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ASBMB TODAY

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

ASBMB

2015

Annual Meeting

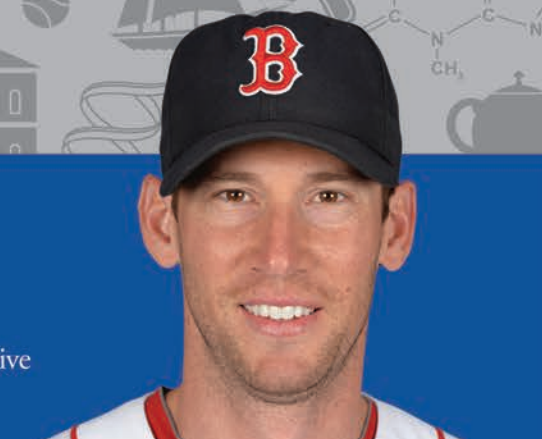
BOSTON

March 28 – April 1

DEFYING STEREOTYPES:

Major league biochemist

Baseball player Craig Breslow proves athletics and science are not mutually exclusive



2015 CALLS FOR SUBMISSIONS

HOBBIES

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

GENERATIONS

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

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

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

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

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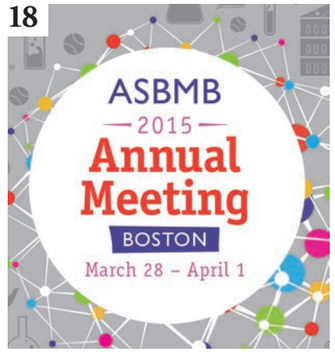

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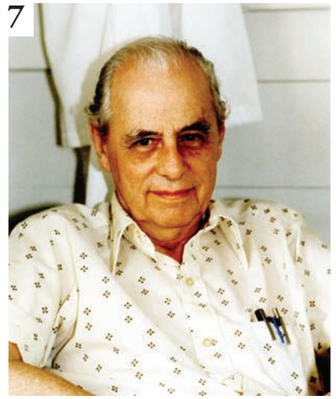

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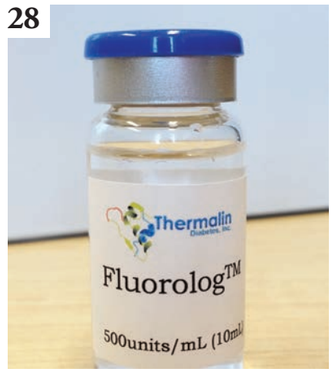

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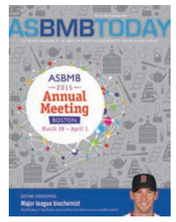
Find out about the scientific programming coming up at the 2015 ASBMB annual meeting in Boston in March.

Craig Breslow image courtesy of Brita Meng Outzen



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

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Pretty fly (for a science magazine)

Last month, we launched the first installment of our "Defying stereotypes" series by printing three articles under the banner of "Punks who publish." The articles profiled the lead singers of The Offspring, Descendents and Bad Religion, all of whom are punk rockers and scientists. The package was the brainchild of our public outreach coordinator, Geoff Hunt, a punk rock aficionado. He co-wrote it with our science writer, Rajendrani Mukhopadhyay, who is a singer but who knew little about the genre at first.

Each has written on the ASBMB Today website a personal essay about the reporting and co-writing experience. Their essays offer a behind-the-scenes look at the highs and lows of the endeavor. Even after serving as their mediator, cheerleader and veto-empowered holder of the red pen, I have to admit that their essays taught me quite a bit about them as writers, as science advocates and as music fans. Check them out at www.asbmb.org/asbmbtoday.

For me, the "Punks who publish" coverage served as a 20-year time warp. When The Offspring's album "Smash" began climbing the charts in 1994, I was finishing up my sophomore year of high school and torturing my mother with my grunge fashion choices. I spent many afternoons blasting the radio to drown out the innumerable injustices that only teenagers can perceive. Based upon the reader responses, I wasn't alone on that flashback.

One reader commented on our profile of Milo Aukerman of Descendents: "Huge influence in my life. (Now 40.) Descendents demonstrated for me the importance of critical thought, healthy (but not aggressive) skepticism of positional authority, pride in individualism…I still listen to them LOUD." Another recalled lugging around a boombox while skateboarding. Yet another said songs by one of the bands were on the soundtrack for her wedding. No shortage of nostalgia there!

More importantly, though, the articles achieved what we had hoped: They reached readers who ordinarily wouldn't read a specialized science magazine like ours. In fact, our Web traffic was unprecedented last month, which, I think, is a clear measure of impact.

We hope to keep up that momentum with the next installment of our "Defying stereotypes" series, found in this issue. That feature is about a brainy baseball player, Craig Breslow. He is a pitcher for the Boston Red Sox, and he trained during his undergraduate years at Yale University in the lab of distinguished scientist Joan Steitz. You can read about Breslow on page 26.

Sincerely,
Angela Hopp
Editor, ASBMB Today

Cite me

By Steven McKnight

It long has been the case that a strong correlative relationship exists between the importance of a scientific publication and the number of times it is cited in subsequent research publications. If a discovery is significant, it gets referenced. If the discovery is in a hot field, citations may come quickly. Alternatively, there are examples of discoveries far ahead of their time that come to be recognized and cited only once their significance is appreciated. Up until recently, measures of citation impact have represented a reasonable correlate to the value of a scientific contribution.

Regrettably, the value of this commodity has been recognized and biomedical researchers have begun to game the system. Likewise, diminished attention to the scholarly process of referencing has eroded the foundational underpinnings of the citation impact system of measuring the value of research publications.

Starting with the latter of these problems, I give a humorous example of how things have gone haywire. Several years ago my colleagues Jian Wang, Peter Alexander and I reported our discovery that mouse embryonic stem cells consume threonine as a hydrocarbon fuel (1). Mouse ES cells grow at an incredibly rapid clip. Their mitotic doubling time is only four to five hours in duration, exceeding that of the most rapidly growing cancer cells and approaching the doubling time of laboratory strains of yeast. Hypothesizing that this might reflect the possibility that ES cells exist in an unusual metabolic state, we measured the levels of scores of metabolites as a function of ES cell differentiation. When cued to differentiate upon withdrawal of leukemia inhibiting factor and administration of retinoic acid, the growth rate of ES cells slows from a four- to five-hour doubling time to 24 hours.

Those who have learned to game the system operate at a distinct advantage – allowing them to sport stratospheric H-factor scores. The idiots who ignore this stuff do so at our peril; what a pathetic, devolved state of affairs we find ourselves in.

By observing profound changes in the levels of metabolites associated with one carbon metabolism, we stumbled over the fact that pluripotent ES cells express the threonine dehydrogenase, or TDH, enzyme at a 1,000-fold higher level than any mouse tissue or cell line that we tested, and they use the enzyme to consume threonine as a metabolic fuel. Depletion of threonine from the culture medium killed mouse ES cells (1), and specific inhibitors of the TDH enzyme kill mouse ES cells while having no effect on any other cultured cells tested to date (2). We recognized this to be analogous to the metabolic state of rapidly growing bacterial and yeast cells, and we made reference to microbiologists upon whose shoulders we stood (3, 4).

Three years later, the Harvard University labs of Lewis Cantley and George Daley published a nice follow-up paper in the journal Science (5). My colleagues and I were delighted to see the replication and extension of our earlier work, yet I was mortified to see that the Harvard manuscript made reference to a paper that I had entirely missed. Yes, the Cantley/Daley paper did cite our paper, yet it also attributed the discovery of threonine dependence of mouse ES cells to a paper from the laboratory of Eric Lander of the Broad Institute (6). The latter paper was published a full year before our 2009 Science paper.

I immediately downloaded the Broad paper and scoured it from end to end. To my confusion, I could not find the word threonine in the entire paper, much less threonine dehydrogenase or anything to do with the metabolic state of mouse ES cells. Inquiries to Cantley and Daley led me to a postdoctoral fellow who instructed me to view the supplemental data included in the Broad paper. Sure enough, the study listed thousands of genes selectively expressed in undifferentiated ES cells, and the gene encoding threonine dehydrogenase was embedded within the list. This was an "Alice in Wonderland" moment for me, showing that an entirely new era of attribution had evolved. Any discovery that stems from any gene listed in the supplemental data of the Broad manuscript can now be attributed to that paper! Instead of thinking "Are you kidding me?", I recognize that we are now adapting to the new reality: Citations are no longer your father's Oldsmobile.

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Years ago I was asked to provide "key words" to accompany the publication of one of our papers. Being unusually dense, it did not occur to me why this was of any utility. In the meantime, I began to notice that the titles of more and more papers were littered with trendy names or terms – sirtuins, epigenetics, NFκB, TGFβ, p53, mTor and so forth. These key words and littered manuscript titles are, of course, the beacons for search engines that have grown to dominate how our work is packaged for the digital age. I am reminded of the Cannon camera commercial featuring Andre Agassi, which said – "Image is everything." Those who have learned to game the system operate at a distinct advantage – allowing them to sport stratospheric H-factor scores. The idiots who ignore this stuff do so at our peril; what a pathetic, devolved state of affairs we find ourselves in.

How is a scientist taught the proper manner in which to reference prior work? The answer is simple: We teach this to our trainees one at a time just as our mentors taught us. When Andrew Pieper discovered pro-neurogenic chemicals in an in vivo screen carried out in my lab some years ago (7), we went back to the original work of Joseph Altman who discovered adult neurogenesis in the 1960s (8, 9). When Gelin Wang and Ting Han discovered that our pro-neurogenic chemicals function by activating the rate limiting enzyme in NAD salvage from nicotinamide (10), we went back to the original discovery of NAD salvage by Phillip Handler in the 1950s (11). In aspiring to teach my trainees the scholarly manner of referencing that Oscar Miller, Joe Gall and Donald Brown taught me, am I training my students straight toward failure? Unless things change in a substantive manner, the answer to this question is unquestionably affirmative.

I close with an account of a disconcerting event I encountered this past year. As chairman of the University of Texas Southwestern Medical Center at Dallas biochemistry department, I am charged with nominating members of our faculty for promotion. I work in concert with our senior faculty members to properly time the promotion of assistant professors to the rank of tenured associate professor, as well as promotion of associate professors to full professorship. I then work with the promotion candidate to put together his or her nomination package.

We hold high standards in our department, so approval for promotion by the promotions and tenure committee of our institution has been uniformly positive over the past two decades. This year, however, I ran into a potential roadblock. After having submitted the nomination package, a member of the committee raised the concern that our nominee may not have an adequately strong "national reputation." I admitted that there was some truth to this: The nominee is a quiet scientist who seldom attends national or international meetings. My retort was simple: Instead of asking whether a scientist has a national reputation, let's ask whether his or her discoveries have a national reputation. My instructions were simple: Go look at the most recent editions of Lubert Stryer's textbook in biochemistry or Bruce Albert's textbook Molecular Biology of the Cell. If you find the work of the candidate referenced in the textbooks, this means the science is of clearly confirmed national reputation. The candidate's work was indeed found in the textbooks, and all was well that ended well.

I would far rather my science to be of national acclaim than for me to be of national acclaim. We should consider how it might be possible to perform evaluations at all levels in just this way. If we can find the work of a scientist in the textbooks, is this not the single best way to assess value with respect to the most essential measures of how our enterprise operates?

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OPEN CHANNELS

Steve McKnight's "President's Message" in the September issue – titled "The curse of committees and clubs" – prompted several reader comments on our website. We have reprinted them on page 43.

Here's an excerpt from one from Fred Schaufele to whet your appetite: "Good but seldom awe-inspiring work in narrow areas can be agreed upon by narrow experts. Outside of that, it's a turn of the roulette wheel."

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

Bucket of ice water – dose of reality

By Benjamin Corb

The summer of 2014 was marked by friends, relatives, neighbors, celebrities and politicians pouring ice-cold buckets of water over their heads in support of the Amyotrophic Lateral Sclerosis Association and donating to research funds to help us better understand the underlying mechanisms of the disease. By all measures, the Ice Bucket Challenge was a rousing success. In August 2013, through the course of normal summertime donations, the ALS Association collected $2.3 million. In August 2014? More than $100 million.

Many in the science advocacy community first turned blue from the cold but then green with envy. Suddenly, seemingly everyone in the country was talking about donating to the ALS Association for research. Other disease groups took the opportunity to redouble their own efforts, saying, in effect, "ALS is important, but so is our disease of choice." Some charities took a different approach and issued press releases saying the Ice Bucket Challenge, while doing a great good for those with ALS, actually was stealing donations from other worthy causes.

Eventually, the conversation cycled to the research community and the cold, hard fact that biomedical research investments in this country have been falling for a decade. While people nationwide dumped ice water on their heads, scientists in labs all across the country sweated more than a few buckets' worth while stressing about where their next grants were coming from and how they could continue their investigations in a funding environment that had run cold.

By and large, the American public doesn't understand how biomedical research is funded — particularly academic research. The connections between taxpayer, university, researcher and patient are dots that the average citizen rarely connects. Many believe that the $100 million donated to the ALS Association is such a large amount of money that a cure for ALS is surely right around the corner. While well-intended, the amounts of donations for research don't correlate with the mortality rates of diseases.

What is the leading cause of death in this country? Heart disease. Total dollars donated per heart-disease death last year? A mere $90. What disease received the most in donations for research? Breast cancer. Dollars donated per breast-cancer death? A staggering $6,400 (1).

Charitable donations for research on a disease that means something to you are noble and should continue. No one should suggest that you not cut a check to the disease charity of your choice in honor — or memory — of a loved one. However, researchers know that investments in biomedical research have been stagnant for more than a decade. Researchers also know that the more likely path to treatments and cures for deadly diseases is to increase the federal investment in basic research.

So the next time someone challenges you to do something for a disease charity, make sure he or she knows the role of the federal government in research. And the next time you write a check or pour water on your head, challenge your friends and family to register to vote or to pick up the phone to tell their elected officials just how important supporting federally funded research is to this nation. And make sure you do the same.

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1. Centers for Disease Control and Prevention (2011).

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

Mori and Walter win the 2014 Lasker Award

MORI

WALTER

ASBMB members Kazutoshi Mori of Kyoto University in Japan and Peter Walter of the University of California, San Francisco, and the Howard Hughes Medical Instutute won the 2014 Lasker Award for basic medical research for their studies of the unfolded protein response. The Lasker Foundation noted: "Mori and Walter's work has led to a better understanding of inherited diseases such as cystic fibrosis, retinitis pigmentosa and certain elevated cholesterol conditions in which unfolded proteins overwhelm the unfolded protein response." It continued, "So important is protein folding to biology that a previous Lasker Award recognized Ulrich Hartl and Arthur Horwich for their discovery of a molecular chaperone that helps proteins fold in the cellular cytoplasm. This year's award is given for showing how problems with a different class of proteins — membrane-bound and secretory — are dealt with. Together, the awards demonstrate the elegant and complex mechanisms that cells have evolved to cope with proteins that do not fold correctly." Hartl and Horwich, the 2011 winners mentioned above, also are ASBMB members. Each Lasker Award category carries an honorarium of $250,000. The awards were bestowed in New York in September.

McKerrow appointed dean of UCSD pharmacy school

MCKERROW

James H. McKerrow is the new dean of the Skaggs School of Pharmacy and Pharmaceutical Sciences at the University of California, San Diego. McKerrow, an alumnus of UCSD, earned his Ph.D. in biology in 1973, focusing on peptide chemistry and molecular genetics. He then went on to receive his M.D. from the State University of New York, Stony Brook, and completed his residency in pathology at the University of California, San Francisco. After becoming chief resident, McKerrow remained at UCSF, where he became full professor of pathology until his latest appointment. UCSD officials emphasized his expertise in neglected tropical diseases and noted that he offers the school a wealth of experience in natural product research and drug discovery and development. McKerrow has co-authored more than a dozen book chapters and has published more than 250 articles. His honors range from teaching awards spanning more than two decades at UCSF to the Gregor Mendel Honorary Medal from the Academy of Sciences of the Czech Republic and the 2005 Distinguished Alumnus Award from SUNY, Stony Brook.

James Wittliff receives cancer research award

WITTLIFF

The American Association for Clinical Chemistry issued one of its major awards to James L. Wittliff. A distinguished investigator and educator, Wittliff received the Morton K. Schwartz award for his "significant contributions in cancer research diagnostics." Wittliff is director of the Institute for Molecular Diversity and Drug Design and a professor at the University of Louisville in Kentucky. His previous research team at the University of Rochester created methods for purifying steroid hormone receptor proteins to study their relationships to human breast cancers. Wittliff was among the first investigators to discover that estrogen receptors serve as biomarkers of both a patient's risk of recurrence of breast cancer and the likely response to hormone therapy. After his move to Louisville, his team helped the National Surgical Adjuvant Breast and Bowel Project establish tamoxifen as a treatment for breast cancer and the use of tissue receptor proteins as biomarkers of a patient's prognosis and probable response to therapy.

Bailey named new dean at Mount Mary

BAILEY

Mount Mary University's School of Natural and Health Sciences named Cheryl Bailey this summer as its new dean. Bailey had been a senior program officer at the Howard Hughes Medical Institute in Maryland. In addition, Bailey is a co-principal investigator for the American Society for Biochemistry and Molecular Biology Concept-Driven Teaching Strategies in Biochemistry and Molecular Biology project funded by the National Science Foundation. Previously, Bailey was an associate professor at the University of Nebraska–Lincoln and worked for two years as a senior scientist for Promega Corp. in Wisconsin.

Written by Nicole Parker

George Gilbert 'Gil' Ashwell, 1916 – 2014

Editor's note: George Gilbert "Gil" Ashwell, a National Institutes of Health glycobiologist who won the ASBMB–Merck Award for outstanding contributions to biochemistry and molecular biology in 1984, died in late June in Bethesda, Md. He was 97. In recognition of his contributions and to draw attention to two seminal publications in the Journal of Biological Chemistry (see box on page 8), the journal in 2006 published a "Classic" article about his life and work. Here, we've republished that JBC "Classic" article (edited for length, clarity and style).

Hepatic carbohydrate binding proteins and glycoprotein catabolism

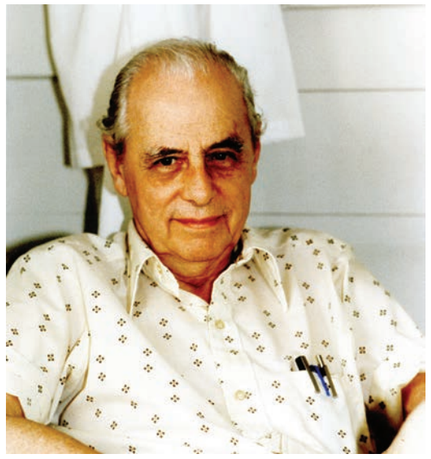
By Nicole Kresge, Robert D. Simoni and Robert L. Hill

G. Gilbert Ashwell was born in Jersey City, N.J., in 1916. He attended the University of Illinois, where he earned his B.A. in 1938 and his M.S. in 1941. Ashwell then went to Columbia University and received his M.D. in 1948. After graduating, he remained at Columbia as a research fellow for two years.

In 1950, Ashwell joined the National Institute of Arthritis, Metabolism and Digestive Diseases at the National Institutes of Health. The institute later split into the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the National Institute of Diabetes and Digestive and Kidney Diseases, where Ashwell remained.

Ashwell is perhaps best known for his work with Anatol G. Morell. They proposed that membrane lectins remove senescent circulating glycoproteins and discovered one of the earliest known carbohydrate receptors.

Ashwell met Morell when he was on sabbatical leave at Columbia University in 1965. Morell, who was at the Albert Einstein College of Medicine in the Bronx, was interested in devising a method for labeling serum glycoproteins to study the role of ceruloplasmin in Wilson disease. Together, Ashwell and Morell devised a labeling procedure (1) that involved enzymatic removal of the glycoprotein's terminal sialic acid residue, thereby exposing galactose, which was then treated with galactose oxidase and tritiated borohydride, resulting in the incorporation of tritium into the protein.



George Gilbert "Gil" Ashwell was a recipient of the prestigious Gairdner Foundation Prize, the Alexander von Humboldt Foundation Senior Scientist Award and the Society for Glycobiology's Karl Meyer Award. He was a member of the National Academy of Sciences and, in 1984, was named NIH Institute Scholar, a title created to recognize his scientific achievements.

When they injected their radioactive ceruloplasmin into rabbits, Ashwell and Morell noticed that the asialoglycoproteins rapidly disappeared from the serum and appeared in parenchymal cells in the liver (2). Further investigations showed that this phenomenon occurred with a variety of naturally occurring plasma glycoproteins (3) and that the plasma membranes of the liver were the primary site of binding for the circulating glycoproteins (4).

This led to the hypothesis that the exposure of terminal, nonreducing galactosyl residues by the removal of sialic acid provides a means by which the liver recognizes and removes the defective molecules from circulation as part of their normal catabolic pathway.

As described in their 1974 Journal

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of Biological Chemistry article (a), Ashwell and Morell eventually isolated the asialoglycoprotein binding protein from rabbit liver using an affinity column composed of asialoorosomucoid covalently linked to Sepharose 4B.

Several years later, Ashwell and Toshisuke Kawasaki isolated an avian hepatic binding protein that was specific for terminal N-acetylglucosamine residues on glycoproteins. This is the subject of a 1977 JBC paper (b). They compared the avian and rabbit proteins and found that they had many properties in common, such as similar carbohydrate constituents and a requirement for calcium.

However, the two proteins also differed in many ways. For example, the avian protein, in contrast with the mammalian protein, exhibited only minimal binding activity for asialoglycoproteins but interacted strongly with agalactoglycoproteins. The structures of the two proteins also differed. The rabbit protein consisted of two different subunits that were 48,000 and 40,000 daltons. The avian protein contained a single subunit with an estimated molecular weight of 26,000.

Ashwell's work on hepatic binding proteins has served as a stimulus for the identification of a host of carbohydrate-specific receptors on various cell surfaces and has inaugurated the current concept of a cellular lectin.

Ashwell's "Classic" articles in the JBC

(a) The isolation and properties of a rabbit liver binding protein specific for asialoglycoproteins
Hudgin, R.L.; Pricer, W.E. Jr.; Ashwell, G.; Stockert, R.J.; & Morell, A.G. *J. Biol. Chem.* **249**, 5536 – 5543 (1974).

(b) Isolation and characterization of an avian hepatic binding protein specific for n-acetylglucosamine-terminated glycoproteins
Kawasaki, T. & Ashwell, G. *J. Biol. Chem.* **252**, 6536 – 6543 (1977).

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In memoriam

Paul D. Ray


RAY

Paul D. Ray, professor emeritus at the University of North Dakota, died in July of cancer. He was 79. Ray, a native of Illinois, grew up on his family's farm south of Monmouth. He completed his undergrad studies at the nearby Monmouth College in 1956 and then earned his doctorate in biochemistry in 1962 under Nobel laureate Edward Doisy at St. Louis University. He took on a postdoctoral stint with Henry Lardy at the University of Wisconsin–Madison and later accepted an assistant professorship at the university's Enzyme Institute. In 1967, he moved to the University of North Dakota, where he dedicated 47 years to studying liver enzymes, diabetes and blood sugar and educating new generations of scientists. In particular, he participated in the American Indians into Medicine Program (called INMED) and, sports fan that he was, helped recruit student athletes with affinities for fundamental science. Both his teaching and research were recognized with numerous awards. Though he retired in 1997, he continued to lecture as an emeritus professor until just a couple of months before his death.

Colin A. Wraight

Colin A. Wraight, professor emeritus and a former administrator at the University of Illinois at Urbana–Champaign, died of cancer in July at the age of 68. A Londoner by birth, Wraight earned his bachelor's degree in 1967 and his Ph.D. in 1971, both at the University of Bristol. He held postdoc positions at the University of Leiden in the Netherlands and at Cornell University in New York. His first faculty position was at the University of California at Santa Barbara, but he found his true professional home at Urbana–Champaign in 1975, rising from an assistant professor to director of the Center for Biophysics and Computational Biology in the 1990s and then chairman of the biochemistry department in the 2000s. In his lab, Wraight used biochemical and biophysical techniques to study membrane proteins and how they catalyze electron and proton transfer in biological energy conversion. He is recalled by colleagues as a passionate teacher and mentor and an endlessly hospitable and generous host.

Death by phosphorylation

A tale of protein overproduction in Parkinson's disease

By Alok Upadhyay

In a recent issue of the journal Cell, a group of scientists from Johns Hopkins University School of Medicine identified a cause of brain-cell death leading to neurodegeneration in Parkinson's disease. Their research findings not only are a significant achievement in Parkinson's disease research but also may open avenues to explore new drug targets for the devastating disease.

Parkinson's is a neurodegenerative disorder affecting about 1 percent of people older than 60. The cause is unknown, but a majority of patients show genetic predispositions. A number of genes have been found to be mutated; one such mutant gene, leucine-rich repeat kinase 2, or LRRK2, plays a significant role and appears in up to 40 percent of Parkinson's cases in North African Arab and Ashkenazi Jewish populations. The mutation leads to the hyperactivity of LRRK2, but how elevated kinase activity contributes to neurodegeneration and disease progression was unknown until recently.

In their study, lead authors Ted and Valina Dawson and first author Ian Martin revealed the role of LRRK2 and identified its mysterious substrate contributing to Parkinson's disease. They found that mutant LRRK2 phosphorylates ribosomal protein s15 at a higher rate than normal LRRK2, resulting in a significant increase in protein synthesis and leading to neurotoxicity.

"We have achieved a significant milestone in Parkinson's disease research by identifying LRRK2 kinase substrate," Ted Dawson says. The team is working on multiple hypotheses to understand "why bulk mRNA translation (protein synthesis) kills dopamine-(producing) neurons."

One of the leading hypotheses his team testing is "if mutant LRRK2 kinase can change the gene-specific translational profile in dopamine-producing neurons that underlies mutant LRRK2 toxicity in Parkinson's disease," Dawson says.

He suggests mechanisms that might be responsible for the death of neuronal cells after hyper-phosphorylation: "Since translational output of a cell depends upon environmental conditions and cellular requirements, an aberrant increase in protein synthesis may make neurons energy deficient or result in extra stress on the protein folding/degradation pathway, leading to failure of protein quality control, or it may impair the ability of cells to respond to stress and lose tight translational control."

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

Upcoming ASBMB events and deadlines

OCTOBER

Oct. 15: Fall application deadline for ASBMB degree-accreditation

Oct. 16 – 18: ASBMB exhibits at the annual meeting of the Society for Advancement of Hispanics/Chicanos and Native Americans in Science, Los Angeles

NOVEMBER

Nov. 6: Deadline for volunteered abstracts for the 2015 ASBMB annual meeting in Boston

Nov. 7: The ASBMB and Florida Biomedical Career Symposium, Jupiter, Fla.

Nov. 11: Deadline for travel-award applications for the 2015 ASBMB annual meeting in Boston

Nov. 11 – 15: ASBMB exhibits at the Annual Biomedical Research Conference for Minority Students, San Antonio, Texas

DECEMBER

Dec. 1: Deadline for proposals for ASBMB 2016 special symposia

Dec. 7 – 9: ASBMB exhibits at the American Society for Cell Biology annual meeting in Philadelphia, Booth 1004

Dec. 31: Deadline for Undergraduate Affiliate Network Chapter renewals

The structure and applications of isolated alpha helices

By Indumathi Sridharan

A recent minireview in the **Journal of Biological Chemistry** focuses on the isolated, stable single α-helical, or SAH, domains of proteins.

SAH domains are monomeric, extended α-helices that join globular domains in proteins. They contain a subset of characteristic amino-acid sequences composed of glutamic acid (E) and arginine (R) or lysine (K) called the ER/K motif or ER/K linker. The structural features of SAH domains play important roles in protein function.

In the JBC minireview, authors Carter J. Swanson and Sivaraj Sivaramakrishnan of the University of Michigan review the structure and function of SAH domains and the tools used to identify and predict them. They also discuss the ER/K linker in the context of protein- and cellular-engineering applications.

The minireview introduces the structural conditions that lead to the formation of SAH domains and the differences between SAH domains and coiled-coil motifs. The α-helical structure of SAH domains stems from a combination of the inherent helix-forming tendency of amino acids, such as alanine, and electrostatic interactions between oppositely charged side chains.

The authors discuss studies on the helicity and structural features of synthetic alanine-based helices, such as (EAAAK)n, which laid the foundation for identifying and predicting the stability of isolated α-helices in natural proteins. The unique structural features of the synthetic peptides have useful molecular-engineering applications, such as controlling the bioactivity, expression level and intermolecular spacing of fusion proteins.

Next, the authors highlight techniques used to identify and characterize the SAH domains in natural proteins, such as the smooth muscle caldesmon; human programmed cell death 5 protein, or PDCD5; B. sterthermophilis and others. In each protein, the SAH domain has a specific function. For example, while the SAH domain in smooth muscle caldesmon modulates the actin-myosin interaction, the SAH domain in PDCD5 is purported to play a role in nuclear targeting of PDCD5. Furthermore, bioinformatics analysis of the primary sequences of many other proteins suggests SAH domains may be more prevalent than previously thought. In fact, up to 0.5 percent of all proteins in the human database contain an SAH domain.

The minireview authors also describe studies on the role of mechanical properties of the ER/K motif in myosin function, ER/K linker-based polypeptide sensors for controlling protein–protein interactions, and modulation of the protein interactions and enzymatic activity of focal adhesion kinase.

The authors conclude that the ubiquity and modular nature of the ER/K motifs make them versatile tools for manipulating proteins and understanding their roles within cellular systems. Furthermore, they suggest, the ER/K-based sensor platforms have direct implications for identifying small-molecule therapeutics.

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The importance of iron in birch allergies

By Kathleen McCann

Seasonal allergies affect millions of people every year, causing itching, sneezing and runny noses. While many of the molecules responsible for provoking allergic reactions have been identified, the way these molecules sensitize our immune systems and cause allergic reactions has remained mysterious. However, Franziska Roth–Walter and colleagues at both the Technical University of Madrid and the Medical University of Vienna have begun to shed some light on this mystery.

In their recent publication in the **Journal of Biological Chemistry**, they identified the mechanism behind sensitization to Bet v 1, the major allergen in birch pollen.

While all people are constantly exposed to pollens, only those with a sensitized immune system become symptomatic. Sensitization occurs upon an initial exposure to the pollen. This exposure activates special immune cells called B cells. The B cells produce specific immunoglobulin E antibodies that attach themselves to mast cells, which are immune cells that mediate the inflammatory response.

Upon a second exposure, the immunoglobulin E antibodies exclusively recognize the allergen. This recognition results in the destruction of the mast cell and the release of its stores of histamine and other powerful chemicals into the surrounding cells, ultimately leading to the onset of allergy symptoms.

The birch tree is just one of many types of plants to which people commonly develop allergies. Interestingly, in birch tree pollen, a single protein, Bet v 1, is responsible for binding immunoglobulin E and initiating the allergic response. Even though Bet v 1 was first identified in 1989 and has been the subject of numerous studies, it is still not clear how people become sensitized to this protein.

Roth–Walter and colleagues decided to look into how Bet v 1 causes sensitization by comparing the structure of Bet v 1 to that of human lipocalin 2, or LCN2, a member of the lipocalin protein family, which

contains many known allergens.

Comparison of the structures of Bet v 1 and LCN2 revealed that both proteins have a hydrophobic pocket surrounded by a similar core structure. The hydrophobic pocket characteristic of the lipocalin family acts as a binding site for small, iron-chelating molecules. Additionally, docking analysis of the Bet v 1 protein and its possible ligands suggests that Bet v 1, like LCN2, has a strong affinity for iron-catecholates.

Interestingly, the presence or absence of iron in LCN2 determines whether LCN2 can initiate an immune response. As Bet v 1 is structurally and biochemically similar to LCN2, Roth–Walter and colleagues compared the immune response after exposure to apo-Bet v 1 (noniron bound) and holo-Bet v 1 (iron bound). Significantly, as with LCN2, exposure to apo-Bet v 1 resulted in an immune response and the production of immunoglobulin E antibodies, whereas exposure to holo-Bet v 1 inhibited the immune response. Therefore, the presence or absence of iron dictates whether Bet v 1 instigates an immune response.

This result suggests that under normal cellular conditions, when iron is more abundant, Bet v 1 is immune suppressive. However, when immune cells are challenged by infection or inflammation, iron stores are depleted. Under those conditions, Bet v 1 is present in the apo-, or noniron-bound, form, which results in the activation of B cells, production of immunoglobulin E antibodies and sensitization. Thus, the presence or absence of iron in the immune cells is a critical determinant of the allergenicity of Bet v 1 and potentially other lipocalin proteins.

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Metabolic clearance of cholesterol

By Umesh D. Wankhade

Cholesterol is a critical player in many biological processes. At an optimal concentration in the cell, it performs essential roles such as maintaining cell-membrane structure and acts as a precursor to several necessary metabolites, including steroid hormones and bile acids. An unperturbed cholesterol efflux process is necessary to maintain the right amount of intracellular cholesterol, because most cells cannot break it down. Conversely, deficient choles-

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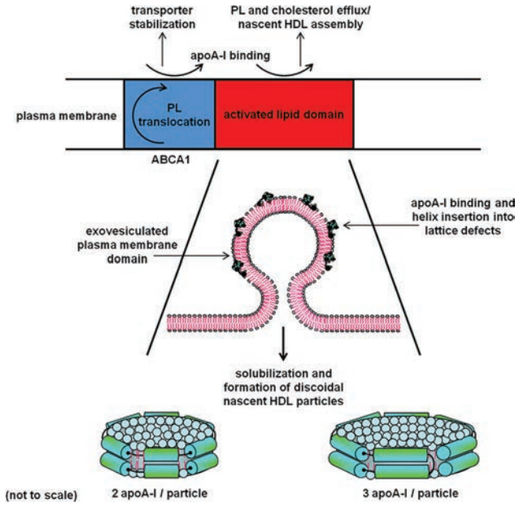
terol efflux, leading to cholesterol overloading in cells, can cause fat-laden immune cells and the development of atherosclerotic plaques that can lead to heart attacks and cardiac strokes.

In a recent minireview published in the **Journal of Biological Chemistry**, Michael Phillips at the Perelman School of Medicine at the University of Pennsylvania discussed the molecular mechanisms of cellular cholesterol efflux. He explained the basic mechanism of cholesterol turnover in the body and covered the latest developments in the field.

Appropriate carriers and acceptors of cholesterol, such as high-density lipoprotein in the extracellular medium, clear cholesterol through the liver and prevent overloading of the molecule in the blood system. Cholesterol transport is initiated through efflux of free cholesterol from the plasma membrane to HDL. Cholesterol efflux in a cell via HDL is performed through passive and active pathways.

The passive process includes simple diffusion via aqueous phase and facilitated diffusion, which is mediated by a protein called the scavenger receptor class B, type 1. The active pathways are mediated by the ATP binding cassette, or ABC, transporters ABCA1 and ABCG1. The necessity of these transporter proteins in cholesterol efflux is well known, because the combined deficiency of these transporters leads to an accumulation of cholesterol in macrophages and accelerates atherosclerosis in mice.



Summary of the molecular mechanism by which ABCA1 activity in the plasma membrane of cells promotes efflux of PL and cholesterol to extracellular apoA-I and formation of nascent HDL particles.

As explained in the review, our bodies need cholesterol for basic metabolic functions. An in-depth understanding of the cholesterol efflux transport process will help researchers formulate better therapeutic alternatives that will increase HDL cholesterol and speed up the efflux process to tackle the problem of cholesterol disorders, such as dyslipidemia, in which there is an abnormal amount of cholesterol in the bloodstream.

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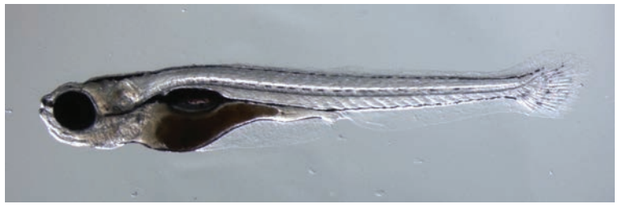
Stop the fat

Holding back intestinal lipids from going into circulation in a zebrafish

By Mary L. Chang

A research team at the University of Utah recently discovered a protein in zebrafish that apparently determines how long the intestine stores dietary lipids before they are delivered to tissues and the bloodstream. This delay, it seems, ultimately reduces blood cholesterol and triglyceride levels. The team's findings were reported in the **Journal of Lipid Research**.



A juvenile zebrafish IMAGE COURTESY OF THE NATIONAL INSTITUTES OF HEALTH

After we eat a meal, our intestinal cells repackage the cholesterol and fatty acids from food so that they can be delivered to other parts of the body. Amnon Schlegel, who led the research team, says the intestine "appears to serves as a transient reservoir of absorbed lipids." In this study, the zebrafish version of liver X receptor a, or LXRa, a protein that inhibits cholesterol absorption and promotes reverse cholesterol transport when activated, was identified as a previously unrecognized pacesetter of intestinal lipid transport.

Based on their own studies and the studies of others, Schlegel's team knew that high bloodstream levels of triglycerides right after a meal were "strongly predictive of cardio-vascular disease," Schlegel said. So the team was interested in learning more about the molecules that control the pace of lipids returning to the bloodstream.

The team decided to study zebrafish, because their larvae are transparent and therefore can be stained for intestinal, liver and vascular lipids. The team also studied enterocytes, intestinal absorptive cells that have roles in secretion and transport of lipids.

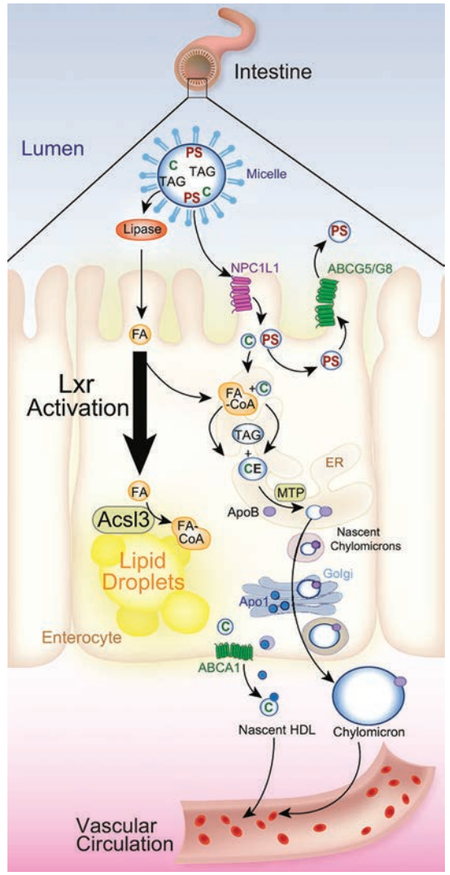
Three types of larvae — wild type, those that had sustained activation of the zebrafish LXR and those that had no LXR activity — were fed a high-fat meal and then stained. In the wild type larvae and larvae with no LXR activity, the ingested lipids were located in the vasculature. In stark contrast, the lipids in larvae with sustained LXR activity did not have the same staining pattern, suggesting that something was holding back the lipids from returning to circulation. Later examination of fed larvae at three time points over three days showed complete digestion of lipids in wild type larvae and those without LXR activity, whereas there were still lipids persisting in the intestines in the larvae with sustained LXR activity.

These results support the idea that overexpression of the gene delays lipid transport and absorption.

"Our genetic evidence in zebrafish indicates that sustained activation of LXR in the intestine alone protects the animals from increased blood and liver cholesterol and triglyceride levels caused by high-fat feeding," Schlegel concludes.

"This is a crucial finding, because many LXR-activating compounds have not advanced to drug development, because they trigger accumulation of neutral lipids in the liver, a process termed hepatic steatosis. It is conceivable that such intestine-limited LXR-activating drugs would be useful in treating human lipid disorders. Indeed, while several excellent drug classes – statins foremost – are available to treat these disorders and reduce the risk of cardiovascular disease, these drugs do not fully lower the chance of developing cardiovascular disease."

He added that not all patients tolerate existing cholesterol-lowering drugs and "intestinal LXR activators hold the promise of offering an alternative treatment."



After digestion and micellar suspension of neutral lipids in the lumen of the intestine, lipids are absorbed across the apical surface of enterocytes. Fatty acids and cholesterol are re-esterified into triacylglycerol, phospholipids and cholesteryl esters that are repackaged into chylomicron, which are secreted across the basolateral surface. Liver X receptors, nuclear receptors for oxysterols, set the pace of transport of ingested lipids across the intestine by directing the development of a temporary storage depot of lipids in cytoplasmic lipid droplets, in part, by inducing expression of Acsl3, an enzyme that directs acyl chains into incorporation in lipid droplets. This delay in delivery of absorbed lipids protects animals from high-fat-diet-induced dyslipidemia and hepatic steatosis.

The researchers concede that long-term studies are needed to see what effects zebrafish LXRa overexpression has on zebrafish life span, fertility, atherogenesis and obesity. There is also the question of what other molecules may affect the pace of lipid absorption, and the researchers already have begun a comprehensive follow-up study to determine if genetic activation of LXR in the intestine of zebrafish prevents atherosclerosis.

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How can lipids cross the Rubicon?

By Tamas Balla

An everyday question in eukaryotic cell biology is how water-soluble molecules cross the membrane barriers of the elaborate, membranous architecture of the cell.

Membrane penetration depends on lipid solubility of molecules, but hydrophilic molecules, ions and even water itself require specific proteins called channels or transporters to help them cross biological membranes.

Interestingly, we ask the reverse question less frequently: How do lipid molecules cross the aqueous barrier that separates the membranes? The importance of this question, however, is increasingly recognized in light of recent developments in the field of nonvesicular lipid transfer (1).

It has been well documented that membranes of distinct organelles have unique lipid compositions. Most of the cells' structural lipids are synthesized in the endoplasmic reticulum or are taken up from the cell exterior via specific receptors by endocytosis, and they need to reach their ultimate destinations.

Given the very intense vesicular trafficking between organelles, this was assumed to be the primary mechanism by which lipids move from one membrane compartment to another. However, several observations suggested that vesicular trafficking might not be the sole mechanism of lipid transfer and that, in fact, cells have to ensure that vesicular trafficking does not alter the lipid profiles of the various organelles.

One of the first indications of the requirement for a soluble protein for lipid transport was the discovery of the StAR protein that is needed for cholesterol to cross the intermembrane space of mitochondria (2). Other examples include the inability of cholesterol to be recycled from the lysosomes in Niemann–Pick disease type C (3) or the requirement for the CERT protein for the transport of ceramide from the endoplasmic reticulum to the Golgi (4). Other lines of research showed that soluble Sec14 proteins are needed for yeast to support transport or utilization of phosphatidylinositol and phosphatidylcholine (5).

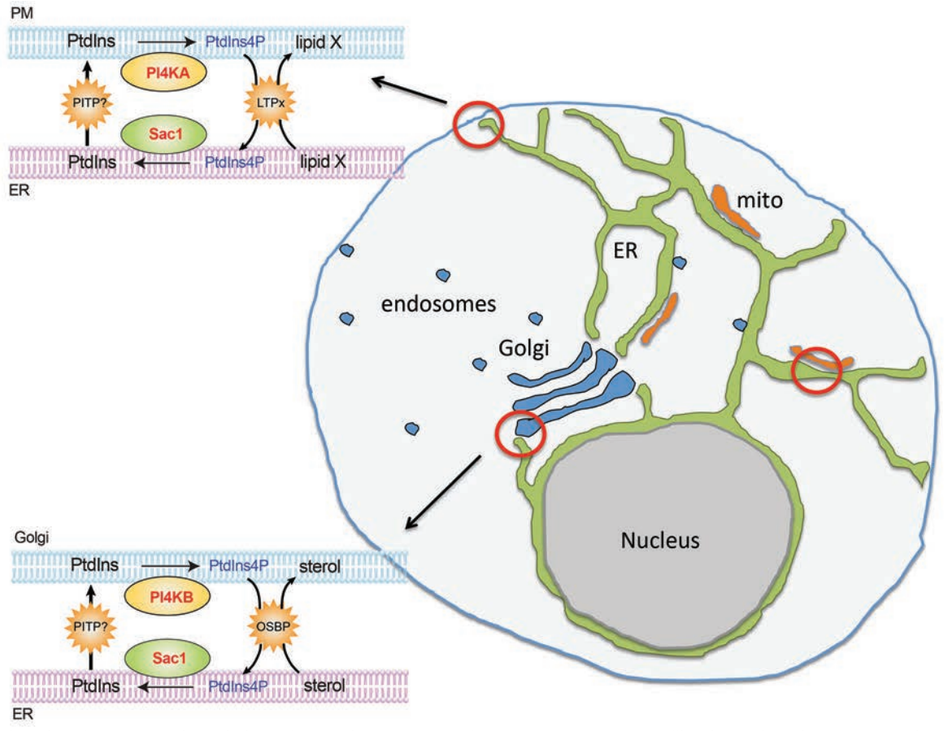
A unique relationship exists between some of the soluble lipid-transfer proteins that carry out nonvesicular lipid transfer of phosphoinositides. The discovery that the presence of a phosphatidylinositol 4-phosphate (PI4P)-binding pleckstrin homology domain is a common feature of several proteins involved in lipid transport initially highlighted this relationship (6). Subsequent studies showed that pleckstrin homology domain interaction with PI4P helps to dock these lipid-transfer proteins to their target membranes, which happened to be the Golgi for OSBPs, CERT and FAPP2 (7).

While this view is still valid, further research showed that some OSBP proteins (OSBP in mammals and Osh4 in yeast) can transport PI4P back from the Golgi to the endoplasmic reticulum, where the PI4P phosphatase Sac1 converts PI4P back to phosphatidylinositol (8, 9). These findings suggest that PI4P phosphorylation in the Golgi and dephosphorylation in the endoplasmic reticulum maintain a PI4P gradient that is required for the efficient transport of cholesterol from the endoplasmic reticulum to the Golgi.

While this PI4P-gradient-energized transport phenomenon was described in the Golgi, some data suggest that it might be a more general principle governing lipid fluxes between other membranes. For example, in yeast, the Osh3 protein was found to enable the endoplasmic reticulum-bound Sac1 enzyme to dephosphorylate PI4P made by the plasma-membrane-localized STT4 phosphatidylinositol 4-kinase in endoplasmic reticulum–plasma membrane contact zones (10). These data can be interpreted as demonstrating the ability of Sac1 to act on plasma-membrane-localized PI4P in trans when Osh3 is present or as indicating that the Osh3 brings PI4P back to the endoplasmic reticulum to be acted upon by Sac1. We speculated that the latter case would be more consistent with the model suggested by the studies on cholesterol transport (11).

More studies will be needed to explore the universality of these models. However, it is already notable that, in either case, endoplasmic reticulum-synthesized phosphatidylinositol (the precursor of PI4P) has to reach the membrane where it is converted to PI4P (at the Golgi, plasma membrane or endosomes).

It long has been postulated that soluble transport proteins – PITPα, PITPβ or Nir2 (and Sec14 in yeast) – can either help transport phosphatidylinositol from the endoplasmic reticulum to their target membranes (12) or help the various PI 4-kinases utilize phosphatidylinositol in their respective locations (13).



Schematic cartoon of a cell showing the contact zones formed between membranes of various organelles (red circles). Sterol transport from the endoplasmic reticulum to the Golgi was shown to be mediated by the OSBP protein, driven by a PtdIns4P gradient between the Golgi and the ER. OSBP transports PtdIns4P in the reverse direction in exchange for cholesterol. Hypothetical model of a PtdIns4P-driven lipid exchange at the ER-PM contact zones. Yeast studies showed that the ER-localized Sac1 enzyme can hydrolyze PtdIns4P generated in the plasma membrane by the PI4KA ortholog Stt4p in the presence of the OSH3 protein. The mammalian lipid transfer protein (LTPx) is still to be identified. It is possible that a different PI transfer protein (PITP) facilitates the transfer of PtdIns between the ER and the partner membrane in the different contact zones.

The small phosphatidylinositol transfer protein, PITPβ, works at the Golgi, while the larger Nir2 protein was found both at the Golgi and in endoplasmic reticulum–plasma membrane contact zones in stimulated cells (14).

Deciphering the integration of these pathways will allow us better to understand how cells maintain their unique membrane compositions and how defects in nonvesicular lipid transfer contribute to human disease.

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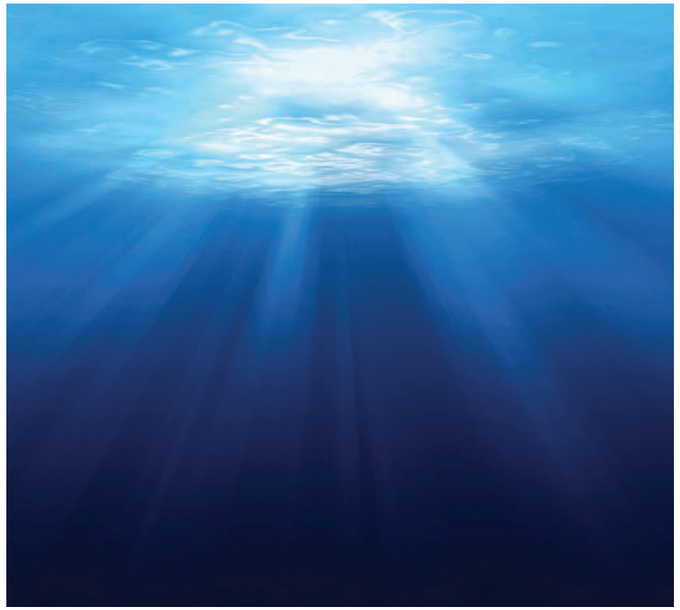
Wild Types

Highlights from the blog by Rajendrani Mukhopadhyay

Surviving in the Pacific Ocean, bacterial style



Oceans cover 70 percent of the earth's surface. Given this vast area, how do you thoroughly study how a particular organism survives in it? In a paper just out in Science, researchers analyzed how a type of cyanobacteria ekes out an existence in a 2,500-mile stretch of the Pacific Ocean. The researchers were able to measure for the first time changes in absolute protein concentrations of the community of this cyanobacterium as it weathered scarcities of different nutrients. In another paper in the same issue of Science, a different group of researchers focused on a particular enzyme that helps marine cyanobacteria and other microorganisms survive under conditions of nutrient deficiency and discovered what makes the enzyme tick. The oceans harbor "much of Earth's biological diversity," points out Mak Saito at the Woods Hole Oceanographic Institution, who was the first author on the first Science paper. Researchers want to know how the microorganisms, which are the foundation of the marine food web and are essential to the cycling of biologically important elements, survive in oceans. The researchers want to understand how changes in carbon, phosphorus, nitrogen and other elements, caused by natural means or human activity, affect the survival of these critical microorganisms.

But Saito says experiments to analyze the effects of nutrients on marine microorganisms are difficult to do and tend to give only a glimpse of what's going on. So Saito's group turned to proteomic technologies, because they could use them to study quantitatively the details of the biochemical changes happening in the microorganisms across the Pacific Ocean. The investigators spent a month on a ship, traveling across the Central Pacific Ocean from Hawaii to Samoa and collecting microbial protein samples from as deep as 1 kilometer in the ocean. The path they traveled cut through northern regions that were rich in iron to areas near the equator that were plentiful in phosphorus and nitrogen but lacked iron. For each sample, the investigators filtered 300 – 800 liters of seawater over four to six hours through 0.2-micron filters and froze the samples.

When they got back to Woods Hole, they used two different proteomic methods to study how the protein content changed in the samples that they took from the 2,500-mile stretch of the Pacific Ocean. Saito says that previous studies identified many proteins in the oceans and their relative abundances. In contrast, the measurements he and his colleagues carried out are the first quantitative marine protein concentration measurements "in units of femtomoles of protein per liter of seawater," he says. "By measuring the concentrations of proteins, we can map changes in the microbial biochemistry across the ocean basin."

From their data, Saito and colleagues showed that multiple nutrient scarcities affected the cyanobacterial community they chose to track. Their conclusion refutes the notion that microbial growth and protein production are at the mercy of the single scarcest nutrient, on which previous work in the field was based.

Indeed, "biogeochemists have realized that the availability of more than one inorganic nutrient may simultaneously restrict growth of microorganisms, particularly if the concentrations of the nutrients are linked by biological processes," says Ben Berks at the University of Oxford in the U.K., who led the team in the second Science paper that identified a critical cofactor for an alkaline phosphatase found in cyanobacteria and other microorganisms. The team on the second Science paper is unaffiliated with Saito's team.

The phosphatase, PhoX, was reported to be a calcium-dependent enzyme. "However, we noticed that the purified protein had a purple color, and we knew this could not arise from calcium ions," says Berks. "This observation prompted us to investigate the nature of the PhoX cofactor."

Although PhoX activity is critical in many microorganisms, the enzyme has not been characterized in detail. "Possibly it reflects the fact that, although the enzyme is widespread in environmental organisms, it is not present in commonly studied model organisms," suggests Berks.

The investigators crystallized the enzyme and then used an X-ray spectroscopic technique called micro-PIXE as well as electron paramagnetic resonance spectroscopy to identify the metals that were a part of the enzyme. They identified an iron-calcium cofactor.

Previously, PhoX was thought to be a simple calcium-dependent enzyme. Calcium is abundant in seawater. If calcium was readily available, Saito says, "people wondered how microbes were maintaining the PhoA zinc alkaline phosphatase."

Zinc is a rare commodity in marine environments. Why would a microorganism go through the trouble of relying on zinc when there is plenty of calcium to spare for enzyme activity? Now that Berks and colleagues have shown that PhoX depends on iron and calcium to function, says Saito, it is clear the microorganisms are forced to make do with two different scarce elements.

The discovery of a new enzyme cofactor also means that the work of marine biochemists has a long way to go. As Berks notes, "The work demonstrates that there are still novel biological cofactors to discover within the pool of currently unstudied microbial proteins."

Model to explain cellular sensor organization

Cell-surface receptors are like radio antennae: They pick up signals and transmit the information to the appropriate cellular equipment. But how do cells know where best to position receptors to cleanly and efficiently pick up the numerous signals coming at them?

In a paper recently published in the Proceedings in the National Academy of Sciences, Garud Iyengar at Columbia University and Madan Rao at the Raman Research Institute and the National Centre for Biological Sciences in India came up with a theoretical model inspired by observations made in cell biology. They noted that different kinds of cell-surface molecules involved in sensing, such as receptors, share a common organizational motif. Sensors are either organized as dynamic clusters or as monomers. What was the organizing principle?

Iyengar and Rao used information theory to model how cells come up with an organizing principle for cell-surface receptors. In their model, cells must balance two contradictory needs. They must cluster some types of receptors at a given location to reduce the statistical 'reading' error but spread out other types of receptors across the cell surface. To figure out which ones to cluster and which ones to keep as monomers, cells assess the number of receptors they have at their disposal, how well the receptors function as sensors, and how long it takes for the receptors to pick up signals in space and time.

The model by Iyengar and Rao predicts that receptors that bind to more than one ligand, and therefore are more susceptible to inadvertently picking up wrong ligands, are more likely to be clustered; receptors that selectively bind to one or two ligands roam freely on the cell surface.

Rao and Iyengar explain that the model doesn't apply to just cellular organization of receptors. Rao says, "This research may have implications for many different contexts, from ad-hoc sensor networks to immunology." The investigators point out that the distributions of integrins and E-cadherins in mammalian cells or the organization of receptors on bacteria for chemosensing may follow this model.

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OUTREACH

Improv for STEM professionals: creating engaging conversations

By Geoffrey Hunt

Effective science communication relies on the ability to be aware of and responsive to both verbal and nonverbal feedback from an audience. Yet the techniques that make this possible (listening deeply, being flexible and responding spontaneously) are learned through practice that is rarely part of our scientific training. More than knowing what to do, scientists need opportunities to experience and practice what to do.

During a workshop at the 2015 American Society for Biochemistry and Molecular Biology annual meeting, sponsored by the ASBMB Public Outreach Committee, attendees will participate in improvisational theater exercises that stretch the communication muscles needed to give engaging professional talks or participate in outreach activities.

improvscience™ founder Raquell Holmes will lead a series of experiential, highly interactive exercises that will help participants develop listening skills and create a rapport with the audience.

Among the planned activities are the following:

- "Recruiters delight," in which participants practice talking about their work through interviews and introductions;
- storytelling exercise; and
- workshop debriefing to analyze key themes and identify next steps.

Join us for this unique session; it's guaranteed to get you up and out of your seat!

Geoffrey Hunt (ghunt@asbmb.org) is the ASBMB's public outreach coordinator. Follow him on Twitter at www.twitter.com/thegeoffhunt

WHAT'S NEW IN MEMBRANE TRANSPORT PROTEINS

Gateway to life

By Olga Boudker and Emad Tajkhorshid

All living beings are distinct entities. What makes them distinct are the lipid membranes – tiny bubbles of the import and export of goods and the flow of information. These are the channels and transporters that carefully orchestrate what, when and how much enters and leaves the confines of the cells.

The knowledge that such molecules exist dates back more than 60 years, and the functional studies of them constitute the lion's share of nearly a century of biophysical research. Yet during the past decade, a revolution has occurred in the extent to which we understand their mechanisms and the kinds of question we aspire to answer.

Much of that success is the result of a seemingly mundane achievement – the development of techniques to purify and study these proteins in isolation, allowing us to barrage them with biophysical methods, some drawn from existing arsenals, others developed specifically for this class of molecules.

In two sessions of this 2015 ASBMB annual meeting theme, we will showcase the successes of X-ray crystallography and nuclear magnetic resonance in revealing the molecular architectures and the mechanics of channels and transporters.

In the third session, we will focus on experimental and computational approaches that transcend static structural pictures to learn more about the dynamics of transporters, in which perpetual conformational changes are key to function.

Finally, in the fourth session, we will hear about novel functional properties of known transport proteins and the newly discovered molecular identities behind the well-known cellular-transport phenomena within from the world without. And as in an ancient city, there are gates and sentinels that permit and control

ORGANIZERS: Olga Boudker, Weill Cornell Medical College, and Emad Tajkhorshid, University of Illinois at Urbana-Champaign

CAREERS, MENTORING AND CHANGES IN MEDICAL EDUCATION

Adapting to the evolving employment landscape and accommodating new training requirements

By Cheryl P. Bailey and Mark A. Wallert

The importance of establishing a highly trained, technical STEM workforce to support the global economy has been a matter of great discussion over the past decade. For individuals who have earned or are working toward Ph.D.s in STEM disciplines, it appears that this should be an ideal time to enter that workforce. While that is true for the most part, the employment landscape for STEM graduates at all levels has changed dramatically.

Today it is estimated that 61 percent of those with STEM doctorates will have careers outside of academia and that as few as 15 percent will go on to have tenure-track academic positions. These statistics point toward a need for a broader perspective on careers and a need to diversify career mentoring, advising and training.

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This 2015 American Society for Biochemistry and Molecular Biology annual meeting will include three sessions that address the changes in the employment landscape and training requirements across the STEM spectrum. These sessions are as follows.

Diverse career opportunities for scientists

This session will address the diverse spectrum of career opportunities available to STEM Ph.D. holders with a specific focus on biochemistry and molecular biology jobs. The speakers will cover job opportunities outside of academe and preparation for diverse careers.

Industry careers

Invited speakers will address the need for diversifying training options, increasing multidisciplinary knowledge and experience, and gaining work experience at the academic-industry interface.

Professional development

This session will cover the tools and mechanisms available to those who'd like to establish professional-development plans.

Changes in medical education

The final session will address changes in medical-school education and admissions. Educational leaders will cover changes at the undergraduate and graduate levels that are driven by MCAT 2015 and the admissions process. Their presentations will highlight changes to academic preparation and the need to address new competencies for MCAT 2015 as well as the rationale behind and effort by the American Association of Medical Colleges to promote a more holistic approach to medical-school admissions.

Whether you are an undergrad, a master's student, a Ph.D. candidate, a postdoctoral fellow or a faculty member who mentors, these sessions will offer valuable information that will enhance your professional life.

This theme is sponsored by the ASBMB Education and Professional Development Committee.


ORGANIZERS: Cheryl P. Bailey, Mount Mary University, and Mark A. Wallert, Minnesota State University Moorhead

MOLECULAR MECHANISMS OF INFECTION AND IMMUNITY

It's not Greek to me! Biochemical advances in a historically rich field

By Brian Baker and Eric Sundberg

Mammals have evolved sophisticated, interlocking mechanisms to provide immunity against pathogens of all kinds. As a field, immunology is ancient: According to that always-accurate online encyclopedia, the ancient Greeks provided the first written description of bacterial immunity.

While that perhaps explains why immunology historically has seemed like so much Greek to many biochemists and molecular biologists, more recent history has seen tremendous advances in our understanding of the biochemical underpinnings of the immune system and the immune responses to pathogens.

Cultural divides and language barriers are breaking down, with tremendous implications for health and disease. This 2015 ASBMB annual meeting theme will focus on some of these recent advances, bridging concepts from glycobiology to structural biology. For the biochemists and molecular biologists among us, the view from the Parthenon never has been better!

Glycobiology in infection and immunity

One of the main classes of biomolecules, the glycans provide targets for both innate and adaptive immune responses and are key for engineering molecules for improved function and stability. The intersection between glycobiology, infection and immunity will be the focus of the first session.

Antigen presentation and recognition in cellular immunity

T cells orchestrate one of the most intriguing and complex molecular-recognition phenomena in biology: the recognition of a foreign antigen bound and presented by a major histocompatibility complex protein. The second session will explore the biochemical and structural underpinnings of antigen presentation and subsequent recognition by T-cell receptors.

Biochemistry and systems biology of host-pathogen interactions

The immune system and its response to infection involve responses on multiple levels. While reductionist approaches continue to yield enormous insight, systems-level investigations can connect the dots and provide new insight into global mechanisms. The third session will emphasize metabolomic, proteomic and network studies in infection and immunity.

Visualizing multicomponent structures in infection and immunity

In structural biology, while bigger may not always be better, bigger is always awesome. The fourth session will present the latest structural studies of large multicomponent complexes important in infection including not-so-irreducibly complex flagella, secretion systems and fibril structures.


ORGANIZERS: Brian Baker, University of Notre Dame, and Eric Sundberg, University of Maryland School of Medicine

MECHANISTIC IMPACTS OF POST-TRANSLATIONAL MODIFICATIONS

Decidedly crucial chemical decoration

By Philip Cole and Paul R. Thompson

While DNA encodes our genetic blueprint, it is clear that much of the information that leads to precise biological outputs governing cell division, growth, differentiation and movement comes from chemical decoration of the genetic output known as protein post-translational modifications, or PTMs.

There are more than 200 distinct kinds of PTMs that are often reversible in nature but play key roles in health and disease. Much research now is dedicated to exploring the sites and extent of PTMs in the proteome; identifying the proteins that add, subtract and bind to these PTMs; understanding the precise functions of individual and clusters of PTMs; and investigating the potential for therapeutic interventions that inhibit disease-associated PTMs.

PTMs of lysine

Originally detected in our chromatin histone proteins, PTMs affecting lysine, including acetylation and methylation, are now understood to be widespread in the human proteome – with literally thousands of sites identified. This session will discuss emerging technologies that allow for the structural and functional analysis of protein lysine acetylation and methylation and the development of specific small-molecule therapeutic agents with anticancer potential that can target the enzymes that attach or remove these lysine PTMs.

PTMs of arginine

The sidechain guanidinium group of one or more arginines in a protein is often critical to that protein's function, but PTMs can alter this, including methylation, phosphorylation and hydrolysis to citrulline. This session will touch on each of these arginine modifications and reveal new insights into the extent and function of these PTMs in biology and human disease.

PTMs of cysteine

Among the least abundant amino acids in proteins, cysteine residues are especially reactive both in nucleophilic and redox transformations, leading to a diverse array of PTMs. While undoubtedly important, many of these cysteine modifications are transient and difficult to characterize because of their instability. This session will discuss unraveling the biological pathways and functions of acyl and nitroso modifications on cysteine using a series of novel methods.

O-GlcNacylation

Reversible carbohydrate modification of cytosolic and nuclear proteins by N-acetyl-glucosamine on serine and threonine residues has become an exciting area of study in cell signaling. This session will discuss new functions of O-GlcNAcylation in health and disease and new insights into the complicated enzyme that catalyzes this PTM.


ORGANIZERS: Philip Cole, Johns Hopkins School of Medicine, and Paul R. Thompson, University of Massachusetts Medical School

PLANT METABOLISM

The science behind food and fuel

By Edgar Cahoon and Ruth Welti

It's likely that not a soul would make it to the 2015 ASBMB annual meeting if it weren't for plant metabolism. And even if a few did make it, they might not have clothes. Or chairs. This most important theme will explore the ways in which plants produce food, fiber, fuel and more under sometimes harsh and changing conditions.

The essentials

The first session will explore how plants make the vitamins and essential amino acids that humans require. Can we encourage plants to produce more for the expanding human population?

Plants + -omics strategies = fruitful

The potential for genetic manipulation and availability of genetic variants make -omics strategies particularly productive when applied to plant systems. The second session will highlight proteomic and lipidomic strategies for understanding plant metabolism.

Seed da lipids

Lipids – your essential fatty acids and fatty-acid derivatives protecting plants from invaders, signaling friends, supporting photosynthesis, saving for the future and assuming control – are the topic of the third session.

Go for the burn

Plants use the energy of the sun to create biomass. The fourth session will examine how we can maximize and harvest green energy to do work.


ORGANIZERS: Edgar Cahoon, University of Nebraska-Lincoln, and Ruth Welti, Kansas State University

RNA EXPRESSION AND POST-TRANSCRIPTIONAL REGULATORY EVENTS

A well-orchestrated symphony

By Grace Gill and Yan Jessie Zhang

Although "DNA codes for RNA, which codes for proteins" has long been viewed as the central dogma of molecular biology, this concept fails to reveal the complexity involved in synthesizing RNAs and the surprisingly diverse functions of mature RNAs.

This 2015 ASBMB annual meeting theme will focus on the players and events involved in transcription, RNA processing and chromatin modifications – and how the coordination and crosstalk between these processes influences cell fate.

Getting to know the maestro and his orchestra

RNA polymerase II does not act as a solo artist. The synthesis of mRNAs and ncRNAs by RNA polymerase II is regulated by features of the DNA template, post-translational modifications and interactions with accessory factors. A combination of structural, biochemical and genomic studies is providing new insights into the coordinated activities of RNA polymerase II and other factors involved in transcription.

Perfecting the composition

Synthesizing a chain of ribonucleotides is not enough to make a functional RNA. Most nascent RNAs go through multiple steps of processing before reaching maturity. We are continuing to learn about how diverse maturation steps – including capping, splicing, modification and more – are carried out for specific types of RNAs and often coordinated with transcription.

Working in harmony

It turns out that RNA is not only the product of transcription but also an important regulator of the process. Recent studies continue to provide surprises and reveal new mechanisms of crosstalk among RNA, transcription and chromatin.

Reaching a crescendo

RNA expression acts as a maestro to shape cell fate and is highly regulated to stay in tune with cell function. New studies continue to provide insights into how transcription and RNA processing are regulated in specific biological contexts.

Since deregulation of the transcription process underlies many diseases, understanding how the orchestra produces such a magnificent symphony may allow us to restore harmony to sick cells. We look forward to your participation through submission of abstracts, oral and poster presentations, and lively discussions.


ORGANIZERS: Grace Gill, Tufts University School of Medicine, and Yan Jessie Zhang, University of Texas at Austin

THE HUMAN MICROBIOME AND HEALTH DISPARITIES

How diet influences quantity and quality of microbiota

By Sonia Flores and Catherine Lozupone

Trillions of microbes inhabit the human body, forming a complex ecological community that influences normal physiology and susceptibility to disease through its collective metabolic activities and host interactions. Disruptions to the normal balance between the microbiota and the host have been associated with a number of diseases that disproportionately affect the health of minorities. This 2015 ASBMB annual meeting theme will focus on how diet influences the quantity and quality of microbiota that inhabit the human body.

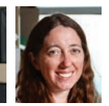
We will take a slightly different angle from more classical microbiome themes and discuss how microbiota differ across people and populations and address the role that they may play in areas of importance in health-disparities research, such as obesity, undernutrition, asthma and preterm birth.

The first session will discuss how diseases, such as chronic diarrhea and undernutrition, in developing countries influence the microbiome.

Sadly, in many instances, early changes have lasting effects and cause irreparable damage to the immune system and contribute significantly to morbidity and mortality in infants and the young. These changes, in many cases, will lead to obesity, metabolic syndrome and even diabetes later in life. In more developed countries like the United States, where fresh fruits and vegetables are often too expensive, over-reliance on cheap, processed foods has both short- and long-term impacts on the obesity epidemic, particularly in low-income children. Two sessions will address these issues.

The final session will explore an area of microbiome research that largely has been ignored: how race and ethnicity affect microbiome composition in various mucosal compartments.

This theme is sponsored by the ASBMB Minority Affairs Committee.

ORGANIZERS: Sonia Flores and Catherine Lozupone, both of the University of Colorado, Anschutz Medical Center

OUTREACH

Show off your outreach program – for free!

By Geoffrey Hunt

One of the biggest challenges in the field of science outreach is to facilitate opportunities that bring scientists and informal science-education experts together. Often, each group has several members in the same local community who are interested and willing to engage with the other but have no way to do so. On occasion, there are individuals able to

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bridge this divide. Yet if the broader push to enhance science outreach as an endeavor is to succeed, it will be necessary for even more willing participants to come together and join forces.

For the past two years, the American Society for Biochemistry and Molecular Biology has hosted at its annual meeting a poster session dedicated exclusively to showcasing outreach activities and programs, thereby providing an opportunity for scientists to get a sense of all that informal science-education entails. This year, we are happy again to offer this poster session on the first night of our meeting, directly after the Herbert Tabor Research Award plenary lecture on the evening of March 28.

As an added bonus, we have made registration for the outreach poster session free of charge. That means that if you have a program or activity that you want to show off to the Experimental Biology 2015 attendees, all you have to do is complete our online form. No registration fee. No abstract fee. Just fill out the online form and show up.

This poster session is a great opportunity to showcase your pet project, start recruiting others to your effort, or just see what outreach actually is by meeting some of the people who are doing it and finding out how you can get involved.

So if you have an outreach project, informal science-education activity or community program or just want to learn more about outreach, come join us in Boston.

To submit your poster abstract for the outreach poster session, visit www.asbmb.org/PublicOutreach/EB2015PosterSession/.

Geoffrey Hunt (ghunt@asbmb.org) is the ASBMB's public outreach coordinator. Follow him on Twitter at twitter.com/thegeoffhunt

LIPIDS – IN VIVO DYNAMICS, PROTEIN PARTNERS AND SIGNALING

There's nothing bland about them!

By Michael Best and Wonhwa Cho

This year marks the 42nd anniversary of the publication of the fluid mosaic model of cell-membrane structures by S.J. Singer and G.L. Nicolson. While theirs was a seminal paper in the lipid field, the authors did make one unfortunate mistake: depicting lipids as bland molecules that serve primarily as a passive barrier and a host for membrane proteins, an idea many standard biochemistry textbooks have adopted.

Multitalented lipids

Much has changed since 1972, and now it is hard to find any area of biology in which lipids do not play crucial regulatory roles. The critical roles of lipids are expanding to many unsuspected areas, and that is the subject of our first session.

Two sessions and a workshop

Recent advances in chemical biology and molecular imaging technologies have allowed researchers to identify new lipid-binding proteins, specifically manipulate diverse lipid signaling, and directly monitor lipid dynamics and lipid-mediated cellular activities with high spatiotemporal resolution. These exciting new developments will be covered in two sessions, titled "Lipids meet chemistry" and "Lipids caught in action," as well as a workshop, titled "Chemical and optogentic manipulation of lipid signaling."

Lipid magic: How do they do it?

With all this functional information, the time is ripe for mechanistic investigation of how lipids perform such diverse regulatory roles, with a special emphasis on how lipids regulate the structure and function of their effector proteins. In the final session, we will witness how state-of-the-art structural and analytical tools lead to mind-boggling new discoveries that answer this important question.

Overall, these sessions not only will present new functional information on lipids and new technologies to study lipids but also will help change the way both experts and nonexperts think about and study lipid-mediated cellular processes. Everyone is invited to this celebration of lipids.

ORGANIZERS: Michael Best, University of Tennessee at Knoxville, and Wonhwa Cho, University of Illinois at Chicago

THE HUMAN MICROBIOME

Measuring and understanding our bacterial symbiotes

By Andrew Goodman and Matthew Redinbo

The full genome of the human–microbial symbiote is composed of our few (23,000) and their many (2 million). The products of this complete genome interact in complex and dynamic ways that we are only now beginning to fully appreciate. The human microbiome theme at the 2015 ASBMB annual meeting is focused on recent data concerning how we measure which microbes are present and how they interact in microbial communities, how microbes interact with us as their willing and grateful hosts, key chemistry performed by our bacterial symbiotes and how bugs affect drugs and our responses to diseases.

Who goes there? The usual suspects and known associates

One session, "Measuring and predicting microbial community dynamics," will examine gut microbial genomics in action, both by computational modeling and by experimental analysis, including how bacteria sense and respond to the gut environment and the evolution of the great ape microbiome.

Being neighborly: chatting across the backyard fence

The second session, "Microbe–host interactions," will focus on how our microbial symbiotes react and are resilient when inflammation is in play, specific molecules employed by bacteria to work with the mammalian immune system, and the detente constantly negotiated between the microbiota and the gastrointestinal epithelium.

Many chefs, one kitchen: our commensal chemistry

The "Chemistry of commensal biology" session will cover recent data on how the microbiota that arises from milk impact the developing mammal, how glycans are uniquely processed by members of the gut microbiota and which ligands the microbiota use to exist in relative prosperity in the complex mammalian symbiotic landscape.

It's on: bugs and drugs

The final session, "Gut microbes, drugs and toxins," will discuss our emerging ability to control how symbiotic bacteria process drugs and toxins, how the gut microbiota affect anticancer drug efficacy and how mobile genetic elements affect antibiotic resistance in human and environmental microbiota.

ORGANIZERS: Andrew Goodman, Yale University School of Medicine, and Matthew Redinbo, University of North Carolina at Chapel Hill

DEFYING STEREOTYPES:

Major league biochemist

Baseball player Craig Breslow proves athletics and science are not mutually exclusive

By Geoffrey Hunt

There's a scene in the 1989 comedy "Major League" where Tom Berenger's character, a baseball player attempting to impress and woo back his former flame, is seen reading "Moby Dick." Except what he is actually reading is a comic-book version of Herman Melville's lengthy classic. The message is clear: Athletes and intelligence don't mix.

So how would Hollywood cast Craig Breslow? A 10-year veteran of Major League Baseball, Breslow majored in molecular biophysics and biochemistry at Yale University, showing that it is possible to excel in both athletics and academics. A "cursory conversation (with me) would dispel both the dumb jock and science geek stereotypes," Breslow says. "I like to think that I am a well-rounded person with diverse interests." It just happens that one of those interests involves throwing a baseball 90 mph.

As far as professional baseball careers go, that of a middle reliever is one of the most challenging. Underappreciation and uncertainty are themes, featuring infrequent playing opportunities and constant career turnover. Here, Breslow does fit the mold, having played for six major league teams, including two stops in Boston with the Red Sox, for whom he currently plays. Breslow's most successful season arguably came in 2013, when he posted some of his best stats and helped pitch the Red Sox to their third World Series championship since 2004.

The lessons Breslow learned in the lab actually have carried over to his game. "Scientists have a particular way of thinking and approach to problem solving," explains Breslow. With pitching problems, for instance, "I attempt to use data to discern whether or not there is an underlying cause to my struggles or if the sample size is simply not great enough for trends to play out." It's something most major league players would be unlikely to admit.

As an undergraduate, Breslow worked with Joan Steitz with an eye toward a future in medicine. "For a long time I had envisioned leaving my mark on the medical community as a physician," remembers Breslow. He even took the MCAT and applied to medical school after graduating from Yale. But Breslow was also a standout on the Yale baseball team and was named a 2002 College Baseball All-American by the Jewish Sports Review. Torn between his two passions, Breslow chose to pursue his dream of playing professional baseball. His decision paid off when he was drafted in 2002 by the Milwaukee Brewers and then made his major league debut in 2005 pitching for the San Diego Padres.

Sports writers have called Breslow "The Smartest Man in Baseball," a mantle he reluctantly accepts. "Having gone to Yale, and having majored in a complex science curriculum, I am often asked questions about everything ranging from the weather to the collective bargaining agreement," he says. Breslow takes his revered status in stride, especially when the conversation with his teammates turns to more appropriate topics for a locker room, such as performance-enhancing substances. "It is quite ironic for me to think about metabolic intermediaries and pathways as they relate to (nutritional) supplements," he explains. "I feel uniquely qualified to explain the role of branched-chain amino acids, creatine and nitric oxide!"

Craig Breslow IMAGE COURTESY OF BILLIE WEISS

Science is never too far from Breslow's mind thanks to his role running the Strike 3 Foundation, which he founded in 2008 to "raise funding and awareness for pediatric cancer research and treatment." Breslow was inspired to establish the charity after watching his older sister, Lesley, successfully undergo treatment for pediatric thyroid cancer. The charity has distributed more than $1 million in research grants to scientific labs since its inception and is currently supporting work at University of California-San Francisco, the Dana Farber Cancer Institute and the Yale New Haven Children's Hospital. In addition, the foundation supports young investigator awards through the Conquer Cancer Foundation of the American Society for Clinical Oncology.

Breslow sees an increasingly prominent role for science in baseball. "Baseball has tended to resist change quite stubbornly over the years," he explains. "However, over the last two decades, baseball has begun to embrace data." He notes that he sees baseball management personnel "making data-driven decisions in contrast to reacting to gut feelings and hunches." But among players, Breslow appears to be the exception rather than the rule. A 2008 study from USA Today of athletic programs at 118 universities found science majors to be the least popular with college athletes (1). A 2014 report from the Pittsburgh Post Gazette confirmed these findings (2).

Breslow is uncertain if he will ever get another chance to pursue his dream of having an impact in science. "As I get older and start a family, it is becoming more difficult to see myself in a medical-school classroom," he says. For now, Breslow will have to content himself with being a successful athlete, albeit one who is known for his intelligence as much as his accomplishments on the baseball diamond. He's OK with that. "We all face stereotypes in our lives," says Breslow. He will keep on battling those that he has faced, one pitch at a time.

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Insulin for all

Michael Weiss wants to make insulin analogs that meet the needs of diabetics, both rich and poor, all over the world

By Rajendrani Mukhopadhyay

When Michael Weiss decided to pursue diabetes research in the 1980s, some of his mentors tried to change his mind. "There was this impression that diabetes was a static field," says Weiss. His mentors wondered why an M.D./Ph.D. from Harvard University like Weiss would want to study insulin when everything important about the hormone, which regulates blood glucose, was deemed to be known already.

"But it seemed on my clinical rotations as a medical student that so many of the patients in the intensive care units and the cardiac catherization lab had diabetes," says Weiss. He had a feeling that diabetes would become a bigger global health problem as time went on.

Compounding what Weiss saw in Boston-area hospitals was what he experienced during one pivotal year of his life. In 1980, Weiss took a year off from graduate and medical school to travel through Europe, Africa and the Middle East. In underdeveloped parts of Africa, Weiss was thunderstruck to see how difficult life was for people without access to resources that were taken for granted in the developed world. He heard stories from local physicians about how villagers struggled to use medicines, such as insulin, that degrade without refrigeration. As he listened to the tales, Weiss recalls, he couldn't help but think "that would be an easy problem to solve." He says, "One would be able to engineer ultra heat-stable insulin."

But it wasn't an easy problem to solve. "Such is the naiveté of a 23-year-old," remarks Weiss.

Now, 34 years later and a whole lot savvier, Weiss is closer to having an ultra heat-stable insulin analog that doesn't require refrigeration. The work in Weiss' laboratory at Case Western Reserve University has been spun off as Thermalin Diabetes, a company in Cleveland, Ohio. The company is gearing up to do human trials in 2015 of the ultraconcentrated, rapid-acting insulin analog.

An American abroad

In 1978, Weiss entered Harvard Medical School in the M.D./Ph.D. program after completing his undergraduate physics degree at Harvard University. "Harvard has all these obscure endowments. For example, they have one endowment that makes sure that all freshmen get ice cream every day," says Weiss. Another endowment was the Frederick Sheldon Travelling Fellowship, which Weiss received in his second year of the M.D./Ph.D. program. The fellowship allows undergraduate seniors and students at graduate or medical schools to take a year to travel abroad. Undergraduate seniors can't stop in any one place for too long, but graduate and medical students can have a home base in a foreign country and travel from there. "My parents thought that it was ill-advised to interrupt my training," says Weiss. "But it turned out to be a turning point in my scientific interest."

Weiss made Oxford University his home base in the U.K. One of his mentors, Irving London, who was based in both Harvard and the Massachusetts Institute of Technology, had connections with several scientists at Oxford and made introductions. At Oxford, Weiss met Dorothy Crowfoot Hodgkin and her lab members. Hodgkin had won the 1964 Nobel Prize in chemistry for her X-ray crystallography work on biologically important molecules. In meeting her, Weiss' curiosity in insulin was piqued, because it was a molecule whose crystal structure Hodgkin had been pursuing for decades.

Insulin was first described in 1922 by Frederick Banting and Charles Best in John Macleod's laboratory at the University of Toronto (for the work, Banting and McLeod received the Nobel Prize in medicine and physiology in 1923). Once insulin's role in glucose homeostasis became apparent, researchers began to study its biochemical and structural underpinnings. Hodgkin herself started to work on the crystal structures of insulin in the 1930s but didn't get any results until the 1960s. Her perseverance and tenacity made a powerful impression on Weiss.

Weiss traveled next through Greece, Israel and Kenya further deepened his interest in insulin. In Kenya, Weiss was struck by the number of villages not connected to the electrical grid. When he visited a few Kenyan clinics, he listened as doctors described to him the lengths to which patients went to use insulin and other Western drugs, even going so far as burying the medicines in the ground to keep them cool.

Once he completed the Sheldon fellowship, Weiss continued with his medical and scientific training at Harvard and MIT. After he completed his M.D./Ph.D. (his Ph.D. was done under Martin Karplus, who received the Nobel Prize in chemistry last year) and became a research resident in the Boston area, Weiss found his interest in insulin solidifying.

IMAGE COURTESY OF CASE WESTERN RESERVE UNIVERSITY

Michael Weiss

While most scientists around Weiss were doubtful that the study of insulin had much to yield, he had several supporters, one of whom was Leo Neuringer, who headed an NMR laboratory and whose son had developed diabetes. Neuringer "encouraged the students, fellows and young doctors who were coming through the lab to focus their efforts on diabetes," says Weiss. "I remember being teased by one of my peers that finally Leo found someone gullible enough to do this!"

In the dead zone

In 1988, Weiss started his laboratory in Boston with a focus on the

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molecular underpinnings of insulin's structure and mechanism of action. (The lab eventually moved to Weiss' home state of Ohio after a stint at the University of Chicago.) "The easy things were already known, all the low-hanging fruit," he says. "But the really important questions of how proinsulin folds, how the hormone binds to the receptor, how it degrades – none of these were known."

Insulin starts off as proinsulin, which has to be processed in the beta cells of the pancreas. The insulin monomer forms a hexameric complex for storage purposes. When the hexamers get secreted from the pancreatic beta cells, the complexes dissociate to liberate the active monomeric form of the hormone that can go on to bind to its receptor.

For one of its early projects, Weiss' group wanted to use NMR spectroscopy to analyze the structure dynamics of the insulin monomer. Because the monomers are designed by nature to form hexamers, the protein thwarted the investigators by clumping. So Weiss collaborated with Eli Lilly's Bruce Frank, who "was the pioneer of the biosynthetic expression and purification of insulin in the early 1980s," says Weiss.

Frank had been part of the team that made the Eli Lilly blockbuster drug Humulin. Until the introduction of Humulin in the 1980s, diabetics had to take insulin isolated from porcine and bovine pancreases. The insulin from animals was expensive, not totally pure and didn't lend itself well to scaling up production. Humulin, made in bacteria by recombinant DNA technology, bypassed those problems.

Weiss' group, with Frank's help, focused on developing monomeric models of insulin that were biologically active under physiological conditions so that they could study its dynamics. As work got under way, Weiss watched as insulin analogs, which are modified versions of natural insulin, began to hit the market in the late 1990s. Eli Lilly got another blockbuster drug out of its first rapid-acting insulin analog, Humalog. Novo Nordisk, Sanofi and Merck introduced insulin analog products into the clinical marketplace.

The first-generation analogs came in two types: rapid-acting and long-lasting. But Weiss noted problems with these analogs. "The bottom line was that the rapid-acting insulin still took too long. The long-acting insulins were still too short. All were too unstable," he says. "There was a lot of room for continued improvement that could make an even more marked clinical impact on the long-term health of patients." Weiss confesses that while his laboratory was making the early monomeric analogs, it didn't occur to him at that time that they may have some commercial value.

In a way, it worked in Weiss' favor that he didn't immediately jump in on the action. In the mid-2000s, many of the companies in the business of making insulin analogs decided to exit the market because it seemed saturated. But by 2007 Weiss was getting excited about the analogs his laboratory was producing, because one of them was the heat-stable insulin he had thought of as a youthful, backpacking student.

As the work matured, Weiss pitched it to the Bill and Melinda Gates Foundation to see if the organization would help get the heat-stable insulin analog out to the developing world. But he was stopped in his tracks. "One of the Gates Foundation leaders advised me that I had to take off my academic hat and at least, part time, put on a business hat," recalls Weiss. "You can't have a charitable mission in the developing world without having a sensible business plan in affluent societies that makes the whole enterprise possible. HIV medicines are a major market in the west. That provides the foundation for charitable humanitarian use in the developing world."

The Gates Foundation leader, Richard Klausner, the former head of the National Cancer Institute, urged Weiss to think about how his heat-stable insulin analog would be helpful in the developed world. And that was the same message he heard from one of his good friends.

Live long and prosper

One day in the late 1970s, Richard Berenson and his two college roommates decided to push open the fire door between their undergraduate dorm suite and the adjoining suite at Adams House on the Harvard campus. In the next suite, they found Weiss, who at that time was a senior undergraduate.

A friendship was struck up between the four men, and from then on, the fire door between the rooms was kept open. A cornerstone of the friendship was a devotion to "Star Trek." On nights there was a "Star Trek" rerun at 6 p.m. on TV, the four friends would go to dinner early so they could watch the show together. Weiss was already a fan of the original TV series, because he used to watch it with his father back home in Ohio.

Weiss and two of the roommates, Alan Stern and Hamish Norton, went off to get Ph.D.s in science (in Weiss' case, he added an M.D.); Berenson headed to law and business schools at Harvard ("I am the black sheep," he quips). Berenson built up a career in venture capital and private equity, working with a string of startups in the biotechnology, technology and media spheres in the Boston area.

One day, when both men were successfully entrenched in their respective career paths, Berenson got a phone call from an excited Weiss. "Mike called me up and said, 'Rick I've invented an insulin that is perfect for the developing world that never needs refrigeration.' I said, 'Mike, that's fantastic. Do you have anything that works in the west? You can't start a company just on a program for the developing world.'"

Berenson repeated exactly what Weiss had heard from the Gates Foundation. Weiss had to identify a niche for the heat-stable analog in more affluent countries.

In establishing the company Thermalin Diabetes in 2009 with Berenson as its CEO, Weiss and the rest of the team identified things that made Weiss' new monomeric insulin analogs special for developed-world purposes.

The company's first candidate is Fluorolog, a rapid-acting, ultraconcentrated insulin analog. Fluorolog gets its name from the fluorine atom present in an ortho-monofluorophenylalanine substituted for a phenylalanine in the analog. The fluorine atom acts to stabilize the entire molecule so it no longer needs to form a hexamer to be stable. Because the molecule doesn't have to form a hexamer to be active, the analog is not prone to clumping and can be formulated at high concentrations.

Berenson says Fluorolog actually has two market niches in developed countries. One is for type 2 diabetics with high insulin resistance. Right now, these patients have to inject 0.5 mL of insulin into their skin, which is very uncomfortable, explains Berenson.

He adds, "More importantly, when you have that large a volume, it really slows down how quickly the insulin absorbs. The consequence is it's no longer a meal-time insulin."

Higher concentrations of insulin don't help either, because the protein clumps and still would be too slow to act. "There's no solution for these patients" at the moment, says Berenson, but he sees a place for Fluorolog, because its high concentration will allow diabetics to take in small amounts. Weiss points out that Fluorolog will have a humanitarian

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Fluorolog is a rapid-acting, ultraconcentrated insulin analog.

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benefit in the U.S., because insulin resistance is most prevalent in poorer communities.

The second application is in miniaturized insulin pumps geared for type 1 diabetics. "Today, the constraint in shrinking the size of a pump is the size of the insulin reservoir. If you can make insulin five times as concentrated without losing the rapid action, then you can shrink the reservoir by 80 percent," explains Berenson. "You can make a matchbook-sized insulin pump or an insulin pump that lasts a whole week."

The first-generation insulin analogs are scheduled to go off-patent starting this year. The management team at Thermalin Diabetes suggests that the timing is right to start introducing Fluorolog and their other second-generation insulin analogs to a market that is expected to grow from $17 billion today to $70 billion by 2030. Earlier this year, the company received a $1-million pledge from the Juvenile Diabetes Research Foundation International to support its efforts.

Weiss says the company is getting ready to do phase I trials of Fluorolog in which he expects to enroll 12 to 24 volunteers for a single injection of the drug. "One of the amazing things is that so many neighbors and friends in the Cleveland community are volunteering to be in our phase I studies," says Weiss. "Their families have been touched by diabetes, and this is a way they can make a contribution. It's really heartwarming."

Even though he has Berenson as the seasoned businessman at the helm of Thermalin Diabetes, Weiss did some introspection after the Gates Foundation meeting and acknowledged that he knew little about the business management world. To rectify matters, as he reached his 50s, Weiss went back to school, this time to Weatherhead School of Business at Case Western for an MBA. "It was a fantastic experience even though I was twice as old as the other students," says Weiss, admitting that taking exams again was a struggle.

Berenson has watched his friend combine his scientific, medical and business training. "There are a lot of scientists who might get an MBA and decide that, even without having done it before, they know exactly what to do to run a company," says Berenson, adding that Weiss has used his MBA training to be more attuned to the business problems and decisions involved in creating products. In meetings with stakeholders, Berenson says he watches Weiss walk the fine line between the idealistic scientist who sees his work changing the lives of ordinary people and the savvy businessman who has an eye on the bottom line. "It's really interesting to see him navigate that huge desire to make a difference with the need to make sure to stay committed to making a return for our investors," says Berenson.

Making a difference in the lives of those less fortunate is important to Weiss. Berenson says his friend's constant consideration of others, such as his graduate students, and care for those in desperate need, such as the villagers he saw in Kenya, are always in the forefront in his day-to-day business.

As the chair of the biochemistry department at Case Western, Weiss gets to uphold some of the values he cherishes in the form of framed Star Trek: The Next Generation posters on the walls of the department office. To Weiss, the posters of the characters Data and Worf illustrate the values highlighted by them, such as conflict resolution and honor. While Berenson identifies himself "as more of a Spock guy," from the original Star Trek series, Weiss says his favorite character is the doctor, Bones McCoy, because of all the characters in the original TV series, to Weiss, McCoy seems to be "the most human and humane."

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

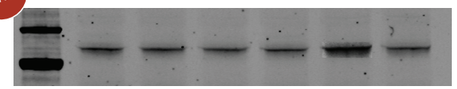
HEY, RESEARCHER! LEAVE THAT BLOT ALONE!

Good practices for preparing publication-quality figures

1. Before preparing figures, read the Journal's Instructions for Authors.

2. Adjust brightness/contrast equally across image.

BAD — *Enhanced contrast of one area*



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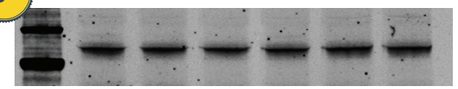

3. Spliced image must include dividing line at the splice junction and be described in the Figure Legend.

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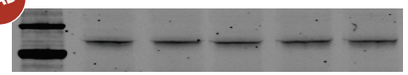

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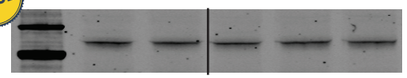

4. Do not make adjustments that hide any part of the image, including erasing background.

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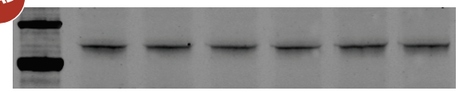

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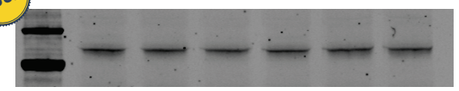

5. Avoid excessive contrast adjustment that removes background.

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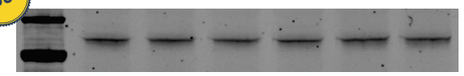

6. Final figures must be high-quality TIFF or EPS files. Avoid preparing figures in PowerPoint to avoid loss of image resolution.

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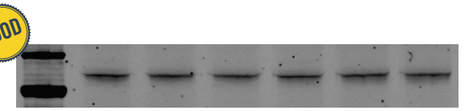

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My study-abroad experience

By Marilee Benore

I've wistfully counseled many students as they have prepared for adventure abroad, wishing I could go along. So, when an opportunity came for me to spend two summer weeks immersed in bioanthropology in northern France, I jumped.

The chance came in the form of collaboration with Megan Moore, a professor at Eastern Michigan University. Moore, a forensic bioanthropologist, had begun working with French scientists and physicians to study the bones unearthed during a construction project in Saleux, France, in 1993. The construction site had been a burial ground for Merovingians and contained nearly 2,000 individuals buried between 700 and 1200 AD. The collection of artifacts, now housed near an estate that is open to the public, offers a rare opportunity to learn from the ancient bones and teeth about diet, nutrition and injury. The estate is where we worked.

My experience in chemistry and molecular biology and my willing attitude to do anything was useful to the project. Thus, I traveled by plane and train in late June to Saint-Valery-sur-Somme, a village located near the salt flats of northern France. A charming village originally home to fishermen, it still has the ramparts and walls of the castle dungeon that held Joan of Arc. There, I met the group, which had arrived a few days earlier, and spent the weekend in cultural pursuits to Paris museums and sites.

Marilee Benore of the University of Michigan-Dearborn traveled to France this summer with a group of students and researchers to study artifacts unearthed from a burial ground used between 700 and 1200 AD.

The 13 participating students shared one large house, while the faculty and family members shared a house around the corner in the shadows of the medieval castle walls. Students from the University of Michigan–Dearborn, Eastern Michigan University and the University of Nebraska all had been well-trained in advance, and each one was assigned a specific research project.

All the students were familiar with osteology — impressively so, as they often patiently explained the skeletal parts to me. (Disclaimer: Trained as a chemist, I have never become overly familiar with bones, tendons and other working parts of the human form.) In addition to their skills, the students had learned the ethics of working with the bones, showing reverence, respect and a bit of awe for the population.

Moore specializes in nutrition and osteology, and Emily Hammerl, a bioanthropologist at the University of Nebraska–Lincoln, brought her expertise and equipment including a portable X-ray machine and 3-D imager. Thus, everyone was busy for the next two weeks evaluating, cataloguing, measuring, celebrating the Fourth of July, dining as a group and journeying to see the impressive Notre Dame gothic Cathedral in Amiens about an hour southeast of Saint-Valery-sur-Somme.

My primary role was to assist student Linda in her sample preparation for studies on the isotope analysis of the dental plaque and rib bone. Although not widely appreciated by many of us teaching photosynthesis, differences in how heavy isotopes are assimilated by C3, C4 and CAM plants provide important clues about diet. Research has demonstrated that both dental calculus (the hardened plaque) and bone collagen provide relevant data about food sources.

In addition to my personal desire to experience and learn something new, I wanted to find out more about study-abroad experiences. Many biochemistry and molecular biology students are interested in study abroad – as an opportunity to experience a different culture, to learn or to perform humanitarian work. There are commercial and campus opportunities, with those in the category of helping typically aimed at educating children, working in the environment or participating in some medical relief. Rare are opportunities that include biochemistry research with history and culture.

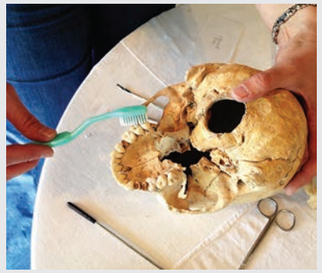
I also went to find out how much work is required to offer such an experience to students. It is not easy to run the program and requires months of preparation, fundraising and organization. Moore never stopped moving, and as the only person fluent in French, she was called upon to be faculty expert, driver, interpreter, organizer, diplomat and fun maker. It was hard work.

Just as important: I found a new research collaboration. The experience was insightful, rewarding and fun. I hope that more study-abroad opportunities can be created for students interested in research and cultural experiences.

Marilee Benore (marilee@umich.edu) is a professor of biology and biochemistry at the University of Michigan-Dearborn

Travelogue

I kept a diary of the adventure on Facebook. In this way, I was able to reflect on the adventure but also reach an audience of scientists and relatives who were happy to have insight into a scientific investigation. Here are some example posts:



Professor Megan Moore points out a feature in a bone structure. They were making 3-D images of small bones, mandibles (to see hidden teeth), jaws and skulls. Structures in the jaw along with knowledge of diet are useful indicators of the food eaten, jaw strength and mastication, while vertebrae damage indicates other stressors.

Linda is studying the plaque on the teeth. Yes, these individuals do indeed have dental plaque, which is a thick mass of mineralized biofilm, microflora (bacterial debris) and minerals that harden on your teeth. We humans still deal with plaque!

If we are lucky and find an individual with minimal dental decay and a tooth that has not been ground down to the dentine, there is a chance that inside the tooth is some DNA. Using this DNA we can perform "DNA fingerprinting" and learn about the history and migration patterns of the individuals or other specific details. For example, this might help us identify the sex in a juvenile skeleton.

Several of us traveled to Amiens to take the samples for isotope and DNA analysis and to have a select group of bones X-rayed. Emily identified teeth samples indicating hyperplasia due to stress, and now long bones from these individuals are examined by X-ray for Harris lines that confirm growth stressors. From the position, they can determine the age of stress. Many thanks to Christophe Obry and colleagues at Victor Pauchet private hospital in Amiens!

Shouldn't we make biochemistry an exact science?

By Bob Eisenberg

Exact science is useful. The physics of X-rays is exact. Biochemists can trust X-ray crystallography, because the equations of X-rays are exact. But we rarely trust the equations that describe our own experiments, and that is for good reason. The equations fail so often. Biochemists know that the law of mass action we use every day is not exact. The rate constants of that law change as conditions change. When we try to use that law, we must change parameters, but we do not know how. The law of mass action is not exact and not very useful, because we often cannot transfer it — parameters unchanged — from one set of conditions to another. This fact is known to every enzymologist, but sad to say, other scientists often are not aware of this reality.

Biochemists have tried to make their theories exact by increasing resolution. Our models of enzymes include thousands of atoms in cathedrals of structure. The hope has been that computing all the atoms of those cathedrals would produce exact simulations, if not exact equations. But as the calculations of molecular dynamics reach from atomic to biological scales, we face disappointment once again: Enormous resolution does not guarantee useful biological results.

We know very well that most enzyme reactions are controlled biologically by trace concentrations of ions like Ca^{2+}. No atom simulations are large enough, however, to deal with the 55 M water that dissolves each calcium ion. The atomic resolution of simulations will have limited use if we cannot deal with the trace concentrations that control enzymes in health and disease.

I argue here that exact equations have not been possible because mathematics has not been available to deal with the interactions that occur in ionic mixtures like seawater. Biology occurs in modified seawater, and changes in ion concentration change the reactions of most enzymes. All the ions in seawater are linked by the electric field. Many are linked by steric interactions as well. Some are linked by orbital delocalization of electrons shared with water or other molecules (i.e., chemical bonds). Exact theories in biochemistry must use the mathematics of interactions.

These interactions are not small effects

Most biological ionic solutions, like seawater, are far too concentrated to behave like ideal fluids or electrolytes even without chemical bonding. They are, in fact, complex (not simple) fluids.

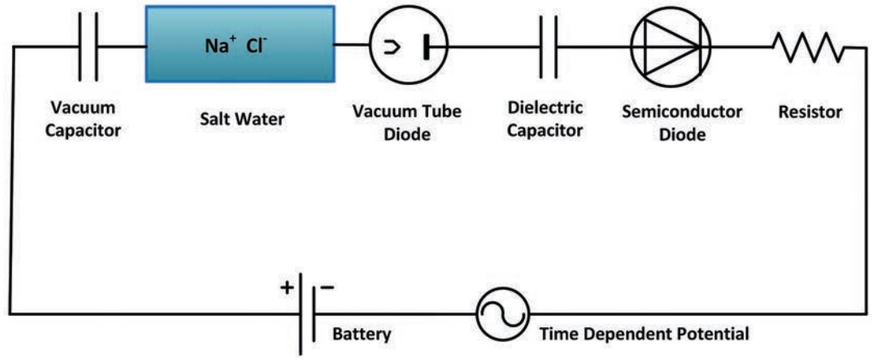
The free energy per mole (the experimental quantity called the activity of an ion, extensively measured in the literature) is the simplest property of an electrolyte. Activity plays a role something like height in a gravitational field and voltage in an electric circuit. In seawater, the activity of the bio-ions Na^+, K^+, Cl^- and Ca^{2+} does not vary linearly with concentration (as in an ideal fluid) or even with the square root of concentration (as in extremely dilute solutions of NaCl).

Interactions and nonideality are not small effects, because ions are highly concentrated where they are most important: in and near active sites, ion channels, binding proteins and nucleic acids; near the working electrodes of electrochemical cells; at charged boundaries in general. There, concentrations are often more than 5 molar, and solution properties are dominated by interactions. The activity of one ion depends on the individual concentration of every other ion. Everything interacts with everything else. Some of the interactions usually called allosteric may in fact arise in the highly concentrated solutions in and near active sites of proteins.

The mathematics of interactions has been understood for a very long time when the systems involved are conservative and do not involve friction. Hamiltonians and variational calculus are the language of high-energy physicists when they build their bright X-ray sources.

Hamiltonians have not been used in most biological systems, because biology occurs in condensed phases where friction is always present. Until recently, no one knew how to use Hamiltonians in systems with friction. Friction accompanies all ionic movement and conformation changes in biology, because atomic collisions occur on a 10^{-16} time scale in solutions. That is why

Charge is an abstraction with different physics in different systems.



solutions are called condensed phases, and only three or four collisions are enough to convert deterministic motion into the random motion we call heat.

Theory of complex fluids

Recently, mathematicians have developed a theory of complex fluids that generalizes Hamiltonians into an energetic variational calculus dealing with friction. The theory has had striking successes.

Variational methods deal successfully with liquid crystals, polymeric fluids, colloids, suspensions and deformable electrolyte droplets that fission and fuse including the interfacial properties such as surface tension and the Marangoni effects of oil on water and tears of wine. It is a little early to say the theory of complex fluids provides exact equations in general, but the theory certainly provides a productive pathway toward that goal.

The perspective the variational calculus offers is striking even if its results are immature. Complex fluids must be analyzed by variational methods, because everything interacts with everything else. If those interactions are not addressed with mathematics, the interactions are bewildering, and the results cannot be analyzed. A mathematics designed to handle interactions is needed to produce exact equations. Otherwise, interactions vary in so many ways that fixed parameters cannot deal with them.

Life at equilibrium is usually death

Biochemical systems always involve ionic solutions in which the electric field links everything with everything else. Exact equations must be consistent equations in which all the variables satisfy all the equations and boundary conditions in all conditions.

In particular, the electrical forces and potentials must be computed from the concentrations of all charges present — in solution, in macromolecules and in layers near boundaries — because those electric forces can change qualitatively and quantitatively when charge changes anywhere.

The equations of electricity are global. The flow of charge at one location changes the flow everywhere. Flow must be dealt with consistently in biochemistry, because life does not occur without flow. Life at equilibrium is usually death.

Charge is an abstraction

The global dependence of the electric field is glimpsed in the cartoons of Kirchoff's current law used in computational electronics. But Kirchoff's law is so intertwined with Maxwell's exact equations of electricity that they are inseparable.

The key idea in Maxwell's theory is charge. Charge is abstract. Charge changes its physical nature as it flows through a circuit (see figure). It is electrons in a vacuum tube; it is ions in salt water; it is quasi-particles in a semiconductor; and it is nothing much (i.e., displacement current) in a pure vacuum. Yet the flow of current is the same in every element in a series circuit, although the physical nature of that current is strikingly diverse.

The global nature of electric flow prevents the law of mass action from being exact. The law of mass action — with rate constants that are constant — does not know about charge. Its rate constants do not depend on charge in a way that guarantees Kirchoff's current law (as shown in the supplementary material at http://arxiv.org/abs/1409.0243).

The law of mass action is about mass conservation. It is not about charge conservation. The laws of electricity guarantee the current will be the same for all reactions in a series. The law of mass action does not.

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How do we make changes?

How can we fix this problem and remake our laws so that they deal well with interacting systems and electric charge? I do not know a general answer, but I know where to look for help.

Physicists for years have used consistent analysis of flow and diffusion of charges to design transistors for devices. Those devices have increased in capability by billions in 60 years, and that striking success may have something to do with the exact laws that those devices follow.

I believe biochemistry can add to its own substantial successes of the past 60 years by trying to make its laws exact. If the spatial dependence of the electric field is built into a new version of the law of mass action, we surely will do better than we have done in understanding how enzymes, channels and nucleic acids do their work.

Consistent treatments will not be easy

Giving up inconsistent treatments will be like giving up part of our intellectual heritage.

We can no longer look the other way when rate constants vary. We must use activities, not concentrations, to describe reactants in crowded active sites when studying allosteric interactions. We no longer can compute fluctuating concentrations of charge and assume electric fields do not fluctuate. We must learn to deal with fluctuating electric fields in our treatments of Brownian motion of ions so that results will not seem so anomalous.

We must incorporate boundary conditions and finite-size ions into the law of mass action. Algebra and ordinary differential equations must give way to field theories, partial differential equations and variational calculus.

We must even incorporate spatial inhomogeneities and electric fields into our treatments of covalent chemical reactions in ionic solution, because those spatial inhomogeneities are likely to produce very large local concentrations lasting long enough that reactions occur quite differently from reactions in a spatially uniform system.

We cannot just calculate models with higher and higher resolution. We must compute consistently with the electric field, on all scales, with theories appropriate for each scale.

Mathematics is now available

Mathematics is finally available to deal with diffusion and electric fields in a consistent way, and the theory of complex fluids and simulations of computational electronics have shown that mathematics can describe complex fluids and devices (nearly) exactly. Now let's try that mathematics on the classical problems of biochemistry to see if we can construct a consistent theory of reactions that is exact and useful.

A fully cited version of this paper and supplemental figures and materials are on the arXiv at http://arxiv.org/abs/1409.0243.

Bob Eisenberg (beisenbe@rush.edu) is chairman of Rush University Medical Center's molecular biophysics and physiology department

The many hats of an academic researcher

By Andrew D. Hollenbach

I had done it: I had achieved my career goal. I was a professor at a large university running my own lab and directing my own research! I sat looking at my dream come true: an empty office, an empty lab and no idea how to fill either of them! So I pulled out the laboratory-supply catalogues and began paging through them, making a list of everything I needed to get started. Little did I know that this was only the beginning of my on-the-job training.

I always had thought that being a professor meant that I got to sit in my office and think about science all day. I knew that writing grants, publishing my research and presenting my work at meetings was part of this job. What I didn't know was that as soon as I signed on the dotted line there would be a multitude of other hats that I would need to put on with little to no guidance other than my instincts. Let me give you a brief overview of the many hats I learned how to wear:

THE BUSINESSPERSON: All of sudden, not only do you have to fill an empty lab, but you also need to juggle your finances so that your lab stays solvent to perform quality research! You must establish a monthly budget. You must learn when to economize (No, we don't need that Qiagen Cube) and when to splurge (Yes, we need those results for an important manuscript). You also must learn how to develop a grant budget so that everyone gets paid, fringe benefits are covered and money for supplies remains.

THE SALESMAN: Although I knew I would have to write grants and publish my work, I had no idea that to be successful I had to sell my ideas. I thought it would be simple enough to describe a logical line of experiments or the results we had obtained and that they would speak for themselves. Nope. Far from it! You have to sell yourself. You have to learn to put everything into context and convince your audience that your work is important, significant and innovative!

THE WRITER: I learned how to write in high school and college; little did I know that as a scientist I would also need to write a lot (as in, pretty much every day of my career) and to write well! If you can't write grammatically while putting together a flowing line of logic, how can you expect to sell your ideas and your work?

THE REVIEWER/EDITOR: I also needed to learn how to read, evaluate and constructively criticize other people's writing and science (with an emphasis on the word "constructively"). I needed to learn how to help my colleagues and students reorganize their thoughts and words to help them become better salespeople and writers!

THE PERFORMER: Yep, you read that correctly! What makes people good performers? They are unique in what they do, they engage with their audiences and they convey passion for their crafts. This is no different from what we need to do whenever we present our work. We must learn to present our results in a manner that tells a story, we must be connected and engaged with our audiences, and we must let our passion for our work shine through.

THE TEACHER: If you work at an academic institution, this one is pretty obvious. However, tell me honestly, where did any of us learn how to teach a class? It is not something that is necessarily required of students in graduate school and definitely not in your postdoctoral years. Therefore, we need to find our own teaching voices and teaching styles.

THE MENTOR: Again, pretty obvious. If you run a lab in an academic institution, you will have students training in your lab. However, what is not obvious when you start is that every single student is unique. It is your job to figure out what makes that person tick. You must learn how to identify student strengths and weaknesses and then determine the best approaches to take so that you can release their inner diamonds.

THE THERAPIST: The part of being a mentor that is not obvious is learning how to say the correct thing to bring that distraught student back from the edge. You need to learn how to listen to your students, intuit their psychological makeup, learn why they act (and react) the ways they do and then use all of this information to console, counsel and support them as they learn about what many times can be a thankless profession.

THE MEDIATOR: You are the head of your lab. You employ many different people, regardless of whether you run a small lab (like me) or a

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large lab. It is inevitable, no matter how well everyone gets along, that at some point there will be differences in opinion, miscommunications and small (or not so small) disagreements. This is where you step in. You must listen to both sides while not taking either side, process what you hear and then meet with the individuals involved to iron out the differences.

THE POLITICIAN: The academic world is all about politics. You'd think it would be about teaching, and it is. However, behind the scenes, it's all about politics. You need to learn about your academic environment: Where are the political land mines? Who truly holds the power? Who interacts with whom, and on what level? What can you say and to whom? How must you say it, and how does this change depending on whom you are talking with? What must you do to advance through the ranks? This is not learned in a day or in a year; in fact, it will be fluid and change as you advance to each new rank and are given more responsibilities.

THE ADMINISTRATOR: As part of your job in academia, you will be asked to serve on committees. To advance in your career, or because you are acquiring more influence or responsibility, you also will be asked to chair committees and make decisions that affect the institution. Until you serve in this capacity, there is nothing in your education or career trajectory that will have prepared you for this role.

I know this all sounds daunting. Rest assured, you won't have to learn all of these things as soon as you start your job. In fact, you won't learn some of them until later. But if you find yourself in a supportive department and identify one or two trusted and successful senior faculty mentors, you can do it. We have all been there, and eventually you too will be where we, as senior faculty, are today.

Andrew D. Hollenbach (aholle@lsuhsc.edu), author of the book "A Practical Guide to Writing a Ruth L. Kirschstein NRSA Grant," is an associate professor in the genetics department at Louisiana State University Health Sciences Center in New Orleans

Letter to the editor

Re: "A president's perspective on Experimental Biology 2014," June/July issue

I found it deeply gratifying that Jeremy Berg chose to discuss the Ruth Kirschstein Diversity in Science Award in his final presidential perspective for ASBMB Today.

HRABOWSKI

The recipients of that award (Michael Summers and Freeman Hrabowski III, honored for their work on the Meyerhoff Scholars Program) have proved that students traditionally marginalized in STEM can excel and achieve in those disciplines.

Summers is a Howard Hughes Medical Institute professor, accomplished and recognized as a leader in his field of research with many award lectures behind him and many more likely to come. And yet I believe that his most significant long-term impact on science will prove to be the effect he has had on increasing minority participation and success in scientific research. For that reason, I didn't quite share the regret Berg expressed over the fact that a discussion about Summers' research in RNA structural biology was not part of the Kirschstein award presentation.

But I was sorry that his award lecture was not better attended. The previous award lecture — the Mildred Cohn Award in Biological Chemistry — was delivered to a standing-room-only crowd of an estimated 1,000 people. At the end of that talk, there was a mass exodus from the room, and some 150 people, primarily educators, remained to hear Summers talk about the Meyerhoff Scholars Program. This stark contrast does not go unnoticed by those most interested in (and affected by) issues of diversity in science.

One undergraduate student wrote: "Just before the (Kirschstein) award ceremony started, I was surprised that many people left after the protein folding talk, but not many new people came into the room. The room felt a lot more empty. It was probably because only a few people are interested in and care about the inequality of races in the science field. I think everyone should be showing an interest … I was inspired and realized that everyone's awareness of inequality is essential, and bringing equality requires everyone's effort."

My colleague Regina Stevens–Truss arranged for a few students attending the American Society for Biochemistry and Molecular Biology annual meeting to interview Summers about his work in the Meyerhoff program after his award lecture. The interview is archived at the ARCUS Center for Social Justice Leadership in the Praxis Center (http://www.kzoo.edu/praxis/category/science/).

At the end of his talk, Summers said, "We are all in the right place at the right time to have an impact." Let's make that impact happen by showing up for this award, supporting inclusivity in science and building sincere interest in the many benefits of diversity in science.

– LAURA FURGE,
THE ROGER F. AND HARRIET G. VARNEY PROFESSOR AND CHAIR OF CHEMISTRY AT KALAMAZOO COLLEGE

Michael Summers gives his award lecture at the ASBMB annual meeting in San Diego in April.

Correction

In the September issue, we incorrectly attributed the lyrics to the Descendents' song "Suburban Home" to Milo Aukerman in the article "Champion of the nerds." In fact, former band member Tony Lombardo penned the song. We regret the error.

Reader response

Re: "Curricular revision: embracing the journey," August issue

By Daniel M. Raben

In a recent excellent ASBMB Today article, Neil Osheroff described how he and others at Vanderbilt University revised the medical school curriculum there, and he highlighted some of the perceived advantages of doing so (1). As Osheroff correctly pointed out, everyone nationwide involved in medical education has felt the push to revise curricula, and that push certainly has stirred a lot of debate. While the changes Osheroff described seem exciting, the educational impacts of such changes are difficult to determine.

Evaluating the success of a curricular overhaul requires close inspection of the details of the curriculum itself and, most importantly, of the outcomes it produces. While it's not possible to assess the latter for quite some time, evaluating the details of curricula may be enlightening. I can't speak for all topics in medical school curricula, but I've certainly seen changes in what has been taught as biochemistry or metabolism.

When the issue of medical school curricular revision first surfaced, some educators expressed concern that we would be dumbing down the biochemistry. And that appears to be happening. Metabolism once was taught in a 16-week course at my institution. It is now taught in about six days. Sixteen weeks can't be condensed into six days without losing a lot of content.

Not surprisingly, the curricular-revision discussion has focused on two content issues:

1. What do budding physicians need to know?

Undergraduate courses lay a foundation that medical school builds upon; or at least that's how it used to be.

2. At what depth do they need to know it?

Some people say that biochemistry, particularly biochemistry beyond carbohydrate metabolism, doesn't need to be covered in much depth. I've even heard it said that an undergraduate course in biochemistry would take care of what is missing from the new medical school curricula. This seems a bit misguided. Undergraduate courses lay a foundation that medical school builds upon; or at least that's how it used to be.

Some people say that what is eliminated from the first year of medical school will be recovered during clinical years. (This notion often takes exotic names, such as "longitudinal strands.") But returning to fundamental concepts of metabolism in the clinical years often is more difficult than anticipated, largely because students at that point are focused on patient care.

At some schools, topics like the metabolism of porphyrins, lipoproteins, nucleic acids and amino acids are all but eliminated but related to discussions during the clinical years. If these topics are addressed, they usually are covered in the context of phorphyrias, atherosclerosis and inborn errors of metabolism. No one would diminish the importance of such discussions, but the underlying biochemistry usually is absent. Of course, such concerns usually are countered with the claim that the students don't need to know a lot of fundamental concepts of metabolism: We are covering what we now know to be important!

If the core mission of the institution is to train students to diagnose and treat people, then there is some validity to the argument that we may have been teaching more than needed. Indeed, this is largely how we train physician assistants, and they diagnose and treat people with great expertise.

However, if the core mission of the institution is to train physicians with a keen ability to recognize new assaults on our health and what could be done about them — that is to say, to not just practice standards of care but establish standards of care — then doing so may require a more in-depth academic training.

This reminds me of an anecdote a friend of mine told me about his years as an M.D./Ph.D. student at Stanford University in the late 1970s. The students didn't understand why they were learning about retroviruses when there was no known human disease caused by a retrovirus. Then, in 1981, HIV showed up.

Author's note: Many thanks to Charles Brenner and Richard Eckhert for their input for this response.

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REFERENCE

1. http://www.asbmb.org/asbmbtoday/201408/Education/

Reader comments

Re: "The curse of committees and clubs," September issue

Interesting take on this, Steve. I would say to you that quality of peer reviewers is largely dictated by the willingness of exceptional scientists to actually sit on the panels. Second, I would like to see some data for your assessment that the average scientist today is not as qualified as the scientist of yesteryear. Can you remind me who trained this generation of less-than-scientists?

– TONY

Steve,
Even the panels of the "olden days" could not distinguish (for example) between the top 8 percent application and the top 12 percent application. This is where fund/no-fund distinctions are taking place. Also, take a look at the names of the ~150 standing study sections, and you will see that only about 10 have a name that appears to reflect basic science. It is time for our community to look at the names of those panels and the science they recommend for funding and ask the question: Are we getting the best quality for our investment? Always asking Congress for more money will not solve the funding crisis soon enough. Young scientists are turning to other careers, given current funding challenges. And sign me up for a panel! I am happy to serve.

– SUZANNE PFEFFER

Having served on study section for a number of years, especially recently when the funding lines have gone down, I think the biggest problem is there are too many grants and not enough dollars. When we were funding 20 percent of the applications, all the best science got funded, even the innovative and creative stuff. As funding eroded, clubs popped up for protectionism, because good science was not a guarantee for funding. Lots of examples of this in Europe as funding eroded over time.

– JEFF

I agree that the lack of a generalist mindset hinders the success of the most innovative proposals. There are colleagues in study sections who consciously or subconsciously think a grant is insignificant if it isn't confirming their own hypotheses in their specialized area. They need to be reminded by their colleagues in study section that their goal is to select the best science. Unfortunately, I seldom see others chiming in when an inspired, novel topic is cut down because somebody is clearly becoming focused on his or her own narrow world. Maybe we need to have study section members declare their expertise and then have them review grants, or a portion of grants, outside that expertise? We need to break those boundaries somehow while still maintaining quality reviews.

But that's only part of the issue. To score highly, one needs all reviewers to agree that the application is outstanding. It would be hard to get three generalists to agree on that. So the most inspired grants may never score above the 20th percentile in the best of circumstances. Today, only competent grants in already agreed-upon topical areas can achieve the fundable range. That is the problem. Good but seldom awe-inspiring work in narrow areas can be agreed upon by narrow experts. Outside of that, it's a turn of the roulette wheel.

I don't claim to know how to get those inspired grants funded. I'll bet they have high innovation scores and poor approach scores. Should the National Institutes of Health use the innovation and/or impact scores to identify grants to go to a second innovation triage study section? Those triage study sections should be purposefully very broad in constitution. They also should be funded beyond the institute level at, say, 10 percent or 15 percent of total NIH dollars to every institute. That has all institutes participating in selecting innovative studies. If we notice that a preponderance of those studies are going to particular areas, then does it also provide feedback to the funders about how to distribute our grant dollars?

– FRED SCHAUFELE

Riffraff = "the lowest of the low, in the underclass, the dregs of society, good-for-nothings, undesirables."
I disagree with almost everything you say, but that is fine. What I do not think is fine for a president of a scientific society is to resort to name calling and abuse. This abusive term is used here to describe hardworking colleagues. I think this is a very sorry article.

– ALEX WEBB

To grant reviewers: Next time you're serving on a study section, look around the room. How many of your colleagues are answering email, shopping for laptops, or otherwise not paying attention to the discussion? To grant writers: You have to work harder than ever to get our attention.

– ANN LORAINE

I find the level of restraint in these comments amusing. As an ASBMB member since grad school, being labeled second-rate riffraff is insulting. Greatest generation indeed.

– DARREN BOEHNING

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