of the place you're going. Korean food is great!"

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

Unlocking the mystery of our genome and ancestry using art

BY LAUREN AMABLE

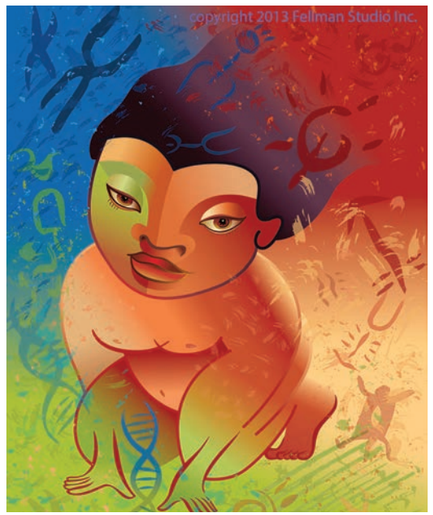
Visual artist Lynn Fellman's journey into the world of biological science illustration began in 2005 with a cotton swab.

Her interest was piqued while participating in National Geographic's Genographic Project. The goal of the project was to use direct-to-consumer DNA-testing kits to reveal insights into these age-old questions: How did modern humans evolve and how did we migrate to populate the Earth?

"I saw how the scientists were going to put genetic data with fossils to understand human evolution," says Fellman. "Unlike any of the other (direct-to-consumer DNA-testing) projects for ancestry, Genographic is the only one that pairs anthropology with genetics for a much richer picture of prehistory."

Curious about her DNA's origins, Fellman, who lives in Minneapolis, ordered the kit and sent her two buccal swabs back to the Genographic project for analysis. She was not surprised by her Northern European ancestry results, but something else grabbed her attention: "My fascination was the molecular story – what scientists now refer to as molecular anthropology – that revealed prehistoric information that we had not (gotten and) could not get from fossil remains."

Fellman's curiosity led her to create art using her results. "The first pieces with my own (mitochondrial) DNA data showed my haplogroup route on a map of



Africa and Europe. I'm haplotype H — no surprise, since 30 (percent) to 40 percent of (women) with Northern European decent are in the H haplogroup," she says.

Her haplogroup artwork led to the "DNA Portrait" project commissioned by the University of Minnesota. She created a series of portraits and wrote companion storyboards, telling the ancestry of several members of the Urban Research and Outreach Engagement Center located in north Minneapolis. Using family history and DNA results from the Genographic

Project, Fellman created a visual narrative for each participant.

Fellman, who received a degree in studio arts from the University of Minnesota, previously earned her living as an independent designer creating print materials and interactive multimedia presentations. Her work always starts out the same way: with "pencils and a stack of 8 ½-by-11-inch white paper, writing and sketching until I have something surprising, something that looks just right." From there, Fellman imports her art using digital software tools and adds layers of color and texture.

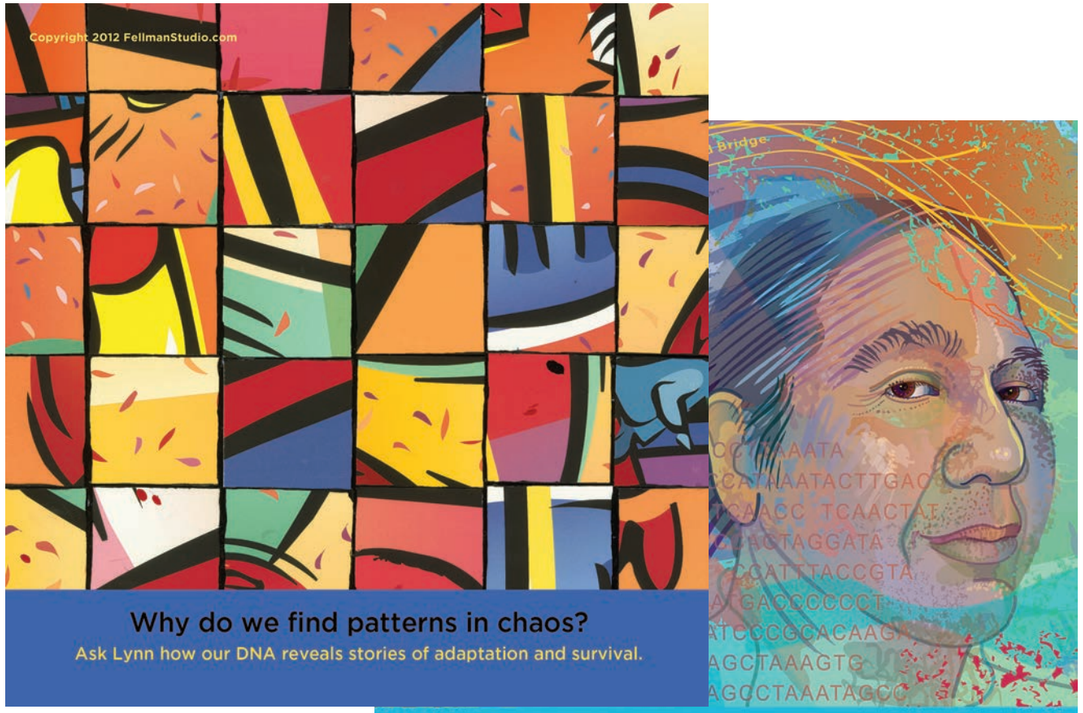
FELLMAN

Fellman set out to ground her art in science. She learned how to read research papers and subscribed to journals like Science and Nature. She also found a mentor, Perry Hackett, a genetics professor at the University of Minnesota. Fellman's understanding of genomic science enabled her to communicate with scientists. "I could speak their language, understand most terms, and was aware of some publications — so the conversation could skip the basics and lead to what their work was really about," she explains.

Fellman adds: "The ability to translate difficult concepts into visual images that convey the message is just what I do with scientific research. It feels like I've been preparing to focus on science for most of my career."

In 2011, Fellman illustrated a video slideshow and wrote a corresponding script commissioned by the American Association for the Advancement of Science for its Member Central website. In the video, titled "At the Crossroads: Finding Family in Bones and Genes," she explains how fossils and genes come together to provide a more complete story of human evolution based on the draft sequence of the Neandertal genome as published in Science in 2010.

Her multimedia art earned her an invitation to give a talk on her work at the Society for Molecular Biology and Evolution's meeting in Dublin in 2012. "It



was a thrill and an honor," she says of giving a talk about her work on paleogenomics at the meeting. "The room, which seats about 100 people, was almost filled. I asked to have all the lights turned off, so when entering all you saw was the large screen with my first slide – big eyes in a face staring right at you. The scientists seemed to enjoy it," she recalls.

One of the best outcomes from that meeting was her current fellowship at the National Evolutionary Synthesis Center in Durham, N.C. NESCent is a cross-disciplinary center that addresses novel emerging topics of evolutionary research. While at NESCent for the remainder of the year, she is working on two projects with the challenge of presenting "complex information for two different audiences in different media with new images in an engaging way."

The first project is an adult-geared lecture entitled "Visions of Neanderkin: Comparing Ancient and Modern Genomes." She bases her lecture on the newer sequence data of the Neandertal and Denisovan genomes, specifically "the analysis of the ancient (hypervariable) regions that is underway at a number of labs."

Fellman's second project is an iBook for children and their parents. Entitled "I Am a Multi," it blends narrations, digital painting and haikulike text about "a young girl whose parents came from different and distant geographic locations," she explains. "This is another way to tell the story of human evolutionary history and make it relevant to all of us."

Questions about who we are, where we came from and how we evolved fascinate artists and scientists alike. Fellman's goal is to inspire wonder and understanding of the fundamental ideas and intrinsic beauty found in human gene stories. "Our DNA shows how we are all connected in tangible ways, and that makes our individual stories part of something much bigger."

For more information about Fellman and her art, visit her website at www.fellmanstudio.com.

Lauren Amable (lauren.amable@nih.gov) is a staff scientist at the National Institute on Minority Health and Health Disparities.

Q&A with UC Berkeley University Medalist of the Year Ritankar Das

BY KAMALIKA SAHA

Ritankar Das, the top graduating senior at the University of California, Berkeley, is the recipient of the prestigious University Medal. The University Medal is awarded to an outstanding graduating student with a minimum GPA of 3.96. With a phenomenal grade-point average of 3.99, 18-year-old Das, is the youngest to receive the medal in at least a century. He double majored in chemical biology and bioengineering and minored in creative writing. His other top honors include the Departmental Citation in Chemistry and induction into the ASBMB Biochemistry and Molecular Biology Honor Society. Ritankar is an exemplary student, excelling in academics, community service and poetry. His future plans include a master's degree from Oxford University and a Ph.D. from the Massachusetts Institute of Technology. In this interview with ASBMB Today, Das emphasizes the importance of seizing every opportunity that comes your way and having the willingness to learn and expand your horizons intellectually, scientifically and artistically.

Q: A GPA of 3.99 is a remarkable achievement. You were the recipient of a chemistry departmental citation followed by the prestigious University Medal, which carries a purse of $2,500. What were the contributing factors to your success?

I think the most important people have been kind and dedicated parents and educators like teachers and professors, as well as other mentors who

have helped and guided me along my academic, scientific, artistic and professional journey. They are definitely the folks responsible. I believe the only reason any of this happened was because of the early help that they provided.

Q: What role did UC Berkeley play in honing your research interests and professional trajectory?

Berkeley is an amazing place. It is a place where you are taught to think across disciplines and across boundaries. One of the main things I learned while I was here was unifying science and the arts. They are both extremely important in solving challenges of the future. Technical knowledge will need to be augmented with creative thinking, and the most promising solutions often lie at the interface. And the best way to learn about science and the humanities is to find common patterns and themes between these seemingly disparate subjects and use these themes to reinforce concepts and theories learned from either perspective. Berkeley is extremely good at that; you could be talking about enzyme catalysis and connect it to poetry, and these kinds of connections make everything come alive.

Q: What was the best experience of studying at Berkeley? Did you have any favorite research interests or a favorite research project?

I wouldn't say any one of them was specifically my favorite. They were all very educational, often in very different ways. You learn different things from different folks. Prior to Berkeley, I worked at the University of Wisconsin–Milwaukee, and my very first lab was my kitchen. During my undergraduate years, I worked at the U.S. Department of Energy, the Energy and Biosciences Institute, on campus. Additionally, I was in Taiwan last summer working at Academia Sinica. All these different experiences in the U.S. and abroad in fields as diverse as government and academia helped me learn how the same problem is approached in different ways. It was very important that I got diverse experiences and learned about scientific methods and strategies to solve problems culminating in a full breadth of knowledge.

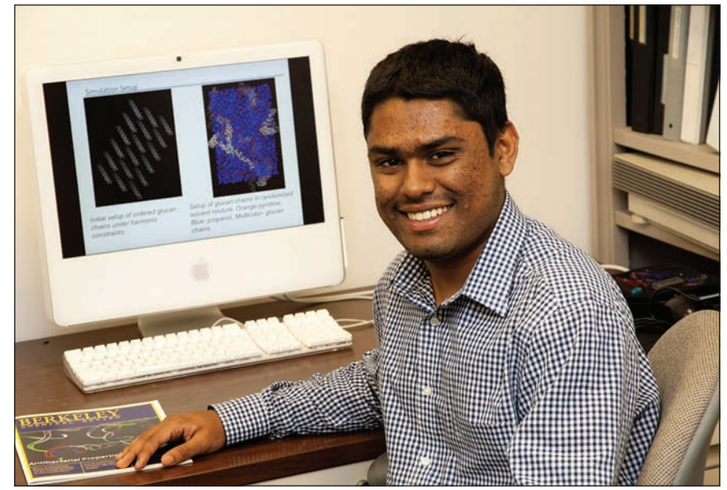
Q: What is your dream research project?

I don't have a specific dream research project. I have a dream of how things ought to look, of what things can happen. I like to be flexible about how I get to the end goal. You have to change and be willing to adapt. I have been very interested in alternative energy as early as high school. In a high-school biology class, I began wondering how the current worldwide energy crisis effectively could be solved if humans were able to extract energy from the sun as efficiently as plants do. This curiosity led me to create a device that worked on the principle of plant biology to harvest solar energy. This was done after extensive research from textbooks and the Internet and fruitful mentor discussions. I began using a blender and other kitchen instruments to perform experiments. My interest in artificial photosynthesis resulted in me applying classroom knowledge to solve real-world challenges. I see an experiment as a means to an end and not necessarily a goal in itself.

Q: You have been involved in numerous community-outreach events and are the founder of See Your Future. What was the source of inspiration behind this?

One of the other things about which I am passionate, besides scientific research, is scientific education and educational access in science, technology, engineering and mathematics. See Your Future is a student-run nonprofit that presents science content to middle- and high-school students through in-class demonstrations, videos, interactive activities and games. The goal is to inspire students with limited resources to pursue careers in science, technology and engineering, and this is a very important societal need. We are really student-centered in the way we approach education.

Let me give you an example: We know that science, technology, engineering and mathematics already play a very important role in young people's lives. Young people have inherent access to a lot of concepts like cell phones, laptops, television, et cetera. As a part of the science class, they are first introduced to a certain law or equation, and they don't see its connection in a real-world scenario. We try to take the backward approach in teaching science: We start with the child's inherent curiosity and then introduce the fundamentals. One of the basic questions that kids ask is "Why is the sky blue?" It seems like a straightforward answer, but that isn't the case. You begin with the fundamental idea of color and then extrapolate it to how the eye detects it and build on it sequentially. Thus we harness the existing curiosity in young minds and build upon it, as opposed to manufacturing curiosity by first talking about diffraction.



One of our current campaigns is the question-answer campaign, where students ask questions on something they experience in their day-to-day life and we answer them in the video format. Some examples are "How does music come out of the radio?" and "How does the scientist predict whether it will be a sunny or a rainy day?"

The answers are quite complicated, and we try to use the visuals in answering them, and that goes back to the whole idea of connecting the humanities and the sciences. Fundamentally, I want to look back and see that I was instrumental in making a big difference in people's lives as a good public servant and give back a lot to the community that made a lot of this possible.

Q: Moving away from academics and work, what are your hobbies?

I love poetry. Here at Berkeley, I have been involved in the Poetry for People program, which is housed in the department of African-American studies. It's an outreach for an underrepresented community in addition to being a program. We organize poetry slams in local community colleges and high schools. I had a chance to publish my poetic works and judge the Bay Area Youth Poet Laureate Competition. It's a really good way to reach out to the community. An apt metaphor to use here is the Sather Gate. It's a main gate that leads to the Berkeley campus on the south side. This gate is very interesting, as it is an open arch and is devoid of doors. It is the best metaphor for the Poetry for People program, as it is in Berkeley but is out for the entire community without any boundaries.

Q: What's your advice to the youngsters in terms of pursuing their goals?

I would like to answer this by reading out a part of my recent commencement speech: "As actor Andy Samberg once said, 'I am as honored to be here today as I am unqualified.' I am just one of the 6,000 graduates who will go on to win Nobel prizes, pen world-changing stories and create industries."

It's extremely humbling to be a part of the group like that and an immense responsibility to try and represent a class as diverse, articulate and accomplished as that of my fellow graduates at Berkeley. For this reason, it's very difficult for me to advise someone. In my brief lifetime, I have yet to experience much. One of the quotes that is very inspirational to me is by Arnold Schwarzenegger: "Never listen to the naysayers when they say it can't be done."

I would like to sum it up with the words of Steve Wozniak: "If you love what you do and are willing to do what it really takes, and if it is within your reach, it will be worth every penny!"

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THE JOURNAL OF LIPID RESEARCH

Gut bacteria may be a source of male steroid hormones

BY RAJENDRANI MUKHOPADHYAY

Looks like there is more than one fount for male steroid hormones in the body. In a paper recently out in the Journal of Lipid Research, researchers show that a bacterial species converts glucocorticoids into androgens, a group of male steroid hormones. The implication is that the host endocrine system may not be the only source of androgens and other regulatory molecules: The gut microbiome may be another.

Phillip Hylemon at the Virginia Commonwealth University explains that there has been evidence since the 1960s that secondary bile acids, which are microbial products made from the primary bile acids secreted by the gallbladder, are associated with gastrointestinal diseases, such as colon cancer and cholesterol gallstones. "A small number of microbes inhabiting the (gastrointestinal) tract are the sole source of these molecules," he explains.

His group and others have worked out how the bacterium Clostridium scindens carries out the primary-to-secondary bile acid transformation. But it turns out C. scindens also can make androgens from glucocorticoids. Why is this important?

Hylemon explains that, in the gut, androgens can be further modified by other members of the gut microbiota to make testosterone-type derivatives. "It is possible that these steroid metabolites interact with host nuclear receptors or other gut organisms. In males, for instance, the prostate gland is against the rectum wall. Therefore, androgens produced by gut bacteria are capable of passively diffusing into this organ, perhaps altering the physiology of cells in the prostate," he says.

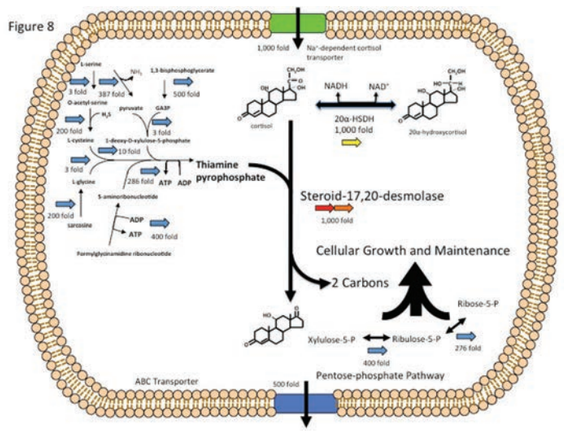
C. scindens is the only bacterium in the human GI tract known to convert glucocorticoids into androgens, but how does it do it?

Hylemon and colleagues decided to use high-throughput nucleic acid sequencing to identify the genes encoding the enzymes involved in this biotransformation. They knew the genes were turned on by cortisol, a stress-induced steroid hormone. By comparing levels of mRNA from C. scindens cultivated in broth with and without cortisol, the investigators reasoned that they would be able to identify candidate genes.

They identified a cluster of genes that encode a transketolase whose sequence is different from those involved in carbohydrate metabolism. A question now is if the C. scindens transketolase evolved to carry out the biotransformation of glucocorticoids into androgens specifically.

The implication of the work is that a bacterium like C. scindens could play an important role in the endocrine system. "It is generally agreed in the field that the gut microbiota constitute a virtual organ. We believe that, like other organs in the body, this organ has specialized cells that produce hormones that may be derived from host-synthesized bile acids and steroid hormones," says Hylemon. Because the gut microbiome can produce hormones, Jason Ridlon, the first author on the paper, says, "we consider the gut microbiome to be an endocrine organ."

The investigators now would like to see if androgen-like molecules produced by the gut microbiome have the same effects on physiology as do the ones generated by the host endocrine system. Hylemon says, "Our next step is to screen bacterial-generated bile acids and steroid hormone metabolites for their ability to bind to and activate host G-protein–coupled receptors and nuclear receptors."



Cortisol metabolism by the human gut microbiome. Members of the human gut microbiome are capable of reducing and epimerizing the 3-oxogroup, reducing the Δ4-bond, oxidation/reduction of the 20-oxo-group, removing the side-chain by steroid-17,20-desmolase, 21α-dehydroxylation, and epimerizing the 17-oxo-group of 11β-OHAD.

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Thematic series: high-density lipoprotein structure, function and metabolism

Introduction
Kerry-Anne Rye

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Cardioprotective functions of HDL
Kerry-Anne Rye and Philip J. Barter

MCP MOLECULAR & CELLULAR PROTEOMICS

The monkey sperm proteome

BY RAJENDRANI MUKHOPADHYAY

We now have the sperm proteome of a primate. In a paper in Molecular & Cellular Proteomics, researchers describe the sperm proteome of the rhesus macaque, the first primate to have its sperm proteome analyzed.

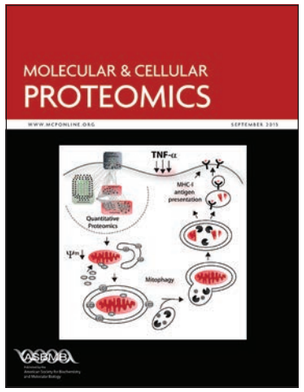
Sperm proteomes from nonprimate species, such as rats, mice and fruit flies, already have been determined. "For comparative evolutionary and functional genomics studies, a primate sperm proteome was highly desirable to include in this growing list of sperm proteomes," explains Tim Karr at Arizona State University.

Rhesus monkeys bear many genetic and physiological similarities to humans, so they are used regularly as a nonhuman primate model system in biomedical research, including human reproduction research. "Knowing the rhesus sperm proteome will greatly expand the possibility for targeted molecular studies of spermatogenesis and fertilization in a commonly used model species for human infertility," explains Karr. (See May ASBMB Today story on sperm and male infertility.)

In their study, Karr and colleagues collected epididymis tissues from male monkeys that contained sperm cells. (The epididymis is a long tubular lumen through which sperm travel after they leave the testis, an essential part of sperm maturation and fertility.) The investigators separated the sperm from the tissue and then proceeded to extract all the proteins from the sperm. The investigators next carried out gel electrophoresis, protein digestion and high-throughput mass spectrometry to identify all the proteins in the rhesus sperm.

From their analysis, Karr and colleagues identified, among other things, new ADAM proteins, ADAMs 3, 4 and 6, in the rhesus macaque that have been lost or are nonfunctional in humans. This gives a glimpse of how the two species evolutionarily diverged.

The investigators also identified almost all components of the 20S proteasome core, including known activators of the proteasome. "This suggests there exists an active form of the proteasome in mature sperm," says Karr.



Karr says he and his colleagues are now "very excited about our developmental work on sperm maturation in the mouse and macaque." Based on what is known about the two animal sperm proteomes, the investigators now are analyzing the process of sperm maturation during epididymal transport.

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jbc THE JOURNAL OF BIOLOGICAL CHEMISTRY

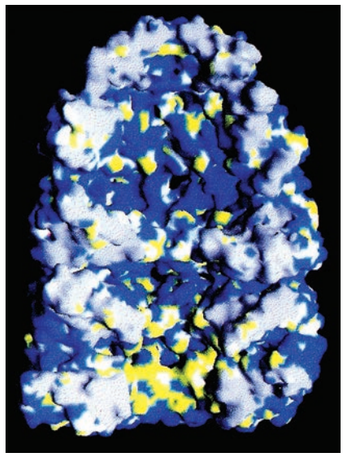
Proteins need chaperones, too

BY PREETHI CHANDER

"I remember walking down the hill to grab breakfast after an overnight fire drill with putting up image plates, shooting X-rays, then fetching the plates and putting them into the Fuji scanner at the F1 beamline … thinking, 'This is really going to change our understanding of this machine.'"

This is how Arthur Horwich relates the excitement during his first data collection on the GroEL protein at the Cornell High Energy Synchrotron Source. Describing his 20-year scientific adventure with the protein-folding machine in his recent Reflections article in the Journal of Biological Chemistry, Horwich takes readers through the initial discovery of the chaperonin, its structural analyses and elucidation of its mechanism.

After his initial training in pediatrics, followed by work in cell transformation and tumor virology, Horwich went on to explore the protein-import machinery in mitochondria. This quest led him to focus on protein misfolding and to discover how the GroEL/GroES chaperonin system refolded proteins. He recollects how a simple phone call led to the fruitful partnership with Ulrich Hartl (his 2013 ASBMB Herbert Tabor Research Award co-winner) that led to this seminal discovery. In collaboration with Paul Sigler and his group of X-ray crystallographers, Horwich then elucidated the structure of the chaperonin and how it works. Through the years, using techniques like electron microscopy, nuclear magnetic resonance and fluorescence spectroscopy, he has been able to unravel the dynamics of protein folding and watch what happens inside the GroEL/GroES ring.



Horwich also writes of the "willingness, personalities and even foibles" of his team members and collaborators. He credits his mentors – Walter Eckhart, Leon Rosenberg and Tony Hunter – not only for their training but also for being great examples of scientists. He remembers Paul Sigler, who "osmotically taught me crystallography"; Helen Saibil, whose electron microscopy images "stunned and reversed our thinking" on the GroEL mechanism; and the "fearless collaborator" Kurt Wüthrich. He writes about his "experimentally fearless" graduate student Ming Cheng, Zbyszek Otwinowski's "brilliance and daring," the "true artist" Kerstin Braig and Jonathan Weissman's "finicky" pet chameleons. He also gives us a glimpse into the scientific thought camps within his lab and the active scientific discussions that led to the great contributions of the Horwich group. In closing, he says the people who made up his team and collaborators "have been just as much fun as the science of working on the chaperonin system."

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Chlamydial virulence factor structure 'very odd indeed'

BY WILL SANSOM

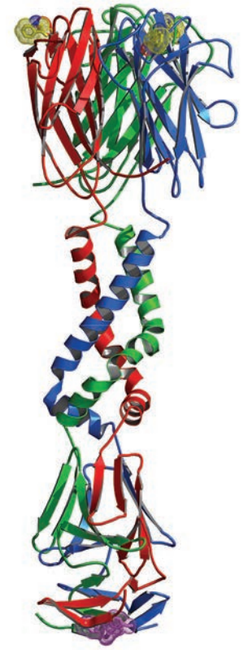
A protein secreted by Chlamydia trachomatis, the bacterium that causes chlamydia, has an unusual structure, according to scientists in the School of Medicine at The University of Texas Health Science Center San Antonio. The shape of the protein Pgp3 is distinctive – sort of like an Eiffel Tower of proteins.

"From a structural standpoint, the protein is very odd indeed," said P. John Hart, senior author of the research, which was described in the Journal of Biological Chemistry. "This long and slender molecule contains a fusion of structural motifs that resemble those typically found in viral and not bacterial proteins."

The Pgp3 protein is a chlamydial virulence factor that is hypothesized to enhance the bug's ability to infect its human host and then evade host defenses.

"Although my lab has worked on this protein for many years and gained a great deal of knowledge on it, we still don't know what roles it may play in chlamydial pathogenesis," said co-lead author Guangming Zhong. "With the structural information uncovered in this paper, we can now test many hypotheses."

Chlamydia infection induces inflammatory pathology in humans, and Pgp3 may contribute to the pathology by activating inflammation via one of its structural features uncovered in the crystal structure, said Zhong. This is the second chlamydial virulence factor that Zhong's laboratory has identified; the first was a protein called CPAF.



The Chlamydia trachomatis immunodominant antigen Pgp3 is a trimer ~150 Å in length with globular assemblies connected by a coiled coil with an unusual right-handed superhelical twist. The single tryptophan (yellow) in each 269-residue chain is prominently displayed in the trimeric C-terminal assembly, which is reminiscent of the trimeric tumor necrosis factor family of cytokines. The three polypeptide chains intertwine and swap structural elements in the globular N-terminal assembly, the interior of which is sealed from solvent by a trio of phenylalanine residues (pink).

The Pgp3 structural work was performed by Hart and his group, Zhong said. Hart's group included Ahmad Galaleldeen, who is the other co-lead author of the research and who is now at St. Mary's University in San Antonio; Alexander Taylor at the UT Health Science Center X-ray Crystallography Core Laboratory; Jonathan Schuermann, now at the Advanced Light Source at Argonne National Labs; Stephen Holloway and Ding Chen, both at UT Health Science Center.

"The independently folded C-terminal domains of the trimeric Pgp3 protein resemble the tumor necrosis factor family of cytokines," Hart said. "The unique N-terminal domain is formed by reciprocal swapping interactions of structural elements coming from each polypeptide chain. The NTD and CTDs are connected by a lengthy triple-helical coiled-coil with an unusual right-handed twist. We used a divide-and-conquer strategy to engineer truncation variants lacking the triple-helical coiled-coil, which permitted high-resolution structure determinations of the Pgp3 NTD and CTDs. The structures of these domains were then positioned into the moderate-resolution electron density map for the ~150 angstrom-long full-length protein. Once properly placed, the electron density for the full-length Pgp3 protein improved significantly, and the connecting triple-helical coiled-coil came into view."

According to the U.S. Centers for Disease Control and Prevention, more than 1.4 million new cases of chlamydia were reported in 2011 across the 50 states and the District of Columbia. But the CDC says as many cases go unreported, because most people with chlamydia have no symptoms and do not seek testing. If left untreated, chlamydia can damage a woman's reproductive system permanently. This can lead to ectopic pregnancy, pelvic inflammatory disease and infertility. The disease burden worldwide is magnitudes greater, with new cases numbering in the dozens of millions per year.

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Making a new ring every 20 minutes

BY LESLEY WASSEF

A healthy bacterial cell begins its cell cycle, grows and divides quite rapidly – every 20 to 30 minutes – which may explain why bacteria can spread so quickly in contaminated food.

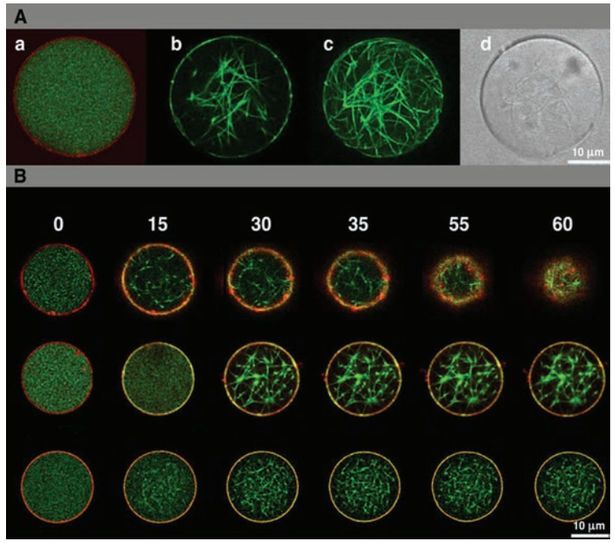
Cell division, the final stage of the bacterial cell cycle, involves a network of molecules to control the position of the division machinery, the divisome, at midcell. In E. coli, a bacterium that lives in our gut, the initial assembly of the division machinery requires three major proteins, FtsZ, FtsA and ZipA, and together these proteins form the proto-ring at midcell. In a recent minireview published in the Journal of Biological Chemistry, Ana Isabel Rico and colleagues from the Centro Nacional de Biotecnologia in Madrid describe the importance of these proteins in the formation, maturation, stabilization and function of the E. coli division machinery.

Firstly, the location of the division site needs to be determined. This occurs through two negative regulatory systems, nucleoid occlusion and the Min system, which inhibit the polymerization of FtsZ at undesired positions. This in turn blocks the assembly of the proto-ring at places that are not the midcell.

The FtsZ polymers need to be organized and stabilized at the division site. The exact arrangement of FtsZ polymers in the proto-ring is not completely known, although two models (ribbon and scattered) have been suggested. In addition, the assembly and stabilization of FtsZ polymers in the proto-ring are regulated by FtsZ-associated proteins known as Zap proteins.

While FtsZ is a cytoplasmic protein, the other components of the proto-ring are associated with the inner membrane, and hence FtsA and ZipA act as anchors for the FtsZ polymers. A stable proto-ring is composed of FtsA and FtsZ polymers arranged in the correct orientation at the inner membrane. ZipA, a transmembrane protein, also provides a physical link of FtsZ to the membrane in either its monomeric or homodimeric form.

After identifying the location and organizing the proto-ring, this initial protein assemblage needs to mature prior to forming the septum. Firstly, preseptal peptidoglycan



Encapsulation and polymerization of FtsZ inside permeable vesicles (A) and vesicle shrinkage and collapse induced by interaction of membrane bound ZipA with FtsZ polymers (B)

synthesis occurs to initiate transversal growth, leading to the production of the septum, and it has been shown that FtsZ, attached to the membrane by ZipA, is needed for this step. Secondly, proto-ring elements need to interact with late-assembling divisome proteins; hence, FtsZ interacts with FtsE, and FtsA interacts with FtsN.

The proto-ring is stabilized once the rest of the divisome proteins are recruited. Some of these proteins include FtsK, FtsEX, FtsQ, FtsB, FtsL, FtsW, FtsI and FtsN, clearly showing that the stabilization of the proto-ring of E.coli is not a simple process.

The membrane constricts, and the formation of the septum begins. It is believed that FtsZ is the driving force for the constriction, which seems to be exerted from the cytoplasm by pulling the envelope inward. Two models have been proposed: the bending or condensation of FtsZ polymers.

The proto-ring is vital for the initial phase of E. coli cell division, and the authors of this minireview summarize the stages and the divisome protein interactions required to form the septum. However, "a description of the detailed molecular mechanisms involved in septation" and "the connection between the biochemical properties of each divisome component" remain unresolved. Clearly, these and other questions still need to be explored, including what happens to the components of the proto-ring once the septum is closed. Key stages of assembling the E. coli proto-ring include the identification of the division site, the organization and stabilization of the structure, the maturation of the protein assemblage, and the formation of the septum. When the conditions are favorable, these stages can be repeated after 20 minutes.

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Plants use a network of modifying enzymes to control hormone action

BY SARAH PERDUE

Anyone who has placed a ripe banana in a paper bag with hard fruit understands the importance of plant hormones: The volatile hormone ethylene diffuses from the banana and binds to ethylene receptors on the unripe fruit, hastening its ripening.

The effects of plant hormones, such as ethylene, auxins or gibberellins, are crucial to the proper growth and development of plants. Equally important, however, is the biochemical regulation of plant hormones in synthesis and modification. In a recent minireview published in the Journal of Biological Chemistry, Corey S. Westfall and colleagues at Washington University in St. Louis highlight the key enzymatic players in hormone regulation, noting the remarkable evolutionary conservation of families of regulatory enzymes as well as the intricate network needed to turn hormones on and off at just the right time.

The first regulated steps in hormone action are at the biosynthetic level, where amino-acid and lipid metabolites are the precursors to most plant hormones. Once synthesized, all hormones are subject to various modifications that alter their chemical activity. These modifications include inactivating methylation by the SABATH family of methyltransferases and activating demethylation by MES methylesterases.

Highlighting the importance of these enzymes' roles in hormone regulation, the authors note that all plants encode multiple SABATH and MES enzymes; within these enzyme families, the active sites are highly conserved, but the overall sequences are divergent, reflecting the widespread use of these modifications on a number of substrates.

An increasing number of crystal structures are adding to the understanding of substrate selection and reaction mechanisms.

Another type of modification the authors discuss is amino-acid conjugation or hydrolysis performed by the GH3 family of acyl acid amido synthetases and the M20 family of peptidases, respectively. These modifications lead to activation, inactivation, targeting for degradation or anti-hormone activity depending on the hormone and the amino acid conjugate.

The authors note that the conserved enzyme families make prediction and discovery of modifying enzymes relatively simple, yet the substrates of these enzymes remain elusive in many cases. Additionally, the identification of more key players and a better understanding of the chemical mechanisms in hormone regulation will help lead to a clearer picture of the network of hormone action that leads to proper plant growth and development.

Sarah Perdue (sp366@cornell.edu) received her Ph.D. in microbiology from Cornell University in 2011 and has spent the past two years teaching at different colleges as a visiting professor. She is currently arranging a postdoctoral fellowship.

Series explores biochemical diversity of cytochrome P450 enzymes

BY ZACHARY R. CONLEY

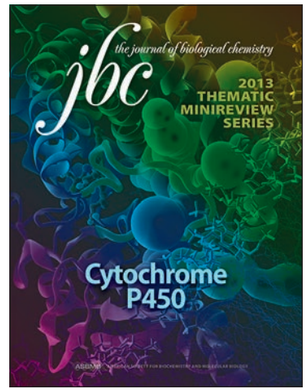
A recent thematic series on cytochromes P450 in the Journal of Biological Chemistry consists of four minireviews covering new trends in P450 research and the many roles they play in disease. As important catalysts involved in hormone and drug biochemistry, these diverse enzymes are the center of attention in a number important fields.

In his introduction to the series, coordinating editor F. Peter Guengerich of Vanderbilt University illustrates how the P450 field has matured over the past 50 years. "With (more than) 18,000 known P450 sequences available and the number increasingly rapidly," Guengerich writes, "it is humbling to realize that we understand the functions of only a fraction of these P450s."

Most of the reactions that are catalyzed by P450s are called mixed-function oxidations and have the following stoichiometry: $NAD(P)H + H^+ + O_2 + R \rightarrow NADP^+ + H_2O + RO$ (where R is the substrate).

Understanding P450s has been instrumental in cancer biology, pharmacogenetics and insect control, and although we have a good understanding of the sheer breadth of applications, Guengerich emphasizes that "prediction of catalytic activities for individual P450s is still difficult."

In the first minireview, Guengerich and Andrew W. Munro of the Manchester Institute of Biotechnology write about unusual P450 enzymes and reactions. Most P450 reactions can be rationalized with the complex FeO3+, an intermediate known as Compound I. Rearrangements of products or intermediates are often the explanation for unusual P450 reactions. "Although the vast majority of P450 reactions are oxidations, reductions are also known," the authors write. Moreover, a minimum of three nonredox reactions have been reported.



In the second minireview, Courtney M. Krest of Pennsylvania State University and colleagues stress the importance enzyme purification played in the capture and characterization of P450 Compound I. The authors discuss techniques involved in the search for reactive intermediates and attempt to clarify controversial reports on the production of P450 Compound I using alternate approaches.

The third minireview, by Eric F. Johnson and C. David Stout at The Scripps Research Institute, highlights the notion that X-ray crystal structures, which are now available for 29 eukaryotic microsomal, mitochondrial and chloroplast P450s, offer a scaffold upon which mechanisms of function may be built. The authors add that "advances in the application of (nuclear magnetic resonance) spectroscopy for structural characterization of membrane P450s could increase our understanding of the conformational heterogenetiy of membrane-bound P450s." The authors also point out that characterizing the structures of additional membrane P450s in insect and plant species would prove fortuitous in maneuvering around pesticide-resistance problems. Likewise, they acknowledge that understanding structures of P450s in microbes and eukaryotes might lead to new drug opportunities.

The final minireview, by Irina A. Pikuleva at Case Western Reserve University and Michael R. Waterman at Vanderbilt University, focuses on P450s in human diseases. The authors discuss 14 monogenic diseases related to altered enzymatic action on steroid hormones, cholesterol, vitamin D3 or eicosanoids. In their final remarks, the authors note that "development of new DNA-sequencing platforms and genome-wide association studies have revealed previously unanticipated associations and P450 contributions to a number of polygenic diseases." They also conclude that within the next 10 years our understanding of P450 roles in various diseases undoubtedly will be broadened significantly.

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Grant-writing workshop recap

BY MARION B. SEWER

Two years ago, the American Society for Biochemistry and Molecular Biology Minority Affairs Committee embarked on an initiative to identify the perceived barriers encountered by faculty members from groups that are underrepresented in the sciences and by faculty members at minority-serving institutions. Although the committee identified several barriers, including an opaque review process, lack of a support network, a leaky pipeline of minority talent and a lack of initiatives directed at underrepresented minorities, the underlying issue common to all participants in the working group was the lack of formal mentoring (1).

To address this issue, the MAC held a mentoring and grant-writing workshop in June in Arlington, Va. Our initial plan was to invite 15 to 20 assistant professors who were in the first four years of tenure-track positions and to pair them with ASBMB members who had been successful in obtaining federal funding. However, in response to unexpected enthusiasm from the community at large and the overwhelming number of applications, we invited 32 faculty members to participate in this inaugural endeavor.

In addition to selecting minority faculty members and faculty members at minority-serving institutions, we selected nonminority applicants at research-intensive institutions and at primarily undergraduate institutions. This strategy enabled us to have a diverse cohort of assistant professors from various institutions, including the University of California, Berkeley; Grand Valley State University; the University of Michigan; the University of Southern Maine; Jackson State University; California State University–Fullerton; the University of Richmond; and the University of Texas at El Paso. Mentors included members of the MAC as well as faculty members with research programs in biochemistry and molecular biology. (See box for a list of mentors.)

The event began with a networking reception, which was followed by two days packed with interactive sessions. Ruma Banerjee of the University of Michigan opened the first day with an inspirational and poignant talk about the importance of developing a personal roadmap, marketing your research program and networking. Program officers from the National Institutes of Health (Barbara Gerratana) and the National Science Foundation (David Rockcliffe, Catalina Achim and Sussanah Gal) talked about funding opportunities and the proposal-submission and review processes.

A mock review panel provided an overview of the logistics of the NSF review process and insights into how panelists discuss the intellectual merits and broader impacts of an application. There also were sessions on the elements of a successful proposal, differences between the NSF and the NIH, and revising and resubmitting an application.

Significantly, prior to the workshop, participants submitted summaries (e.g., an NIH "Specific Aims" page or an NSF "Research Summary" page) of their research proposals and received feedback from the mentors and from the other assistant professor participants.

Perhaps the most valuable component of the workshop was that each participant gave a short presentation that encompassed the background, hypothesis, aims, preliminary data and experimental approach of a research proposal that he or she was expecting to submit. Mentors provided salient feedback with regard to the scope of the proposed studies, the novelty of the research questions and approaches, and the biological or biomedical significance of the areas of investigation.

The meeting closed with group discussions on bal-

Participating mentors

- Takita Felder-Sumter, MAC member
- Squire Booker, MAC member
- Marion Sewer, MAC member
- Ruma Banerjee, University of Michigan
- Vahe Bandarian, University of Arizona
- James Stivers, Johns Hopkins School of Medicine
- Reuben Peters, Iowa State University
- Wilfredo Colon, Rensselaer Polytechnic Institute
- Sarah Woodson, Johns Hopkins University
- David Wilson, MAC member

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Demystifying the chalk talk

BY CHARLES BRENNER

Congratulations! You've succeeded as a graduate student, changed institutions and obtained first-author publications. You've obtained funding for your postdoctoral fellowship or even for your transition to independence. You've identified some schools that are looking for faculty members in your area and have developed a brief, compelling research plan. Your referees are enthusiastic and prompt. You were personable and prepared during a phone call or Skype with the search committee chair, and you've been invited to a two-day campus interview. There, you will have meetings with members of the search committee and other members of the faculty, have lunch with graduate students and postdocs, take tours of shared resources and give two presentations.

On the first day, you'll give your 60-minute public seminar, being sure to finish in 45 to 50 minutes to allow for questions. On the second day, you'll be in the conference room for a 60-minute chalk talk.

Because chalk talks are not generally open to postdoctoral fellows, you've never seen one, but you've heard that great candidates do not always give good chalk talks.

What's a chalk talk?

A chalk talk is your opportunity to present your forward-looking research program to potential colleagues. They will have seen your seminar on the first day, so your research accomplishments will be fresh on their minds.

They will be wondering how you plan to organize your laboratory, what types of experiments you plan to do first, what your funding plans are, what your relationship is with your current principal investigator, who you think your major competition is and how well you have thought out your research plans in case things don't work out the way you think they will.

Do you have to use chalk?

Generally, no, though you should ask.

Channel your inner PI

Never interview as though you are a postdoc with only your two hands. Project your inner principal investigator, who is capable of defending a progressive research plan to successful colleagues and who appears capable of directing a small research group.

Though your plans probably require another two to three people to get off the ground, if you describe plans for your first eight trainees, you are likely to come off as far too ambitious (and expensive) to hire.

Organizing your presentation

Spend the first few minutes on a summary slide or two to remind the audience of your major findings. Don't assume a good memory or great insights into your experimental system.

The next slide is an outline of a couple of fundable directions in which you plan to take your work. You may have three or more ideas, but you won't have time to show more than one or two, and you should not show your third best idea during this hour. Your transition to independence will require intense focus and many tactical decisions. You do not want to look scattered. Determine your best project(s) in advance and practice your chalk talk with faculty members of diverse backgrounds.

As soon as you have sketched out the one or two projects you plan to launch, you might state that you'd like to spend the next 30 to 35 minutes on project 1 and the remaining time on project 2.

The best next slide is a bulleted list of the specific aims in your first project. Here, candidates with funding that will extend into their next positions have a huge advantage. These candidates can list the aims of their R00 or R01 or American Heart Association grant. Such aims are always easier to defend, because the candidates have defended them already to a review panel and because faculty will feel that one of two major risks has been taken off their hands. The first risk is that a new hire might fail to obtain external funding for the research program. The second risk is that, even if start-up and other funding is in place, the project may not work or may work and have limited scientific impact.

Faculty will interject freely during your presentation,

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What, how and why is problem-based learning in medical education?

BY JOSÉ M. BARRAL AND ERA BUCK

What is problem-based learning?

Problem-based learning, or PBL, is a pedagogical practice employed in many medical schools. While there are numerous variants of the technique, the approach includes the presentation of an applied problem to a small group of students who engage in discussion over several sessions. A facilitator, sometimes called a tutor, provides supportive guidance for the students. The discussions of the problem are structured to enable students to create conceptual models to explain the problem presented in the case. As the students discover the limits of their knowledge, they identify learning issues – essentially questions they cannot answer from their fund of knowledge. Between meetings of the group, learners research their learning issues and share results at the next meeting of the group.

How do faculty members participate in this process?

Faculty members often participate as facilitators. Indeed, the role of the facilitator and the nature of the problem are key to successful implementation. Facilitators must be supportive rather than directive. They ask questions to assist students with identifying the limits of their knowledge, monitor the group process (encouraging participation) and provide a framework for constructing models of understanding. Content expertise on the part of the faculty may be helpful but is not considered necessary for effective facilitation. Deeper understanding of the topic may allow the facilitator to guide student discussions to be more comprehensive. It also may increase the challenge of maintaining a nondirective role. Problems presented in cases are constructed at a level of complexity to activate students' existing knowledge and require integration and application of new knowledge. Cases contain contextual information so that the patients become more real to the students and therefore more memorable.

Why are medical schools incorporating PBL?

PBL has become popular in medical schools that have undergone curriculum reforms incorporating multidisciplinary-system-based courses rather than discipline-specific ones. For example, students may learn biochemistry as it relates to organ systems of the human body while they are solving problems presented in clinical cases. This approach provides relevance, encourages self-directed learning, targets higher-order learning and engages students in ways that result in better long-term retention of content than traditional, lecture-based courses.

Can you give me an example of how the process works?

During a traditional, lecture-based system, students learn the basics about the developmental and cell biology of erythrocytes (their lineage, shape, size, absence of nucleus, etc.); the biochemistry of hemoglobin (cofactor requirements, protein quaternary structure, cooperativity and allosterism, etc.); and the various mutations that result in disease states (sickle cell anemias, thalassemias, etc.). When asked about the phenotype of a sickle-cell hemoglobin carrier, a student who learned these concepts in a traditional, lecture-based environment might reply that there is no phenotype, unless the carrier is living in a region with malaria, in which case the carrier may be better able to resist the disease because of heterozygous advantage (classic concepts learned in genetics). However, if a group of students are presented with a case of a patient undergoing a sickle-cell crisis and are prompted to consider the many aspects of the disease, including the implications for family members, they might arrive at a different answer. They may come to the realization that the phenotype of a carrier could include the presence of some elongated cells in a smear of venous blood, particularly after exercise (which appears to occur in the majority of cases). In this manner, knowledge integration leads to critical consideration of how a phenotype is defined and how this indeed can depend on the variable being studied (a concept clearly generalizable beyond the hemoglobinopathies).

What student skills should we encourage for PBL-focused medical education?

Self-directed learning: Students who demonstrate adequate performance in PBL activities are capable of applying their knowledge to think critically. They must be trained to be able to use information rather than merely capable of remembering it. Students in PBL-based curricula increase the level of self-direction they bring to learning. The more self-direction they develop as undergraduates, the more likely it is that they will become independent learners as practicing professionals. Lifelong learning uses a set of skills that develop over time and require practice.

Reflection: Some of the critical skills can be encouraged and practiced in college classes. These include self-assessment, group learning and active learning. Students need opportunities to identify their strengths and weaknesses and figure out what it is that they do not know or thoroughly understand. They need to be encouraged to ask good questions. By encouraging students in formulating good questions, we empower them to identify their knowledge gaps.

Teamwork: Students also must develop skills necessary for learning in groups. They must be able to learn from peers and teach peers, moving readily between those roles. They need to be able to assist each other in integrating and applying knowledge to a given problem. These skills are acquired through active learning. Projects and lab work often promote these skills.

In summary, students need opportunities to assess their knowledge, identify and remedy knowledge gaps, and integrate and apply knowledge to real-world problems as part of a team.


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ancing teaching, research and service and on professional ethics.

A survey of the participants found that the workshop was an overwhelmingly positive experience. Seventy percent reported that the feedback they received about their research objectives was likely to improve their grant-writing skills, and 80 percent said they found the interaction with the mentors valuable. Significantly, 75 percent of the participants who had attended a grant-writing workshop in the past said they felt that the ASBMB workshop was more informative and helpful.

Efforts are underway to hold another workshop. For more information on this and other MAC activities, please visit http://www.asbmb.org/MinorityAffairs.aspx.

Marion B. Sewer (msewer@ucsd.edu) is an associate professor at the Skaggs School of Pharmacy and Pharmaceutical Sciences at the University of California, San Diego, and a member of the ASBMB Minority Affairs Committee.

REFERENCE

1. http://www.asbmb.org/asbmbtoday/asbmbtoday_article.aspx?id=11780

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in part to get their key questions answered and in part to see how you interact and think on your feet. Your ability to interact as a peer is paramount. If you have an advocate on the faculty, this person will help you get to your second project, especially if the discussion bogs down.

In general, you should describe experimental plans with as few slides as possible. You may get some bonus points if you can use the white board effectively in response to a question. You get major bonus points for composure, clarity and cutting-edge approaches to problems that will move your field forward.

If you are reading this column as a trainee who has yet to be invited to give a chalk talk, the best practice is to write a grant proposal to fund your research ideas. You can be assured that reviewers will identify the problems!

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Speaking of fat

ASBMB 2014 meeting in San Diego

BY DANIEL M. RABEN

Communication is a cornerstone of scientific advances. I've always maintained that a large part of science is a dialogue among colleagues within and across disciplines. That's one of the important aspects of the annual American Society for Biochemistry and Molecular Biology meeting. It provides a mechanism for stimulating disciplinary and interdisciplinary discussions among established investigators, new investigators and, perhaps most importantly, budding investigators. In the lipid community, we take this opportunity seriously and work hard to provide a spirited camaraderie that welcomes ideas and inputs for all investigators within and outside our discipline.

The ASBMB annual meeting always includes a wealth of new and exciting lipid research, and the 2014 meeting in San Diego will be no different. This meeting includes programming on lipid chemistry, biochemistry, biophysical chemistry, and biology and physiology. There will be talks focused on chemical probes and pharmacology of lipid systems. New aspects of lipid metabolism, trafficking and biosynthesis will be presented, including exciting new genetic models of lipid metabolism and lipidomic approaches. There will be presentations on lipid organization in membranes and signaling along with new functional roles of lipids in gene expression, inflammation and stress.

As one example, four sessions will be dedicated to the structural and functional complexities of cellular membranes and related proteins that have been revealed by recent biophysical studies. Organized by Karen G. Fleming of Johns Hopkins University and Vinzenz Unger of Northwestern University, this thematic programming will cover membrane-associated scaffolds and scaffold-dependent membrane dynamics, how chaperones rein in the unfolded state, the role of heavy metals in membrane biology, and how proteins conform to allow for passage of drugs and ions across lipid bilayers.

It almost goes without saying that our two lipid award winners will give two of our most notable presentations. Sandra L. Hofmann, a professor at the University of Texas Southwestern Medical Center at Dallas, won the Avanti Award in Lipids, now in its 19th year. Hofmann's research has a distinctive translational flavor in that it focuses on the involvement of fatty-acid acylation of proteins in neurodegenerative disorders. For example, her group showed that disruption of the palmitoyl thioesterases PPT1 or PPT2 leads to the hereditary neuronal ceroid lipofuscinosis known as infantile Batten disease. Recently, she has been studying the role of palmitoylation in neuronal development and plasticity.

HOFMANN

Mary L. Kraft, an assistant professor at the University of Illinois at Urbana–Champaign, won the Walter A. Shaw Young Investigator Award in Lipid Research. Kraft has developed some innovative biophysical approaches to interrogate and understand the dynamics of membrane lipids in living cells. In one interesting study, her lab is developing a mass spectrometry-based approach to analyze the membrane composition at the site of influenza virus budding, and it is developing an imaging MS-based approach to analyze the glycan composition in cell membranes. Hofmann's and Kraft's work will be presented in award lectures in April in San Diego.

KRAFT

Lipids again will play a prominent role in the ASBMB annual meeting, and it promises to be a very exciting meeting. And having it in San Diego just adds to the fun.

Daniel M. Raben (draben@jhmi.edu) is a professor in the department of biological chemistry at the Johns Hopkins University School of Medicine.

Special symposium recap: evolution and core processes in gene expression

BY DAVID ARNOSTI

A major achievement of 20th-century biology was the identification of the fundamental, shared genetic and biochemical properties of all life forms. Now, understanding the nature of biological variation at the population and species levels represents a core question in modern biological research, one that spans disciplines from genetics to biochemistry and genomics. Which cellular processes are most commonly affected to generate diverse phenotypes?

Genetic studies of morphological innovation owe a debt to early studies of homeosis, from William Bateson's observations of aberrant developmental transformations to Ed Lewis's elegant characterization of Drosophila HOX genes. Subsequent work in the field of evo-devo has identified numerous examples in which derived aspects of biological systems can be traced directly to subtle changes in transcription factors and cis regulatory elements.

Indeed, from microbes to man, analysis of population variation demonstrates that these elements are free agents, constantly sampling new functional space and shifting their roles in gene regulatory circuits to generate novel outputs. As we move into more quantitative molecular studies with systems-biology approaches, more general questions are "How predominant are specific changes in the periphery of gene expression?" and "How much does variation at the very core processes of gene expression contribute to evolutionary innovation?"

Responding to these challenges, the first meeting on evolution and core processes in gene expression, sponsored by the American Society for Biochemistry and Molecular Biology, was held July 25 – 28 in Chicago. Speakers from North America, Europe, Israel and Japan shared insights on interdisciplinary topics. The symposium brought together speakers from diverse backgrounds to discuss mechanistic gene expression and evolution, to highlight our current understanding, and to focus on how the field may develop a more global understanding of these processes.

Some of the presentations from microbial research set the scene for how research in higher organisms may develop. Saeed Tavazoie of Columbia University and Eduardo Groisman of Yale University School of Medicine discussed how bacteria can show remarkable "molecular memory" in regulatory systems with precisely tuned outputs. Yet with a few genetic transitions, bacteria can easily shift toward a completely different regulatory paradigm. Their examples focused on transcription factors and signaling molecules.

However, the impact of variation of the core machinery was highlighted by Seth Darst of The Rockefeller University, Robert Landick of the University of Wisconsin and Zach Burton of Michigan State University, who discussed the structure and function of E. coli RNA polymerase. This organism's well-studied enzyme features a derived structure not observed with other bacterial polymerases, a prominent 188-amino-acid insertion connecting a key element of the active site, the "trigger loop," to the outside of the protein. The significance of this structural innovation is unknown, but the element frequently is mutated in bacterial populations grown under conditions of nutritional stress, and certain mutations allow bacteria to ignore facultative pause sites, globally changing gene expression. How frequently such alterations in the enzyme might contribute to innovations in gene expression is an important question for future studies.

A similar, but less complete, picture emerges from research presented by Aviv Regev of the Broad Institute and Ian Dworkin of Michigan State University. These speakers described how genetic background has a critical impact on the function of the mammalian immune system and organ development in the fly. At this point, these and similar studies are still cataloging the numerous loci that affect signaling and developmental outputs; we don't know if the bulk of such modifications occur on the periphery of regulatory networks or might also implicate central nodes, such as the transcription, splicing or translational machinery.

Lawrence Myers of Dartmouth College provided a clue to such a possibility in a discussion of his analysis of the transcriptional mediator complex of Candida albi-

cans, a pathogen in which genes for certain subunits of the mediator have undergone a tremendous expansion. Mutation of these genes affects fungal virulence, indicating that this novelty may be an acquired trait important for growth in certain niches.

Whether human mediator similarly is subject to such evolutionary tampering is unknown, but Jean-Marc Egly at the Institut de Genetique et de Biologie Moléculaire et Cellulaire described how mutations in mediator and some of the other ~200 factors of the basal machinery lead to very tissue-specific effects in human disease. Such genetic variation is present in the human population, although examples of adaptive modifications are unknown.

One clue relating to animal development concerns the conserved heptapeptide repeat of the RNA polymerase C-terminal domain. Most eukaryotes feature such a repeat domain, which is of variable length in different species. Across eukaryotes, from yeast to Arabidopsis to mice, the composition of the YSPTSPS repeats are relatively invariant, except in Drosophila, where divergent sequences are abundant and conserved. Whether this alternative CTD reflects the special gene regulatory requirements of early rapid development in the long germband syncytial embryo, as discussed by Melissa Harrison of the University of Wisconsin–Madison and Julia Zeitlinger of the Stowers Institute for Medical Research, is unknown.

Jeremy Lynch of the University of Illinois at Chicago noted that the long germband developmental program has been multiply derived, as in Nasonia, and that certain patterns of gene expression appear to be bottlenecks that are more conserved than others; thus, it would be interesting to determine whether alternative CTD of RNA polymerase II are similarly selected in these lineages, perhaps to deal with the unique chromatin challenges of rapid development.

How does the biochemical view of gene expression at the level of Ångstrom and kd connect with evolutionary perspectives? How important are variations in core processes of gene expression, which are highly pleiotropic, in sampling the functional gene expression space explored as populations and species evolve? Quantitative genetics and systems biology are providing the raw material to map this landscape; a challenge for future studies will be to develop tools and systems that can provide us comprehensive answers to central questions of evolutionary gene expression.

Organizers: David Arnosti at Michigan State University, Justin Fay at Washington University and Ilya Ruvinsky at the University of Chicago.

Sponsors: Michigan State University Gene Expression in Development and Disease Initiative, the Journal of Biological Chemistry, PLoS Genetics, and the American Society for Biochemistry and Molecular Biology Special Symposium Series.

David Arnosti (arnosti@msu.edu) studies transcriptional enhancers and corepressors in Drosophila with colleagues in the Gene Expression in Development and Disease Focus Group at Michigan State University.

outreach

Bringing science to the people

A look inside the North Carolina Museum of Natural Sciences

BY DAVID J. KROLL

You have another 20 minutes on that enzyme incubation. What to do? Catch up with journal tables of contents on your RSS reader, or maybe jabber with your labmates about the exciting experiment you have going? But everyone's too busy to listen.

What if you could just walk outside the lab and chat about your research with some of those folks who pay the bills – and your salary? You know, taxpayers, otherwise known as the general public.

But when you look down the hall, all you see is that new undergrad bumping into the FedEx delivery person, spilling freshly autoclaved LB agar all over the floor.

At the North Carolina Museum of Natural Sciences in Raleigh, you wouldn't even have to go outside of your floor to show off your mad skills to the public. With floor-to-ceiling glass walls, comfy bench seating in front of the lab and interactive touch-screen videos playing on the lab glass, visitors to the Southeast's largest venue of its kind can learn about the scientific process while it happens. That's just one of several opportunities for museum scientists and our colleagues in the local academic community and around the world to show nontechnical audiences the science that affects their lives. Science communication with the public isn't just lip service. Here, it lives, every day.

DAVID KROLL: NORTH CAROLINA MUSEUM OF NATURAL SCIENCES

Meg Lowman conducts a science cafe.

The N.C. Museum of Natural Sciences began as your typical late-19th-century natural history institution. Founded 134 years ago by the self-trained British naturalists and brothers Herbert H. Brimley and C.S. Brimley, the museum has grown its collection to more than 3 million specimens. Last year, the museum drew more than 1.2 million visitors to its state capital site, making it the most-visited cultural attraction in the state.

Much of the increase in visitors was due to the April 2012 launch of the Nature Research Center wing, a $56-million, public-private partnership that expanded the main museum's space by almost 40 percent. Where the main wing had been traditionally dedicated to showing what we know about the natural world, the NRC was designed to show visitors how we know what we know – and engage them in scientific discovery.

Four new research laboratories build on the museum's traditional strengths in research and collections, addressing some of the major areas of natural sciences research: paleontology and geology, biodiversity and Earth observation, astronomy and space observation, and genomics and microbiology. All of the laboratory directors serve half-time as faculty members at nearby North Carolina State University, North Carolina Central University (one of 11 historically black institutions in the state) or Appalachian State University.

These are augmented by what we call the Window on Animal Health, a veterinary medicine procedure room where visitors can watch gall bladder surgery on a resident frog, with two-way communication between veterinarians, vet students and public visitors. (I recently learned from our veterinary director, Dan Dombrowski, that the local anesthetic for fish surgery, used systemically in ambient water, goes by the brand name Finquel.)

Meg Lowman, the founding director of the new wing and currently director of academic partnerships and global initiatives for the entire museum, specifically recruited world-class scientists with an aptitude – and desire – to bring public audiences into their labs and demystify the scientific process. Her own enthusiasm

KAREN SWAIN: NORTH CAROLINA MUSEUM OF NATURAL SCIENCES

Paleo director Lindsay Zanno and the duckbilled dino.

for nature and pioneering the study of treetop biodiversity is infectious. Lowman, our role model and conduit for all academic relationships, sets a very high standard for all of us to pursue science outreach as a substantive scholarly effort, making our work accessible to anyone, from schoolchildren and teachers to celebrities and civic leaders.

But the science world at the museum is bigger than just our own science. Lowman and our new museum director, Emlyn Koster – all of us, in fact – aim for our community to be the place for all our colleagues worldwide to have their science discussions with the public. Our venues for doing so are as varied as the science our visitors expect to see.

Our main museum building showcases a learning room for local and distance learning as well as an auditorium featuring 3-D science movies and special events, such as our live uplink with the International Space Station and astronaut Tom Marshburn. The new wing expands this space, most notably with the 70-foot-diameter SECU Daily Planet. Externally, it's the largest accurate representation of Landsat Earth images in North America (1:598,000, if you care). Inside, it's a three-story multimedia theatre featuring twice-daily Meet the Scientist interactive presentations and live interviews led by science communications expert Brian Malow.

Applying techniques he learned from doing improvisational comedy, producing Time magazine science videos and working on the Weather Channel's "Hacking the Planet" program, Malow is central to our comprehensive science communications training programs.

Michelle Trautwein, assistant director of the biodiversity lab, describes her experience, one that we offer to our externals colleagues as well:

"Brian Malow is incredibly comfortable with every kind of audience. And his sense of ease and confidence really translates to me when we are doing live interviews together. He makes public speaking fun for me, which is something I would have never said before. Working with him has helped me realize that connecting with the audience is more important than squeezing in more science factoids. He has really helped me tone down jargon that I didn't even realize was jargon."

And with so much of our public interactions in visual media, staff television personality Emelia Cowans mentors every scientist and staff educator who appears in promotional segments on local and statewide television. Everyone from undergraduate student researchers to seasoned principal investigators benefits from Malow's and Cowan's expertise. I even have my NC State science journalism students pitch their semester project stories to the public there.

Webmaster Brian Russell and museum webbie and ace photographer Karen "Nik" Swain work with me on science blogging workshops for staff, students and visiting faculty. A surmountable hurdle with many scientists is convincing them that a significant subset of our visitors is rabid to learn of their expertise. I'm particularly cognizant of this point as a biochemical pharmacologist who joined

Who's Who

- **Emlyn Koster** is director of the North Carolina Museum of Natural Sciences in Raleigh.
- **Meg Lowman** is the founding director of the new Nature Research Center wing and currently director of academic partnerships and global initiatives for the museum. Follow her at www.twitter.com/canopymeg.
- **Brian Malow** is a science communications expert at the museum. Follow him at www.twitter.com/sciencecomedian.
- **Michelle Trautwein** is assistant director of the biodiversity lab at the museum.
- **Emelia Cowans** is the museum's television expert and coaches all affiliated researchers and students on TV appearances.
- **Brian Russell** is the museum's webmaster. Follow him at www.twitter.com/brianr.
- **Karen "Nik" Swain** is a Web editor and photographer at the museum.
- **Katey Ahmann** is deputy director of education at the museum and founded its scientific café program seven years ago.

SECU Daily Planet Theater

KAREN SWAIN: NORTH CAROLINA MUSEUM OF NATURAL SCIENCES

an organization with experts from geology and insect-microbe symbiosis to paleontology and evolutionary genomics. To me, an expert in another area, everything is interesting.

The museum also features science café discussions with the public fashioned after the Café Scientifique movement. Our seven-year-old program was founded by Katey Ahmann, deputy director of education, and originated as monthly programs in local pubs. But with the new wing, weekly programs are held on every Thursday in our on-site restaurant – The Daily Planet Café – featuring a stage and large-screen TVs (think science sports bar) plus a large selection of food and North Carolina microbrews and wine. All the programs are webcasted live by our digital and emerging media specialists, with questions taken on-site and via Twitter and then archived at livestream.com/naturalsciences.

I've learned that one has to be intellectually agile in such a diverse environment of scientists and visitors. As I was about to present a carefully crafted Meet the Scientist talk on the 50-year journey of the Herceptin antibody-emtansine conjugate for breast cancer (Kadcyla), Malow told me that I would have a crowd of 60 first-graders. I quickly opted for a tried-and-tested demonstration of thermochromic substances (think Coors beer labels) and the chemistry of color.

Unquestionably our most involved partner is Rob Dunn, a NC State associate professor of biology. A frequent writer for Scientific American and Smithsonian Magazine and author of the book "The Wild Life of Your Body," Dunn nicely captures the opportunities scientists have to partner with public institutions like museums and science centers:

"Public funding for science is a privilege. That the public entrusts us to struggle toward the truth on their behalf is amazing. It is sometimes said that scientists don't try to communicate to the public what they do. Sometimes this is the case. Some of us have our heads up our, well, labs. But I think more often the issue is that scientists don't have an easy place where they can reach the public. I think museums provide such places, and in an ideal world, I think there is a huge opportunity for museums to better link to scientists and scientists to better link to museums in such a way that thousands of scientists are able to share with the public what they do and why they do it. This can only benefit scientists. Certainly the public is more likely to want to keep paying us if they know what they are paying for."

Dunn adds, "But I think it also benefits science. I know engaging the public at museums has made me a better scientist. If nothing else, it gives me a measure of what the public wants to know. We are so ignorant about the world that we have some choice about what dark hole we plunge into, and I'm delighted to listen to the public more about what that should be, so long as the hole isn't at the end of a pier."

Broad engagement is the key at the North Carolina Museum of Natural Sciences. We provide venues for all manner of scientists to press the flesh with all manner of other citizens. We never really needed funding agencies to tell us that ensuring the public impact of our work was important, although that now may matter much more to you in grant applications. It happens every day here.

So if you're coming through Raleigh or the Research Triangle Park area, drop me a note – david.kroll@naturalsciences.org – or direct message me @davidkroll on Twitter. Someone will want to hear your story.

Stay up to date with all the museum's activities at www.naturalsciences.org, www.twitter.com/naturalsciences and www.facebook.com/naturalsciences.

David J. Kroll (david.kroll@naturalsciences.org) is the director of strategic positioning at the North Carolina Museum of Natural Sciences in Raleigh. He also is an investigator at the museum's Genomics and Microbiology Research Laboratory, an adjunct associate professor of English at North Carolina State University, and an adjunct associate professor at the Duke University School of Medicine and the University of North Carolina at Chapel Hill.

Starting salaries

How to ask for more and to launch a negotiation

BY KAREN KELSKY

Academics tend to struggle with negotiating job offers because of the enduring monkish quality of the scholarly life, which is ideally meant to forsake material gain for a higher calling of dedication to the truth. How this ideal has endured to 2013 is beyond me, but endured it has, and it does a tremendous disservice to the young Ph.D.s attempting to finalize the terms of their first professional positions.

Because the fact is, you have to negotiate to get the best terms possible. Institutions know that young Ph.D.s are loathe to push for more money and other perks, and while most departments do approach the job-offer negotiation with a new hire with considerable good faith and good will, they by no means start out at their absolute upper limit. They'd like to get you for less, thank you very much. At the same time, they know how to negotiate and will engage in a negotiation with a job candidate most of the time. (There is a disturbing recent trend for schools to rescind offers upon the candidate seeking a minimal level of negotiation. See the Chronicle Forum "Universities to Fear" for stories. Thankfully this is still quite rare.)

It is important to approach the negotiation confidently, firmly and courteously, without emotionalism, drama, self-deprecation or insecure justifications. Simply compose a list of things you'd like, with specifics – always name a salary number, a startup figure, a specific teaching release, etc. – and ask for them.

Women, people from marginalized communities and first-generation Ph.D.s have the hardest time with this. They tend to feel as if they are imposing on the department, being selfish, asking for something to which they are not entitled, etc. They may be encouraged in this wrong-headed thinking by some advisers who still tell their Ph.D.s just to be thankful they have an offer at all.

Reject that thinking! Do not allow yourself to be influenced by such concerns. You are entitled to ask for more and to launch a negotiation. The department may not agree to everything, but, as long as you write and speak with collegiality and good will, they will respect your efforts to provide for yourself.

If they say no once, ask again or ask for a lesser amount. Let the exchange go on for a few days; don't allow yourself to be rushed.

Below is an example of a bad negotiation email (from an actual client of mine) and how I corrected it. In the first email, I have set in bold every term and phrase that diminishes, juvenilizes, genders, and sabotages or makes excuses for the hire. Note in particular (1) her overuse of the self-minimizing word "just," (2) the emotionalism in the phrase "I would really appreciate …" and (3) the repeated question form ("would you consider") that I replaced with declarative requests.

The client was successful (indeed, she was a bit of a rock star) and got nearly everything for which she asked. Negotiating is not rocket science! Don't apologize; just state what you want.

> I **just** wanted to get back to you and discuss **a little more** about the offer.
>
> I **would again like to let you know** that (University of X) is my priority, but I also have an offer from (University Y), which is offering me $XXK. **I understand that you many have some constraints,** but **would you consider** increasing the starting salary **to some extent?** Also, **I was wondering if** you could **add** a startup research fund. **I understand that** conference travels are generally covered, but **I would like to make sure** that I get covered for two conferences each year in order to stay productive. In terms of teaching load, **would it be possible to** have a course load of X during the second year? In addition, **I would really appreciate if I could** get covered for the house-hunting trip for my husband and myself. **It is going to be a long move from (current location),** so **we would like to** visit and **make sure that we find a nice place for our family.**
>
> Also, **I would really appreciate if** you **could consider** extending the deadline **just a few more days.** Again, my priority is (University of X), **but I just want to** make sure I know all the options before I make my decision and I am expecting to hear from a few schools within the next week.

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How to compete with a lab diva

BY DONNA KRIDELBAUGH

We all know them — research minions, professor's pets, lab divas — those bench mates who seem to get all the attention and resources even though you are just as talented as they are. They often exhibit selfish behavior (e.g., leave common lab spaces messy, use up lab supplies, etc.), and for some reason, the principal investigator seems to reward them for this science superstar attitude, creating a perception of lab favoritism among team members.

I have encountered this behavior in numerous labs throughout my own research-training years. One incident involved a researcher who threw a diva-quality temper tantrum over a window shade. I was troubleshooting the installation of DNA analysis software on a shared lab computer located in her office, and I had to close the shade partially because the morning sun was blinding me. She instantly freaked out, ranting some nonsense about not receiving enough light, and demanded an immediate solution to the furniture arrangement in the room. Instead of offering any assistance with the software, our PI jumped to her command and devoted the rest of his day to locating a new desk while the software remained inoperative for the entire lab.

I have spent quite a bit of time reflecting on such diva encounters: Why do people get rewarded for this behavior? And why do hardworking team players never seem to get ahead in a research world dominated by lab divas? Upon reflection, I have identified five key characteristics that researchers need to adopt to compete in a work environment overrun with lab divas:

1. As my PI friend once explained to me, those who yell the loudest get what they want, so be more assertive and communicate clearly with your research supervisor about the resources you need to get your projects done.

2. Learn to have more self-confidence, and understand that your career and projects are just as important as your bench mates' (not to mention that your projects are just as important to your research adviser, whose career depends on the productivity of every lab member).

3. Stop cleaning up other people's messes all the time and focus your energy on your own projects. If needed, carve out a spot for yourself in the lab and keep your supplies separated.

4. Develop the foresight to evaluate your projects for career-advancement potential based on the highest return for your time investment (e.g., number of publications, patents, etc.).

5. Evaluate other people's agendas for asking you for help and avoid helping them if the benefits to you are negligible. Likewise, if you need assistance on a project, make sure to show that the request will genuinely benefit the other person too.

While these tips will help give you a competitive advantage, don't put on that rhinestone-studded lab coat and strut around like a research rock star quite yet.

Science relies on collaboration to solve problems; thus, PIs really should focus on promoting the whole team, especially team players (like you and me) who want to see every person and project in the lab succeed.

To get some advice from a real management expert, I contacted Bruce Kasanoff, managing director of Now Possible, a consulting and training firm that helps companies be more humane to both customers and employees.

In a recent article, "How to Get Ahead: Lie, Cheat and Steal," featured on the LinkedIn Influencer program, Kasanoff reprimands employers for promoting takers over givers within management structures (1, 2). (Takers are people who care about only their own needs, while givers put the needs of others in the spotlight.)

Kasanoff says that companies are making stupid decisions by putting takers in charge when givers are the people who sincerely care about the future success of the company and its customers. To put this in perspective for research purposes, the company would be the laboratory, and the customers would be the research sponsors who fund the projects.

In an interview, Kasanoff provided the invaluable insight that "the most successful people are givers with enlightened self-interest, which means that they also have personal goals but they believe the best way to reach these goals is by helping others." However, he warns that givers must be "clear, focused and persistent" to outcompete the takers, who tend to be highly driven in taking care of their own priorities. He says that givers can sometimes be unfocused because of their desire just to be helpful in general; therefore, his personal motto in life and advice to

other givers is to "be generous and expert, trustworthy and clear, open-minded and adaptable, persistent and present" (3).

To avoid workplace favoritism, Kasanoff recommends that supervisors present all employees with equal opportunities instead of equal treatment: "In the end, supervisors have to buy into the concept that diversity creates strength, and I don't just mean racial or ethnic diversity; I mean all the things that make us different."

Every person has unique needs (e.g., communication style or career goals) that should be identified and addressed to ensure each researcher will develop into the most successful scientist possible.

Donna Kridelbaugh is on a journey of self-mentoring to explore alternative science careers with a strong desire to share this step-by-step information with other scientists. Learn more about her Science Mentor blog project at about.me/science_mentor.

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Here is the new version:

> Dear XXX,
>
> Thank you again for the generous offer. (University of X) is my top choice, and I'm excited about joining the faculty there. However, I have a few issues related to the offer that need to be resolved before I can give a final commitment. I want you to know that I have another offer in hand as well as several possible offers that I am to hear about shortly.
>
> My current offer brings a salary of $XXK. I would like to ask if (University of X) can match that.
>
> I would also like a startup research fund of $XX to fund things like travel for research and a research assistant.
>
> In terms of teaching load, I'd like to request a course release for the second year as well.
>
> I would like to make a trip to (location of University of X) with my partner to look at houses, and I'd like to know if the department can cover some or all of that expense.
>
> And finally, I want to ask for a further extension of the deadline by one week. I am very grateful for your flexibility on the deadline so far. But because several offers seem to be pending, I wish to know all of my options before I make a final decision.
>
> I want to reiterate my seriousness about the (University of X) position and hope that we can reach an agreement quickly.

Karen Kelsky (gettenure@gmail.com) spent 15 years as a tenured professor, department head and university adviser. Today she coaches academics who are applying for jobs, grants and tenure. Visit her website at theprofessorisin.com.

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