Science Globetrotters
Why and how do researchers work in two parts of the world at the same time?
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
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 PNA; an increased interest in the importance of membrane proteins; 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 amphipatic molecules, and the micelles formed are the actual subjects of purification.

Second, many 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 homogeneous 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 experimentally differentiate 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 of larger crystals to find small regions that are well-ordered than 10 microns (1). This allows examination of crystals of producing a very intense beam with dimensions of less 0.1 by 0.1 by 0.1 micron. This requires a significant investment in the construction of a beamline and the development of data collection methods and on specific membrane-protein structures. 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 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 membrane-protein structures 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 set aside funds for membrane-protein structural biology. 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.

The number of unique structures grew from one in 1985 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 single protein in a range of conformational states, often captured through the use of different 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, enzymes catalyzing a variety of reactions, etc. These structures reveal dynamic domain motions and other conformational changes. These structures can be integrated to construct complete approximations of functions and pathways, 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 (and watching them dance).

In conclusion, the future is quite bright. I look forward to the next edition of “Biochemistry” with great excitement, and I am confident that the next generation will find the book even more informative and interesting than the last.
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.

REFERENCES

IN MEMORIAM: John G. 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

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, Adam, 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."


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 unrealistic and ill-conceived

American Society for Biochemistry and Molecular Biology staffs 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 for now, curbing 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-Seppäläinen 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 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-Seppäläinen, 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-Seppäläinen 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.

Kamalika Saha (kamalika.saha@gmail.com) is a graduate student in the biochemistry and molecular biology department at the University of Maryland, Baltimore.
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 Thannes-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 Encyclopaedia 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 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 lysosome. 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 arising 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 as 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.”
Jack of a few trades, Master of Science

BY AKSHAT SHARMA

A

time. As I waited for him to arrive, I struck up a conver-
sion with another candidate. As we exchanged phatic noth-
ings, I revealed that I was getting an M.S. in an immuno-
ology 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, per-

haps it was nerves. What else could cause another

candidate to call out so blatantly a relative stranger’s

choice? 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 lured 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 slight-
est hint of how grueling the process of acquiring those

results probably was. Excruciating things happen: stand-

ards fail, proteins unravel, machines become

breakdowns; how to manage my time between teaching,

learning and research; 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!

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his M.S. in microbiology from North Dakota State

University and is a Ph.D. student in the department

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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 asmbtoday@asbmb.org.
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 RNA preparation, which I found unengaging. (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 frustrating. The problem was that my job was to repeat (and hopefully scale up) an observ-ation 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 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 fresh-man 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 (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 with my family on the other side of the world, but 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 with my job 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.

As the number of students moved from the country to university in Sydney: 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.

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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 was a lot of traveling. Occasionally, my family will go with me to China, but with the kids in school, it’s impossible to refuse.”

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 Adern 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

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, 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 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.

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 bit restless in what you’re doing now and this opportunity comes along, you should certainly explore it. If you’re totally satisfied 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!"

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.”

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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.

“From there, Fellman imports her art using digital software tools and adds layers of color and texture.”

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 haiku-like 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. 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 solved in multiple ways. You learn different things from different perspectives. 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.

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 slams in local community colleges and high schools. I had a chance to publish my poetic works and judge slams in local community colleges and high schools.

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!”
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.

Philip 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 bacteria: 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 microbiome can 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 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 Gi-protein-coupled receptors and nuclear receptors.”

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, Kar 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 non-functional 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.

Rajendrani Mukhopadhyay (rmukhopadhyay@asbmb.org) is the senior science writer and blogger for ASBMB. Follow her on Twitter at www.twitter.com/vajmukhop.
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 discovering how the GroEL/GroES chaperonin system refolded proteins. He received a simple phone call led to the fruitful partnership with Ulrich Hartl (his 2013 ASBMB Herbert Tabor Lectureship winner) 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 “cosmologically taught me crystallography”; Helen Saibil, whose electron microscopy images “stunned and reversed our thinking” on the GroEL, mecha-nism; and the “fearless collaborator” Kurt Wüthrich. He writes about his “experimentally fearless” graduate student Ming Cheng, Zbynek Otwinowski’s “brilliance and daring,” the “true artist” Kerstin Braig and Jonathan Weissman’s “fin-icky” pet chameleons. He also gives us a glimpse into the scientific thought cards within his lab and the active scien-tific 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 as fun as the science of working on the chaperonin system.”

Chlamydiad virulence factor structure ‘very odd indeed’

BY WILL SANSON

A protein secreted by Chlamydiad 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 bacterial proteins.”

The Pgp3 protein is a chlamydial virulence factor that is hypothesized to enhance the bug’s ability to infect its host. Hart’s group included Ahmad Galali-ldeen, who is the other co-author of the research and who is now at St. Mary’s University in San Antonio; Alexan-der Taylor at the UT Health Science Center X-ray Crystallography Core Laboratory; Jonathan Schuemann, 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 tri-meric Pgp3 protein resemble the tumor necrosis factor fami-ly of cytokines,” Hart said. “The unique N-terminal domain of the protein Pgp3 is constructed by a manifold swapping 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 proto-ring 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 Dis-trict 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.

Making a new ring every 20 minutes

BY LESELY 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 Branco 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 arranged in the correct orientation at the inner membrane.

While FtsZ is a cytoplasmic protein, the other compo-nents of the proto-ring are associated with the inner mem-brane, 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 mono-meric or homodimeric form.

Persons identifying the location and organizing the proto-ring, this initial protein assembly needs to mature prior to forming the septum. Firstly, peptidoglycan
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 mini-review published in the Journal of Biological Chemistry, Corey S. Westfall and colleagues at Washington University in St. Louis highlight the key enzyme 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 MESH methylesterases.

Highlighting the importance of these enzymes’ roles in hormone regulation, the authors note that all plants encode multiple SABATH and MESH 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.

A new type of modification the authors discuss is amino-acid conjugation or hydrolysis performed by the GH3 family of acyl amide 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.

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 enzymes.”

Most of the reactions that are catalyzed by P450s are called mixed-function oxidations and have the following stoichiometry: NADP(H) + H2O + O2 + R → NADP+ + H2O + RO (where R is the substrate).

Understanding P450s has been instrumental in cancer biology, pharmacogenomics and insect control, and although we have a good understanding of a 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 of enzyme purification played in the capture and characterization of P450s. 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 heterogeneity 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 activity of these P450s, 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.

Zachary R. Conley (zconley@live.com) is a freelance science writer based in the Kansas City area.
Grant-writing workshop recap

BY MARION B. SEWER

T

o 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 and by faculty members with research programs in biochemistry and molecular biology, 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 and by 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 on the importance of developing a personal vision and to pair them with ASBMB members who had been successful in obtaining federal funding. However, in response to unexpected enthusiasm from the community.

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 barriers to representation. Participating mentors

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

Continued on page 35

Demystifying the chalk talk

BY CHARLES BRENNER

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ongratulations! You’ve succeeded as a gradu- ate student, changed institutions and obtained first-author publications. You’ve obtained funding for your postdoctoral fellowship or even for your transi- tion 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 person- able 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, talk 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 post- doctoral 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 in 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 investiga- tor, 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 tacti- cal decisions. You do not want to look scattered. Deter- mine 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 fund- ing 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 candi- dates 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,
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 students’ discussions to be more comprehensive. It also may increase the challenge of maintaining a non directive 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 anemia, 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 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.
C ommunication is a cornerstone of scientific advances. I’ve always maintained that a large part of science is a dialogue among disciplines 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 discriminatory 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 camaraaderie 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, biological 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 School of Medicine and Vinzenz Unger of Northwestern University, this themed 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/steaases 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. 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.

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.

By Daniel M. Raben

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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 Dunwritin 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 albii-
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 noveltly 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 Moleculaire et Cellulaire described how mutations in mediator and the mediator have undergone a tremendous expansion.

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.

Meetings continued

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.
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 featuring 3-D science movies and special events, such as our Ice trip to the International Space Station and asteroid 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 Scientists 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 external 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 factsoids. He has really helped me tone down jargon that I didn’t even realize I 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 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 microbreads and wine. All the programs are webcast 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 Scientists talk on the 50-year journey of the Herceptin antibody-emsntane 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 emerging media specialist, with questions taken on-site and via Twitter and then archived at livestream.com/naturalsciences.

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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/briann.

• 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.

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 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 is a much 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 pretend our 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.
A
cademics tend to struggle with negotiating job
offers because of the enduring monkish quality of
the scholarly life, which is ideally meant to forskate mate-
rial 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 emotionality, drama,
self-deprecation or insecure justifications. Simply com-
pose a list of things you’d like, with specifics – always
state what you want.
Negotiating is not rocket science! Don’t apologize; just
firmly and courteously, without emotionalism, drama,
self-deprecation or insecure justifications. Simply com-
pose a list of things you’d like, with specifics – always
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
funding. 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 it 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.

Continued on page 44
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.

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.

REFERENCES

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.

The Department of Chemistry and Biochemistry at James Madison University invites applications for three tenure-track faculty positions at the Assistant or Associate Professor level beginning August 2014. Positions are 1. Assistant/Associate Professor in Chemistry/Biochemistry/Biophysical Chemistry (0405460), 2. Assistant/Associate Professor in Chemistry - Materials Chemistry (0405461) and 3. Assistant/Associate Professor in Chemistry - Laser spectroscopy or Atmospheric Chemistry (0405462). Establishing an externally funded research program involving undergraduates is expected. Teaching responsibilities include introductory and upper division courses and laboratories. A Ph.D. is required and post-doctoral experience is highly recommended. The modern Chemistry/Physics building is equipped with approximately $7.5 million in instrumentation including facilities for materials characterization, mass spectrometry, lasers and NMR (http://www.jmu.edu/chemistry). Review of applications will begin October 4, 2013. To apply go to JobLink.jmu.edu and reference posting numbers 0405460, 0405461 and 0405462. Salary for all positions shall be commensurate with experience.

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