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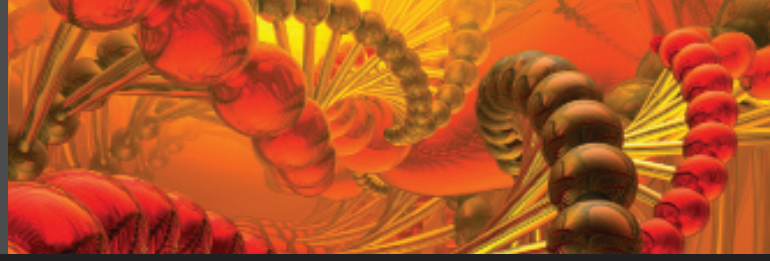
March 2010

The Many Roles of the Na,K-ATPase

American Society for Biochemistry and Molecular Biology

2010 ASBMB Special Symposia



September 30 – October 4, 2010

Registration and Abstract Submission Deadline: August 1, 2010

Transcriptional Regulation by Chromatin and RNA Polymerase II

Granlibakken Resort, Tahoe City, CA

Meeting Organizer: **Ali Shilatifard,** Stowers Institute for Medical Research

Keynote Speaker: **Robert E. Kingston,** Massachusetts General Hospital Harvard Medical School

Plenary Speakers:

Karen Adelman, National Institute of Environmental Health Sciences

Mark Bedford, MD Anderson Cancer Center

Shelley Berger, University of Pennsylvania

Joan Conoway, Stowers Institute for Medical Research

Jacques Cote, Laval University Cancer Research Center

Joaquin Espinosa, HHMI / University of Colorado at Boulder

Jean-Marc Egly, Inst Genet et Biol Mol et Cell

Peggy Farnham, University of California, Davis

Grace Gill, Tufts University

Steven Hanes, Wadsworth Center

Paul Kaufman, University of Massachusetts Medical School

Tom Kerppola, University of Michigan School of Medicine

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David Stillman, University of Utah School of Medicine

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Michael Washburn, Stowers Institute for Medical Research

Johnathan Whetstine, MGH Cancer Center and Harvard Medical School

Jerry Workman, Stowers Institute for Medical Research

Julia Zeitlinger, Stowers Institute for Medical Research

ASBMB
American Society for Biochemistry and Molecular Biology

www.asbmb.org/TranscriptionalRegulation2010

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ASBMB today

A monthly publication of
The American Society for
Biochemistry and Molecular Biology

president's message

Plus the Secret Handshake

BY GREGORY A. PETSKO

apprentice |ah-pren-tiss|, noun
a person who is learning a trade from a skilled employer, having agreed to work for a fixed period at low wages

postdoc |pohst-dock|, noun
a person doing the same thing, only for lower wages

grad student |gr-add stoo-dent|, noun
a person doing the same thing for almost no wages at all

When I was a graduate student at Oxford University, 40 years ago, I learned how to crystallize proteins, collect X-ray diffraction data, program computers and solve protein crystal structures. When I was a postdoctoral fellow at the Institut de Biologie Physico-Chimique in Paris, I learned how to stabilize proteins in solution at subzero temperatures and perform kinetic analysis of enzyme reactions under conditions that could trap productive intermediates.

Then, I went to Wayne State University School of Medicine in Detroit as an instructor in the biochemistry department — my first independent position. I taught courses, wrote grant applications, prepared budgets, wrote papers, sat on various committees and advised graduate and medical students. Once I had more than two students working with me, I hardly ever collected my own data, set up crystallizations or carried out kinetic analyses with my own hands. Note the monumental disconnect between what I was trained to do and what I actually had to do to run a lab.

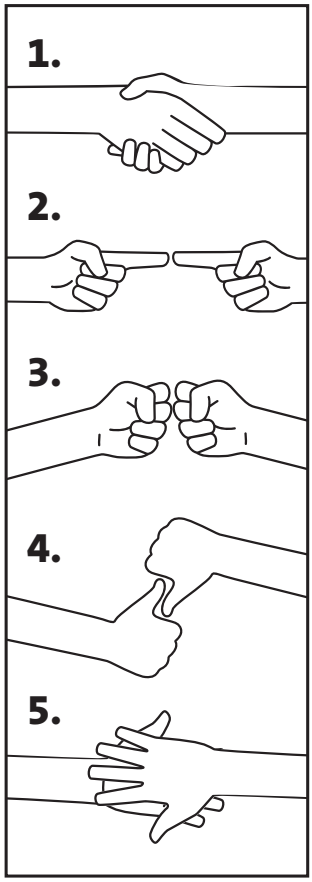
I've remarked before that, once I became a practicing scientist, I realized I had taken all of the wrong courses as a student. Although I started out as a classical literature major, because I was interested in science, I took math, physics, chemistry, biology, biochemistry, biophysics and so on. I should have taken business administration, elocution, basic accounting, creative writing, speed-reading, politics, sociology and abnormal psychology. Now that I'm chair of a department, I really wish I'd taken abnormal psychology.

Getting one's doctoral degree is a watershed moment in the life of a scientist. It indicates that a certain level of training has been successfully attained and that one is qualified to engage the subject at a much more advanced level. In the biochemistry department at Brandeis University, we have a nice custom: At the mini-commencement when our graduate students receive their doctoral degrees, after they have come up to the platform and have been handed the degree, they do not return to their seats in the auditorium; rather, they are seated up on the platform with the attending faculty members, symbolically welcoming them as colleagues in the profession. It always has reminded me of the ceremony at which a medieval craftsman was admitted into a guild.

The guild system began more than 1,000 years ago. It had two functions: to protect the exclusive right of only certain people to make a living in a skilled

trade and to pass on those skills to select members of the next generation, thereby ensuring the survival of the guild.

A guild was made up of experts in their craft, so-called master craftsmen. Before a new employee could rise to the level of mastery, he — they were always men in the Middle Ages — had to go through a two-tier schooling period during which he first was called an apprentice. After this period, he could rise to the level of journeyman. Apprentices, who worked exclusively under a particular master, typically would not learn more than the most basic techniques until they were trusted by their peers to keep the guild's or company's secrets — which, in some guilds, included a secret handshake, thereby enabling members to identify each other.



After being employed by a master for several years, and after producing a qualifying piece of work, the apprentice was promoted to the rank of journeyman and was given documents (letters from his master and/or the guild itself) that certified him as a journeyman and entitled him to travel to other towns and countries to learn more of the art. Journeymen were able to work for other masters, unlike apprentices, and generally were paid by the day. After several years of such experience, a journeyman could be received as a master craftsman (although, in some guilds, this step could be made straight from apprenticeship). This typically would require the approval of all masters of a guild and the production of a so-called masterpiece, which would illustrate the abilities of the aspiring master craftsman.

Sound familiar? The apprentice stage is a close analogy to the graduate student period of an aspiring scientist. The qualifying piece of work allowing passage into journeyman (postdoctoral) status would be, of course, the doctoral thesis. And, aren't today's postdocs almost perfect examples of journeymen? They frequently spend several years with one master and then several more with another, hoping to produce a masterpiece: a high-profile paper (or papers) that establishes him or her as a rising star and earns him or her the modern equivalent of master craftsman status — a good job that, ideally, will allow him or her to work on his or her own ideas.

The problem is that some time during the past half-century, a disconnect developed between what our apprentices and journeymen are learning and the set of skills they actually need to succeed when they set out on their own. This disconnect occurred because the old model of the individual scientist working with perhaps one apprentice and a technical assistant, doing much of the work with his or her own hands, ceased to be valid in academia (though it continues, to some extent, in industry). We continued to train our students in how to carry out good experiments and interpret data, but we often neglect an equally important skill set: namely, the ability to write well, to manage people effectively and to formulate problems in a way that makes them fundable.

Some mentors, to be sure, make it their business to give their students experience and guidance in these things, and some graduate programs even include formal instruction in some of them, but the basic attitude often seems to be that one is supposed to acquire these abilities by osmosis. That works for some people, but not for all.

One difficulty is that students and postdocs usually don't take advantage of opportunities for such instruction when they are offered; this is particularly true of postdocs, who frequently have no organization to arrange formal tutoring in practical matters, and are so absorbed in their work and the business of finding jobs that they rank that sort of help fairly low on their priority lists.

My Brandeis colleague Dagmar Ringe hit upon one way of solving this problem a few years ago, and her solution is worth general consideration. Every biochemistry department that receives funding for students from the National Institutes of Health is required to offer — and the students are required to take — a course in the responsible conduct of research. This course, which we refer to around here as "The Ethics Course," covers such topics as conflict of interest, fraud, disclosure and so forth. Dagmar added, at the end of the course, a couple of weeks of practical workshops on how to give a talk, how to write a paper, how to write a grant, how to manage a group, how to teach a course and so forth. And, the beauty of this idea is not only that there is a captive audience of exactly those who

need this information the most; it's also that new federal regulations are coming that will require all students and postdocs receiving federal funding of any kind — training grants, support from individual research grants and fellowships, regardless of the agency (National Science Foundation, NIH, U.S. Department of Energy, etc.) — to take the ethics course. This makes that course the perfect vehicle for ensuring that all of our trainees receive the kind of practical instruction that they will need in almost any scientific career they undertake.

It shouldn't be hard to find senior scientists in any department who are very good at one of these things and can teach the skills effectively, and a couple of weeks of instruction of, say, three to six hours a week should be enough to impart basic tools, although more elaborate programs certainly could be devised, involving practice talks and writing with critical feedback, for example. The emphasis should be less on how it is done than the fact that it is done, for everyone.

You see, we are a guild, actually, and the apprentice/journeyman system, when properly carried out, is still a superb way for young people to learn the tools of the trade. I hope teaching those tools — including the practical, maybe even mundane skills needed to function as a practicing scientist in this highly competitive environment — become routine in graduate student and postdoctoral training in biochemistry at every institution.

I sure wish I had received instruction like that, instead of being left to stumble my way along by trial and error — mostly error. Because one thing I am completely convinced of is that effective communication, people-management skills and so on, are crafts, not arts, and can be learned, like any other crafts. Different people have different levels of talent for these things, of course, but the basics are accessible to anyone. As I said, I know that many places already do something of the kind, at least for some topics, but it ought to be as much a part of any advanced education as the qualifying exam, thesis or ethics course.

And, if anyone knows what the secret handshake is, I would appreciate them telling me, because I never was taught that either.

Two New Publications from FASEB

BY CARRIE D. WOLINETZ

The Federation of American Societies for Experimental Biology is pleased to announce the release of the publication "Magic Bullets and Monoclonals: An Antibody Tale," the latest article in its Breakthroughs in Bioscience series. The series is a collection of illustrated articles that explain recent developments in basic biomedical research and how they are important to society.

The antibody article describes the century of fundamental immunology research that led to today's cutting-edge monoclonal antibody therapies used to treat millions of patients for several types of cancer, autoimmune and inflammatory disorders and infectious disease. After the late 19th-century discovery that mysterious substances in the blood could be exploited to provide protection against disease through immunization, scientists spent decades piecing together the details of antibody structure and function. All over the world, researchers made breakthrough findings in immunology, racing to discover how antibodies developed the exquisite specificity that allows them to defend the body against a host of diseases. From guinea pigs to papaya enzymes to Darwin's theory of natural selection, the quest to uncover the secrets of antibodies led down some extraordinary avenues of science. In a surprising twist, it was a failed experiment using myeloma tumor cells and the serendipitous development of cell fusion that ultimately resulted in the system used to produce monoclonal antibodies—very pure antibodies that bind to singular, specific targets. Soon, researchers realized that monoclonal antibodies opened up new pathways to study and attack specific diseases, and there are now more than 20 monoclonal antibody-based drugs on the market, including several blockbusters.

Horizons in Bioscience

FASEB also has launched a new series, called Horizons in Bioscience, which provides educational, one-page articles that highlight cutting-edge scientific research on the brink of clinical application and describe the pathways of discovery leading to the current developments. The first article in the series, "How Biomedical Research Provides Fertility Hope to Cancer Survivors," discusses the latest findings in oncofertility — the preservation of a woman's fertility after cancer treatment — and outlines some of the historic scientific achievements in fertility treatment, from in vitro fertilization to cryopreservation.

Horizons in Bioscience is intended to supplement FASEB's existing Breakthroughs in Bioscience series. Whereas Breakthroughs in Bioscience examines treatments currently in use by millions of patients and tells the stories of the science that underlies those clinical advancements, Horizons in Bioscience provides the opportunity to explore exciting areas of science in the very early stages of clinical research and use.

Carrie D. Wolinetz (cwolinetz@faseb.org) is director of scientific affairs and public relations for the Office of Public Affairs at FASEB.

For more information:

Publication Links:

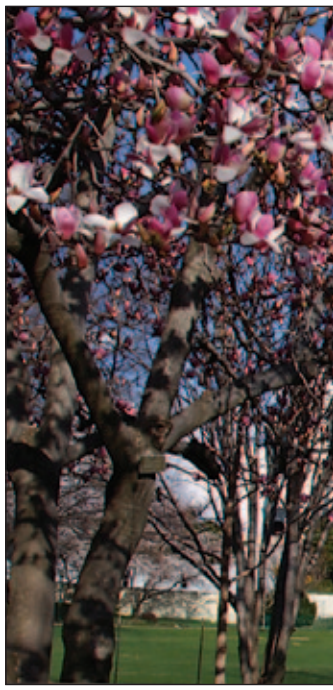
- Magic Bullets and Monoclonals: An Antibody Tale: http://bit.ly/97fLfy
- How Biomedical Research Provides Fertility Hope to Cancer Survivors: http://bit.ly/cUyTuM

Hard copies may also be requested by contacting the FASEB Office of Public Affairs at (301) 634-7650.

FASEB welcomes topic idea contributions for both series. Please send suggestions, with brief descriptions, to cwolinetz@faseb.org.

President Proposes Decent Budgets for Science Agencies

BY PETER FARNHAM



The White House released its 2011 federal budget proposal Feb. 1, and, despite fears of the possible impact of a previously announced freeze on domestic discretionary spending, science funding was a clear winner overall, with most research agencies receiving increases. Although most administration-proposed budgets are modified during congressional consideration, this budget gets science funding off to a good start.

The Numbers

President Obama's budget for 2011 comes in at $3.8 trillion, with a $1.2 trillion deficit. This is the largest budget, and the largest deficit, in history. Due largely to growing public and congressional concern over the size of the deficit, the administration is proposing a three-year freeze in nonsecurity discretionary funding (that is, discretionary funding outside of defense, homeland security, veterans affairs and international affairs), with funding thereafter increasing roughly with inflation. Over the next 10 years, the policy is expected to save $250 billion.

However, this freeze affects only a very small portion of the federal budget, and it is not an "across-the-board" freeze; most science funding, for example, is slated to increase. In addition, all the programs that are frozen at current levels have champions who will be working hard to keep them growing.

The budget calls for $66 billion in nondefense research and development, an increase of $3.7 billion or 5.9 percent overall more than 2010. "The president understands that, more than ever before, science holds the key to the prosperity of our nation, the security of our people, the health of our planet and the richness of our lives," said John P. Holdren, adviser to the president for science and technology and director of the White House office of science and technology policy.

Specific agencies fared well, for the most part.

The **National Institutes of Health** received $32.1 billion under the budget proposal, an increase of $1.0 billion or 3.2 percent more than the 2010-enacted level. Investments will focus on five strategic priorities, first described publicly by NIH Director Francis Collins shortly after his appointment this past fall. They are:

- applying genomics and other high-throughput technologies;
- translating basic science discoveries into new and better treatments and diagnostics;
- using science to enable health care-reform;
- global health and
- reinvigorating and empowering the biomedical research community.

The NIH also will continue to award and oversee the $10.4 billion provided in the American Recovery and Reinvestment Act. In addition, the NIH Common Fund will invest $562 million, an increase of $18 million over 2010, to support cross-cutting, trans-NIH programs that require participation by at least two NIH institutes or centers or that would otherwise benefit from strategic planning and coordination.

Although the American Society for Biochemistry and Molecular Biology would like to see a larger proposed increase for NIH, Federation of American Societies for Experimental Biology President Mark Lively noted in a statement that the president's proposal for NIH was the largest proposed increase in eight years, even though it only allows NIH to keep up with inflation and little else. It is widely believed that the NIH received this increase due to strenuous internal lobbying efforts by Collins, with the support of U.S. Department of Health and Human Services Secretary Kathleen Sebelius.

Of course, the overriding problem of "the cliff" remains — that is, what happens when the $10 billion in extra funding NIH received under the ARRA is spent. This is slated to occur by the end of 2010, a scant nine months away. Thousands of researchers who applied for grants under this special program are expected to resubmit the same grants through NIH's usual funding mechanisms. Unless changes are made to greatly increase the NIH budget in Congress this spring, we are likely to see

dramatically reduced success rates.

For the **National Science Foundation**, the administration proposes an increase of almost $500 million, to $7.4 billion in 2011, or 8.0 percent more than the 2010-enacted level. The budget expands NSF's efforts in climate and energy research and education, networking and information technology research and environmental and economic sustainability. The 2011 budget also provides funding to triple the number of new NSF graduate research fellowships to 3,000 by 2013. (ASBMB was invited to provide written and oral congressional testimony on the NSF budget. You can see excerpts of the submitted testimony in the accompanying sidebar.)

The administration has proposed that the **U.S. Department of Energy's Office of Science** receive $5.1 billion in 2011, or 4.6 percent more than the 2010-enacted level. The budget would fund more research on climate science, continue U.S. participation in international science and energy experiments and expand federal support for energy frontier research centers, intended to explore emerging opportunities in new materials and basic research for energy needs.

The **U.S. Department of Commerce's National Institute of Standards and Technology** invests in technological innovation through research, advanced measurement and standards development. The 2011 budget of $709 million for NIST's intramural laboratories, a 6.9 percent increase over the 2010 enacted level, supports improvements in facilities and research in areas like health information technology and cybersecurity.

Overall, the administration proposal for NSF, the DOE Office of Science and NIST would continue the policy of doubling their budgets as mandated by the "America COMPETES Act," signed into law by President Bush in 2006. The budget proposes completing the doubling funding of these agencies by 2017.

For other science funding agencies, the budget provides:

- $11 billion to the research and development portfolio of the **National Aeronautics and Space Administration** — an increase of $1.7 billion, or 18.3 percent, more than 2010;
- about $1 billion for research and development at the **National Oceanic and Atmospheric Administration** and $2.6 billion — an increase of $439 million, or 21 percent — to the multi-agency **U.S. Global Change Research Program**;
- $1.2 billion (up 1.5 percent) for **Department of Veterans Affairs** research and development; and
- $429 million (up 63 percent) for the **National Institute of Food and Agriculture's** key competitive research program, the Agriculture Food and Research Initiative.

Peter Farnham (pfarnham@asbmb.org) is director of public affairs at ASBMB.

ASBMB Congressional Testimony on NSF

The American Society for Biochemistry and Molecular Biology was invited to provide a witness to testify on the administration's 2011 budget proposal for the National Science Foundation before the House Appropriations Subcommittee on Commerce, Justice and Science earlier this month. ASBMB had arranged for President Gregory Petsko to testify for the society. While the hearing was postponed due to the severe snowstorms that blanketed Washington, D.C., in early February, the testimony was submitted for inclusion in the hearing record. Here are excerpts. The full version is available on the ASBMB Web site.

President Petsko: "I am honored to be here to express our strong support for the president's request for the National Science Foundation for FY 2011. Because, in the overall budget, so many agencies and programs have received smaller increases than NSF's — or none at all — we are encouraged that the administration continues to demonstrate that it understands how important science is as an underpinning for this country's continued economic growth and prosperity. Nevertheless, we hope the Congress will view the president's request as a floor, not as a ceiling, when considering funding levels for the agency in the coming months.

"ASBMB considers NSF to be one of the most underfunded agencies in the Federal government….

"We are, of course, very appreciative that the president has proposed an almost 8 percent increase, almost $500 million, bringing the NSF budget to $7.424 billion. However, in a perfect world, we would like to see the budget increased to $7.68 billion, to conform to the recommendation of the Federation of American Societies for Experimental Biology. This would allow funding for several programs we believe need additional support...

"…we are pleased that the BIO Directorate goes up almost as much as the agency overall, because certain programs within BIO are even more underfunded than the agency as a whole.

"The chemistry division of the Mathematics & Physical Sciences Directorate fares somewhat less well, with the president proposing less than a 6 percent increase there. We hope Congress can make sure that this division gets a bit more money when the agency budget is finalized.

"…the two areas where we consider it vital that adjustments be made are in education and human resources and major research instrumentation.

"The president is proposing only a 2.2 percent increase for education and human resources in 2011. I don't need to go into the many reasons why science education is so important; these have been amply detailed in reports going back at least to the 1980s and "A Nation at Risk;" they have been most lately described in "Rising Above the Gathering Storm." It is sad that the problems so eloquently described in "A Nation at Risk" are still with us in large measure today. It is our hope that we, as a nation, can actually begin to provide a level of funding for science education that does justice to the eloquent titles of these reports. Speaking personally, I love doing research, but training the next generation of scientists is the most important thing I do.

"A second area where we have concern is the flat funding for the major research instrumentation program. Funding for advanced instrumentation in most universities is in serious trouble, as agencies struggle to maintain funding for research programs and cut back in other areas that are, unfortunately, exceptionally vital to a robust research enterprise. We hope Congress can address this problem as well."

TAIRing at Research

BY KYLE M. BROWN

Molecular biologists around the world have come to rely on actively curated genome databases of model organisms. But the National Science Foundation has decided to end its support for The *Arabidopsis* Information Resource, known as TAIR, and *Arabidopsis* and plant biochemists risk losing a vital resource. If the NSF's decision sets a precedent, Wormbase, Flybase and other databases may be similarly at risk.

Plantbase

"TAIR is where you go for plant genome science," said Rebekah Rogers, a Harvard doctoral candidate and former plant molecular biologist.

Like many similar databases, TAIR provides a host of information related to the genetics of the model plant *Arabidopsis thaliana*. At www.arabidopsis.org, TAIR users can find *Arabidopsis* genome information ranging from the very basic to the very applied, said Eva Huala, director and principal investigator of TAIR.

Like a Web-based library, TAIR's unique and integrated set of resources requires an active curatorial effort. The database and its 20 staff members have relied upon funding provided by the NSF for more than 10 years.

The genomic resources of TAIR have helped unlock the research potential of *Arabidopsis* for an entire community of researchers. TAIR has about 40,000 unique users each month from the Americas, Europe and Asia, and the average number of users each month has grown steadily since TAIR's founding.

But those who utilize the database often are interested in more than just *Arabidopsis*. "It's what everyone in plant biology uses, even in crop science," Rogers said.

A Community Shrinks

Having awarded TAIR two, five-year grants, the NSF in May 2009 declined to fully renew TAIR's funding. Instead, the NSF has granted TAIR an additional four years of steeply decreasing funding and encouraged the database to seek funding from other sources. By 2011, TAIR's NSF funding will cease.

The potential collapse of TAIR's funding threatens the field of plant genomics.

"The first people to go will be the computational biologists," Huala said. As these researchers rely upon publically accessible data, they are unlikely to pursue plant research if the information is not readily available. If computational biologists leave plant genomics, plant biology may fall behind animal research, Huala said.

Other biologists also may be driven away from plant research. Because it provides graphical, easy-to-use interfaces, TAIR gives researchers access to genome-based data without requiring them to write computer programs, Rogers said.

Innovation vs. Infrastructure

Continuing to fund research infrastructure often runs counter to the NSF's focus on funding innovative research. When a resource or program like TAIR ceases to be innovative, the NSF would like to use its limited budget in other places, Huala said.

Indeed, TAIR may have fallen victim to an emphasis on new innovations in sequencing technology.

"With the flood of genomic data, it may not be the best expenditure to put so many resources into a few species," said Scott Roy, a postdoctoral fellow at Stanford University. A computational biologist, Roy said model organisms may begin to occupy a smaller percentage of genome data that technological advances have made inexpensive to produce. However, the direction of the field is still uncertain, Roy said.

But, although financial resources may limit their numbers, genomic databases have "a tremendous utility to inform closely related genomes," Huala said.

Additionally, though new sequencing technology can produce staggering amounts of raw data, genome databases integrate sequence information with gene descriptions and relevant publications. Some databases also are repositories for unpublished data and minor comments that would not otherwise be available.

Without genome databases, "that kind of information would be lost," Rogers said.

The Future of Databases

Like other National Institutes of Health-funded projects, many genomics databases are supported by grants that must be renewed every several years. While the NIH continues to support several databases, the grants for two major databases, Flybase and *Saccharomyces* Genome Database, are up for renewal in 2011.

As for TAIR, Huala has discussed the situation with officials at the NIH in hopes that they might fund the database. Although conversations are ongoing, the NIH seems "reluctant to take on another model," Huala said.

For now, TAIR is exploring other funding sources, including corporate sponsorships. Huala said she believes requiring users or institutions to purchase subscriptions may drive away many academic researchers.

Kyle M. Brown (kmbrown@asbmb.org) is an ASBMB science policy fellow.

Highlights from the Blotter

The American Society for Biochemistry and Molecular Biology Policy Blotter posts regular news and commentary about current science policy issues. Below are some recent highlights. You can read them and other posts at http://asbmbpolicy.asbmb.org.

A Strong Science Budget, but NIH Heading for a Cliff (http://wp.me/pFLHF-3j)
In his annual budget request to Congress, President Obama recommended strong funding increases for many scientific agencies that support the life sciences.

NIH Needs $37 Billion in 2011 (http://wp.me/pFLHF-3g)
On Jan. 28, the Federation of American Societies for Experimental Biology and its member societies, including ASBMB, recommended the National Institutes of Health budget be increased to $37 billion during 2011.

Collins: Reinvigorate the Research Community (http://wp.me/pFLHF-2W)
Francis Collins, director of the National Institutes of Health, has given several interviews and authored a high-profile "policy forum" piece in the journal Science. In each case, he continued to encourage robust support for the NIH that he says will bring about great new societal benefits.

What Makes DARPA So Special? (http://wp.me/pFLHF-31)
On Jan. 7, at a meeting of the President's Council of Advisors on Science and Technology, officials from the Defense Advanced Research Project Agency presented what they believed were the characteristics of this defense-oriented research agency that have allowed it to innovate and succeed over its decades-long history.

ASBMB Creates the Stadtman Award

BY NICK ZAGORSKI

The new ASBMB award for "great basic science" honors the accomplishments of Earl and Thressa Stadtman.

From the moment they first set foot on the National Institutes of Health campus in 1950 as a young research couple, Earl and Thressa Stadtman set forth on a six decade journey of outstanding biochemical research and discovery.

Their efforts helped elucidate the role of coenzyme A in fatty acid metabolism, provide an understanding of reversible interconvertible enzyme cascades in cellular regulation and cell signaling via a detailed study of glutamine synthesis, uncover the biochemical roles of free radicals and reactive oxygen species and provide mechanistic insights into vitamin B12 biochemistry and the role of selenoproteins — a body of work that established them as one of the greatest scientific tandems in history.

Of all their great achievements at the bench, however, perhaps one of the strongest contributions the Stadtmans left to the science community is the body of more than 100 trainees they mentored — a group that includes a former director of Merck (P. Roy Vagelos), two Nobel laureates (Michael S. Brown and Stanley B. Prusiner) and countless other scientific luminaries — who owe their success to taking in Earl and Thressa's unique approach to training, known simply as "The Stadtman Way."

So, in honor of this first family of biochemistry (and in memory of Earl, who passed away on Jan. 7, 2008, at the age of 88), the American Society for Biochemistry and Molecular Biology will begin presenting the Earl and Thressa Stadtman Award at the 2011 annual meeting in Washington, D.C.

This award, which honors outstanding achievement in basic research in the fields encompassed by the ASBMB, was established by the Stadtmans' friends and colleagues as a way to give back some of their generous spirit and preserve their incredible legacies as scientists and mentors.

First announced during the Stadtman Symposium held in April in Bethesda, the award now has been finalized, and nominations for the inaugural recipient are ready to be taken.

Much like the diverse breadth of research that the Stadtmans carried out in their lab over their long careers, this award is open to a broad range of fields, so long as they fall under the category of "great basic science." Also, a unique feature of the Stadtman award is that the winner will alternate each year between an established researcher and young investigator, reflecting the assistance and advice the Stadtmans provided not just to their own trainees but to scientific colleagues of all ages.

In essence, the Stadtman award is a perfect embodiment of Earl and Thressa Stadtman.

The Award

The Earl and Thressa Stadtman Award recognizes a scientist for his or her outstanding achievement in basic research in the fields encompassed by the ASBMB. The award will be given annually and will alternate between an established scientist and a young investigator with 10 years or less of post-postdoctoral experience, including medical residency and fellowship. The established scientist will be honored as "The Earl and Thressa Stadtman Distinguished Scientist," and the younger investigator will be honored as "The Earl and Thressa Stadtman Scholar." Nominations must originate from an ASBMB member, but the nominee need not be an ASBMB member. The award consists of a plaque, a $10,000 cash award and travel expenses for the recipient and his or her spouse to the ASBMB annual meeting to present a lecture.

Nick Zagorski (nzagorski@asbmb.org) is a science writer at ASBMB.

ASBMB Introduces the DeLano Award

BY NICK ZAGORSKI

The memory of Warren L. DeLano will be honored with the ASBMB DeLano Award for Computational Biosciences.

Although the term "maestro" is generally confined to the musical arena, those who knew and worked with the late Warren L. DeLano would not be shy about applying this term to his skills with programming.

Perhaps most notably exemplified by PyMOL, an open-source tool for visualizing the three-dimensional structures of proteins and other biological molecules, DeLano, who died Nov. 3 at age 37, had a rare gift for designing computer programs that were complex yet accessible, technical yet elegant.

One of the key innovations of PyMOL, for example, was that it made the molecular visualization of complex biomolecular systems available to the average biologist. DeLano's program was the first of its type to use "click-and-drag" functionality to manipulate structures, allowing scientists to tinker with protein mutants and the configuration or chemical composition of bound ligands.

DeLano's legacy will live on through PyMOL, CNS (Crystallography and NMR system, a software suite to aid in structural determination), Phenix (Python-based Hierarchical Environment for Integrated Xtallography) and the numerous other computer programs he developed. There are few, if any, researchers in the world who work in the areas of structural or computational biology who do not owe a great deal to DeLano's advances.

The American Society for Biochemistry and Molecular Biology will further perpetuate DeLano's spirit by introducing the DeLano Award for Computational Biosciences in 2011. The award will be presented each year to an investigator who develops the most innovative computational tool or application that helps advance the field of molecular life sciences.

This award also will serve to recognize the growing importance of the field of computational biology. As biological disciplines continue to produce an abundance of complex information, whether it's continually higher-resolution, three-dimensional structures, real-time movies of cell activity or even whole genomes and proteomes, computers will become ever more critical in both storing and making sense of this data.

Importantly, the computational advance recognized by the award must be readily accessible to the scientific community; sharing and accessibility was one of DeLano's strongest beliefs. DeLano embraced the concept of open-source technology, making his programs and source code freely available to prospective users, enabling researchers to build on his developments.

This award was established with the help of ASBMB members Axel T. Brunger, professor of molecular and cellular physiology at Stanford University, and James A. Wells, professor and chairman of the department of pharmaceutical chemistry at the University of California, San Francisco. As DeLano's undergraduate and graduate advisers, respectively, Brunger and Wells experienced both his talents and bright personality firsthand and wanted some avenue through which to honor his impact. Together, they worked closely with DeLano's family to bring this ASBMB award to fruition.

Nick Zagorski (nzagorski@asbmb.org) is a science writer at ASBMB.

The Award

The DeLano Award for Computational Biosciences was established by family, friends and colleagues to honor the legacy of Warren L. DeLano. The award will be given to a scientist for the most accessible and innovative development or application of computer technology to enhance research in the life sciences at the molecular level. The contribution should include two key elements — more productive use of computers to accelerate and facilitate research and ready access of those programs by the scientific community. The award consists of a plaque, a $3,000 cash prize and travel expenses for the recipient to attend the ASBMB annual meeting to present a lecture.

asbmb member spotlight

Bandarian Honored with Pfizer Award

Vahe Bandarian, assistant professor of biochemistry and molecular biophysics and assistant professor of chemistry at the University of Arizona, has been named the recipient of the 2010 American Chemical Society Division of Biological Chemistry Pfizer Award in Enzyme Chemistry.

The award recognizes Bandarian's work on various aspects of the biosynthetic pathways for bacterial secondary metabolites. He and his colleagues undertook these studies to aid in understanding the pathways and chemical transformations that underlie the biosynthesis of these natural products, the mechanisms for the evolution of catalysts in these pathways and the broader issues involving evolution of secondary metabolic pathways in bacteria.

According to the ACS division of biological chemistry, "Professor Bandarian's work is a tour de force at the cutting edge of microbial bioinformatics, natural-product biosynthesis, metabolomics and the de-orphaning of open reading frames of unknown function."

Bandarian is especially noted for the identification and characterization of the gene cluster responsible for the production of the deazapurine natural products toyocamycin and sanguvamycin in *Streptomyces rimosus*. Although this class of compounds was discovered more than four decades ago, the biosynthetic pathways that produced them had remained elusive.

Silhavy Elected to GSA Board

Thomas J. Silhavy, Warner-Lambert/Parke-Davis professor of molecular biology at Princeton University, was recently elected to the 2010 Genetics Society of America board of directors. He took office on Jan. 1 and will remain on the board for three years.

"We have a terrific group of new officers and directors this year, and I am looking forward to working with them as we build on GSA's strengths and plan for our future. Their election to the board is a reflection of the esteem in which they are held by their peers and their commitment to serve the community," said GSA Executive Director Sherry Marts in a statement.

A bacteriologist, Silhavy is particularly interested in protein targeting and signal transduction in bacteria such as *E. coli.* He was the first to identify a component of the *E. coli* protein secretion machinery and the first to describe a "two-component system" — a major family of bacterial regulatory elements that sense a variety of environmental signals and transduce the information to transcriptionally regulate gene expression.

Penning to Receive NPA Award

Trevor M. Penning, professor of pharmacology, biochemistry and biophysics at the University of Pennsylvania School of Medicine, has been selected to receive the 2010 Distinguished Service Award from the National Postdoctoral Association. The award is given to an individual or entity that has demonstrated either a profound, sustained or leadership contribution to improving postdoctoral experience.

Penning, who is also director of the Center of Excellence in Environmental Toxicology at the University of Pennsylvania, will receive his award at the NPA's eighth annual meeting in March.

According to the NPA, Penning is "recognized in the postdoctoral community as a longtime advocate on behalf of postdoctoral scholars, both on the home and national fronts." He oversaw the formation of the postdoctoral office at the University of Pennsylvania School of Medicine and served as the director of the office of postdoctoral programs, associate dean for postdoctoral research training and director of biomedical postdoctoral programs. When the NPA was formed in 2001, Penning served on its first advisory board and played an influential role in guiding the nascent organization toward independence and national relevance.

Halpert Receives Brodie Award

James Halpert, professor and associate dean for scientific affairs at the Skaggs School of Pharmacy and Pharmaceutical Sciences, has been awarded the Bernard B. Brodie Award in Drug Metabolism for 2010.

The award is presented biennially to recognize outstanding original research contributions in drug metabolism and disposition, particularly those having a major impact on future research in the field. Named after the scientist known as "the father of modern drug metabolism," the award is sponsored by the American Society for Pharmacology and Experimental Therapeutics Division for Drug Metabolism.

For the past 30 years, Halpert's research has looked at the structure and function of mammalian cytochromes P450. Heterogeneity in the expression levels and/or activities of these important drug-metabolizing enzymes is a major determinant of individual response to medications and environmental toxicants. Because many of the failures in investigational drug development result from suboptimal pharmacokinetics, drug interactions and/or toxicity, methods for predicting cytochrome P450-mediated metabolism of new compounds are currently in great demand. Progress in this area is dependent on sophisticated understanding of the structural determinants and mechanisms of cytochrome P450 function, which Halpert has helped to elucidate.

Young Shares Jung Medical Award

Stephen G. Young, professor of medicine at the University of California, Los Angeles, has been named the recipient of the 2010 Ernst Jung Medical Award. He is being honored for his pioneering research on the mechanisms of lipid metabolism, particularly the elucidation of genetic defects in apolipoproteins, triglyceride-transport mechanisms and the role of farnesylated prelamin A in causing Hutchinson-Gilford progeria syndrome, a pediatric disease that leads to hair loss, heart attacks, strokes and other features of aging.

The Ernst Jung Medical Award, initiated in 1967 by Hamburg merchant and ship owner Ernst Jung and awarded since 1976, is given for pioneering research in medicine. Young shares the award with Peter Carmeliet of the Vesalius Research Center in Leuven, Belgium. As part of the award, both Young and Carmeliet will receive $215,000.

Past recipients of the Ernst Jung Medical Award have included Anthony S. Fauci, David D. Ho, Francis V. Chisari, Judah Folkman and Stuart A. Lipton.

IN MEMORIAM:

Gene A. Homandberg

Gene A. Homandberg, chair of the department of biochemistry and molecular biology at the University of North Dakota School of Medicine and Health Sciences, passed away on Dec. 21, at the age of 59.

An Iowa native, Homandberg pursued his education at the University of South Dakota, where he earned his Bachelor of Science degree in chemistry and a doctorate in biochemistry. He then served as a postdoctoral research associate in the department of chemistry at Purdue University and later at the National Institutes of Health National Institute of Arthritis, Metabolic and Digestive Disorders.

In 1984, Homandberg became an assistant professor at the University of Wisconsin School of Medicine and Public Health and was promoted to associate professor in 1986. He then joined Abbott Laboratories as a senior biochemist and worked there for two years before becoming a professor of biochemistry at Rush Medical College. He eventually was promoted to the Dr. Ralph and Marian C. Falk professor of biochemistry endowed chair. In 2002, Homandberg moved to the University of North Dakota and became the William Cornatzer chair in biochemistry.

Homandberg was a highly recognized researcher in osteoarthritis and cartilage physiology, and, in 1999, he was awarded permanent membership in the Frontiers in Bioscience Society of Scientists, based on his work in the regulation of cartilage metabolism in osteoarthritis.

Raines Wins Repligen Award

Ronald T. Raines, Henry Lardy professor of biochemistry and professor of chemistry at the University of Wisconsin-Madison, is the recipient of the 2010 Repligen Award in Biological Chemistry. This lifetime achievement award, given annually by the American Chemical Society, recognizes outstanding contributions to the understanding of the chemistry of biological processes, with particular emphasis on structure, function and mechanism. Raines is the 25th winner of the Repligen Award.

The award honors Raines and his contributions and wide-ranging impact on science at the interface of chemistry and biology. His efforts have led to both understanding and real-world applications. He has provided fundamental insight on the stability of collagen, leading him to discover a new force — the $n \rightarrow \pi^*$ interaction— that contributes to the conformational stability of nearly every protein. Raines discovered how to convert a human ribonuclease into a toxin with specificity for cancer cells. His ribonuclease is in a human clinical trial as an anti-cancer agent. Raines also has provided mechanistic insight on cellular-redox homeostasis. Finally, he has developed chemical processes to synthesize proteins and convert biomass into useful fuels and chemicals.

IN MEMORIAM:

James B. Peter

James B. Peter, founder of Specialty Laboratories Inc., died on Oct. 30. He was 76.

A native of Omaha, Neb., Peter earned his medical degree from St. Louis University in 1958. He then went to the University of Minnesota, where he earned a doctorate in biochemistry in 1963, working with Paul D. Boyer. Peter then joined the faculty of the University of California, Los Angeles, where he served as professor, clinical professor and College of Letters and Sciences advisory board member.

In 1975, Peter founded Clinical Immunologies Inc. with the mission to "help doctors help patients." His hope was to bring modern biochemistry and immunology to the clinical laboratory marketplace. By the mid-1980s, the company had become Specialty Laboratories Inc., and Peter had created a unique niche in the lab industry. He and his scientific team developed a constant flow of proprietary esoteric tests and assays. In 2006, Specialty Laboratories was acquired by AmeriPath Inc., which was subsequently acquired by Quest Diagnostics in 2007.

Peter also founded the Specialty Family Foundation in 2006 with a mission to help ensure a Catholic education for demographically disadvantaged children. In addition to its focus on education, the foundation is involved in researching methods to support people with alcohol and substance abuse problems.

Retrospective: Paul C. Zamecnik (1912–2009)

BY ARTHUR B. PARDEE

Paul C. Zamecnik, senior scientist at Massachusetts General Hospital and professor emeritus of oncologic medicine at Harvard Medical School, was among the most important biochemical scientists of the 20th century. He passed away Oct. 27, 2009, at the age of 96.

Paul received his undergraduate degree from Dartmouth College in 1933, majoring in chemistry and zoology. He obtained his medical degree from Harvard Medical School in 1936 and followed it with internships at Huntington Memorial Hospital in Boston and Lakeside Hospital in Cleveland, Ohio. During his Lakeside Hospital internship, Paul was awarded a Finney-Howell Fellowship and a Moseley Traveling Fellowship to go to the Carlsberg Laboratory in Copenhagen, where he worked with Kaj Linderstrom-Lang. After he returned to the United States, Paul worked at the Rockefeller Institute for Medical Research in New York for two years, studying protein synthesis with Max Bergmann. He returned to Cambridge, Mass., in 1942 to join the faculty of medicine at Harvard Medical School and established his laboratory at Massachusetts General Hospital.

At Harvard, Paul worked with Fritz Lipmann, and the pair subsequently shared the Massachusetts General Hospital's Warren Triennial Prize for their seminal study on the mechanism of action of clostridium α-toxin. In 1956, Paul became the Collis P. Huntington professor of oncologic medicine at Harvard Medical School, and he remained in that position until his retirement in 1979, after which he continued at the Worcester Foundation for Biomedical Research.

In the 1950s, Paul elucidated, through the development of cell-free systems, the biochemistry of protein synthesis. He and colleagues Philip Siekevitz, Robert B. Loftfield, Mahlon Hoagland and Mary Stephenson showed that ATP is necessary for amino acid activation leading to peptide bond formation, which, therefore, is not a reversal of proteolysis. They discovered transfer RNAs and showed that the linkage of amino acids to these small RNAs was the penultimate step of polypeptide synthesis. Paul's group was also the first to identify the ribosome as the site of protein synthesis.

After that breakthrough, Paul continued to perform outstanding research. His RNA sequencing revealed that Rous sarcoma virus RNA has a 3′-OH tail of poly(A) bounded by a sequence that is identical to one at the 5′ end, suggesting that a cDNA-mediated circularization might occur during reverse transcription. A 13-mer oligodeoxynucleotide complementary to the terminus of RSV inhibited both the translation of viral mRNA in a cell-free system and virus replication. He showed that inhibition depends on both the ability of deoxynucleotides to enter intact cells and on Watson-Crick base pairing. His pioneering studies on antisense DNA and its inhibitory activity arose from that work. Antisense oligonucleotides immediately became important research tools for experimentally silencing gene expression. Those papers launched the era of antisense DNA. He applied those concepts to medicine, targeting the tuberculosis bacterium and the defective cystic fibrosis gene. Paul is regarded as the founder of the antisense therapy field.

Paul's wife of 69 years, Mary Connor, died in 2005. He leaves daughters Karen Pierson and Elizabeth Coakley, son John, seven grandchildren and two great-grandchildren.

Paul's major "side interest" was the company and conversation of interesting people. He learned to ski at Dartmouth and enjoyed skiing every winter. He was a good swimmer and tennis player. Later in life, he and Mary went to St. John in the Virgin Islands, where he loved to swim and snorkle. When he no longer partici-

pated in sports, he enjoyed watching football, basketball and tennis and knew all the players and their quirks.

On a personal note, my first correspondence with Paul led to his pointing out that I should spell his name correctly, but he forgave me for that. In recent years, we discussed science and enjoyed evenings dining at his club, the Somerset, in Boston. A word that characterizes Paul is devoted: As a scientist, he was devoted to ideas and his research, and, as a person, he was devoted to his friends. He was a true gentleman — friendly, sincere and straightforward.

Paul will be sorely missed by friends and colleagues, several of whom have provided reflections below.

By the 1970s, I had come to know Paul Zamecnik from various RNA meetings, and, in 1979, I suggested we collaborate to use psoralen-mediated nucleic acid cross-linking in living cells (which my lab had perfected) to prove to skeptics that his antisense oligodeoxynucleotides that were inhibiting translation were indeed doing so via hybridization with mRNA. We didn't do the experiment and, in retrospect, I suspect he had not been as bothered by the "skeptics" as I had been, which says much about his legendary determination and confidence in his results.

Our years as colleagues at the Worcester Foundation (1979–1997) were delightful. In early December each year, he would send me a handwritten note with the expressed "hope" that I (the director) would not mind if he and his wife took a short holiday vacation. Being Paul's "boss" was a comical situation that amused us both, but those notes were so typical of his manner (and manners). He was a persistent fountain of ideas to us all, a caring mentor to young faculty, a delightful lunchtime raconteur and, of course, a living history of science textbook.

Blessed with extraordinary prescience, Paul Zamecnik was an experimentalist of uncommon talent who transformed the modern era of biochemistry. That he was also a gentleman brought the two strands of his being into helical harmony.

Thoru Pederson
Vitold Arnett professor of biochemistry and molecular pharmacology
University of Massachusetts Medical School

I knew Paul Zamecnik for most of his scientific career, but my closest interactions with him occurred after he returned to the Massachusetts General Hospital and its cancer center in 1997. We discussed his ongoing research about applying the antisense technology that he developed years earlier. He was using in vitro systems to repair the genetic mutation in cystic fibrosis, to block cell wall synthesis in Mycobacterium tuberculosis and to target antibiotics to specific ribosome sites.

In some of our conversations, he reflected on the times after he discovered tRNA and lamented that he probably should not have taken time off in the early 1960s for a sabbatical with Sir Alexander Todd in Cambridge. When he returned to Boston, he found that the scientific floodgates had been opened by many others, including Marshall W. Nirenberg, Heinrich Matthaei, Robert W. Holley and Har Gobind Khorana. He told me, "I felt as if I was left standing on Mont-Saint-Michel while the incoming tide roared past me."

I visited with him frequently in his final days and hours. Even as the curtain was falling, his utterings included phrases such as "Shine-Delgarno sequences" and "ribosome-binding sites." Paul Zamecnik was a remarkably kind, generous, gracious and humble person whose greatest pleasure was scientific discovery.

Kurt J. Isselbacher
Distinguished Mallinckrodt professor of medicine
Harvard Medical School

The Massachusetts General Hospital found room for Paul Zamecnik for more than 20 years in the '60s and '70s. In an enclave in a research building, Paul and his group did their diligent work on cell-free protein synthesis, on the ribosome and transfer RNA, and on other major insights of the early molecular era. Although their laboratories were in a nonclinical area, the scientists could only reach it by passing through the Bulfinch Building, the heart and home of the medical service. This guaranteed interaction and consultation between true basic scientists and the clinicians trying to cope with cancer and similarly poorly understood disorders, and mutual enlightenment was inevitable. The geographical propinquity correlated with Walter Bauer's design of keeping basic scientists and clinicians working together. And it succeeded because of Zamecnik's medical training, his prior clinical experience in a cancer hospital, his scientific brilliance and his approachability.

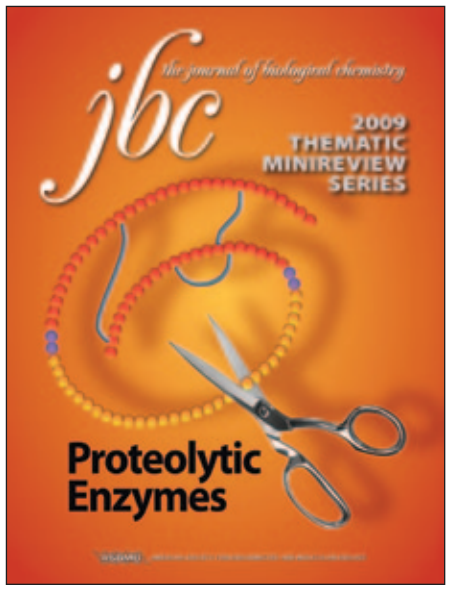
Daniel D. Federman
Carl W. Walter distinguished professor of medicine
Harvard Medical School

Arthur B. Pardee (arthur_pardee@dfci.harvard.edu) is a professor emeritus of biological chemistry and molecular pharmacology at the Dana-Farber Cancer Institute and Harvard University.

JBC Thematic Series Breaks Down Proteases

BY NICK ZAGORSKI

In October 1905, Phoebus Aaron Levene published an article titled "The Cleavage Products of Proteoses" in the very first issue of the Journal of Biological Chemistry. This set the stage for more than 100 years of protease-related research in the journal.



It is perhaps fitting that proteases appeared in the JBC so early on, as proteases are themselves likely one of the earliest enzymes to appear in protein evolution, catabolizing other proteins to generate the amino acids necessary for primitive organisms.

Of course, as a century of research appearing in the JBC and other journals has shown, proteases are more than mere random protein destroyers. These ancient enzymes, which are found in all organisms, from viruses to humans, catalyze a wide range of highly specific reactions that are responsible for modulating protein-protein interactions, creating new bioactive molecules, processing cellular information and regulating molecular signals. As a result of their multiple roles, proteases are involved in almost every physiological process including DNA replication, cell proliferation, tissue morphogenesis, fertilization, wound repair and inflammation.

That's why, in spite of their long history, proteases remain at the cutting edge of biological research today. And that's also why the JBC decided to run a comprehensive minireview series covering these diverse, complex and, ultimately, invaluable proteins.

Started in the journal in May 2009, the thematic series "Proteolytic Enzymes," coordinated by JBC Associate Editor Judith S. Bond, brings together 10 minireview articles that encompass a broad range of topics and many familiar names in the protease community.

Together, these minireviews, and an introductory article written by Bond and Carlos López-Ótin, provide insight into the world of proteases, including the details of their structure, enzymatic activity and regulation. The articles also provide a look back at the molecular evolution of proteases and a look forward at the frontiers of protease research, including studies into the proteolytic regulation of transcription factor activity and protein ectodomain shedding.

Among the minireviews included in the series are a detailed overview of the 26S proteasome by Ami Navon and Aaron Ciechanover; a review of our current knowledge of human caspases written by Cristina Pop and Guy S. Salvesen; a look at the exosite requirements of serpin specificity by Peter G. W. Gettins and Steven T. Olson; a review of the structural and mechanistic features of intramembrane-cleaving proteases by Michael S. Wolfe and a discussion of the proteolytic regulation of epithelial sodium channels by Thomas R. Kleyman and colleagues.

The thematic minireview series provides a valuable overview of the family of protein sculptors known as proteases that decisively influence the rhythms of cell life and death in all living organisms.

Nick Zagorski (nzagorski@asbmb.org) is a science writer at ASBMB.

For more information:

The JBC minireview series "Proteolytic Enzymes" can be found online at www.jbc.org/site/thematics/proteolytic_enzymes, where it is also available for print purchase.

Professional Development at the Annual Meeting

The American Society for Biochemistry and Molecular Biology's annual meeting in Anaheim, Calif., is only a month away. In addition to a great scientific program, we've planned several events that are geared toward the professional development of young scientists — undergraduate students, graduate students and postdoctoral fellows.

14th Annual ASBMB Undergraduate Student Poster Competition

Now in its 14th year, this poster competition provides an opportunity for undergraduate students to showcase their research. The event, which will be held from 1 p.m. to 4:30 p.m. Saturday, April 24, is a great way to meet fellow undergraduate attendees and to make friends and contacts before the meeting starts. The poster session also will have a networking break during which students can visit with prospective graduate school representatives. Prizes for the best posters will be awarded Sunday, April 25, at the ASBMB Award for Exemplary Contributions to Education lecture.

Careers in Biochemistry and Molecular Biology: A World of Options, a Variety of Skills

The lectures in these symposia, sponsored by the ASBMB Education and Professional Development Committee, will occur from Saturday, April 24, through Tuesday, April 27. The lectures cover a variety of topics, including the skills that employers are looking for and tips for grant writing. The symposia also feature a panel on biochemistry and molecular biology careers and a career workshop for undergraduate students.

Graduate/Postdoctoral and Graduate Minority Travel Award Symposium

This event begins at 5 p.m. Friday, April 23, with a keynote lecture titled "Adventures in a Scientific Career: Juggling Research, Teaching and Real Life" by Graham C. Walker of the Massachusetts Institute of Technology. This will be followed by a poster session in which all ASBMB travel award recipients will present their work.

Graduate and Postdoctoral Professional Development Program*

Back for a third year, this popular program will be held from 9 a.m. to 4:30 p.m. Saturday, April 24. It will feature a morning panel on such careers as teaching, patent law and science writing, a networking luncheon and afternoon workshops that address issues particular to graduate students and postdoctoral fellows.

Minority Scientists' Welcome Reception

This year, the ASBMB Minority Affairs Committee is hosting a welcome reception from 6 p.m. to 8 p.m. Sunday, April 25, after the afternoon symposia. Primary investigators, industry professionals, educators, young professionals and students are welcome to attend this networking and mentoring event for discussions on various topics such as career opportunities, mentoring options and issues facing minority scientists.

Naturally Obsessed: The Making of a Scientist

ASBMB will present a special screening of the hit movie, "Naturally Obsessed: the Making of a Scientist" at 6:30 p.m. Monday, April 26. The documentary follows a group of eager students, mentored by Larry Shapiro, along a challenging and uncertain journey toward getting their doctoral degrees. The film was shot over three years' time at Columbia University Medical Center and also documents how X-ray crystallography enables the discovery of the molecular structure of AMP-activated protein kinase, considered prime for targeted drug development because of its relevance to diabetes and obesity.

Research Funding by the American Cancer Society

At 12:30 p.m. Monday, April 26, Charles Saxe, American Cancer Society program director in cancer cell biology and metastasis, will describe the research grant mechanisms available at the ACS and how to best approach the application process. A peer review committee member and a grantee also will be present to provide further insights and to field questions.

Talk with the Editors: New Guidelines for Publishing in the JBC

The Journal of Biological Chemistry is hosting a discussion at 12:30 p.m. Sunday, April 25, for people interested in learning about the Journal of Biological Chemistry review guideline changes and how they affect submissions to the journal.

Women Scientists' Panel and Networking Reception

Join fellow women biochemists and molecular biologists at 6:30 p.m. Tuesday, April 27, for a panel discussion on the gender gap and its impact in the field of science. A reception will follow for informal discussion and networking.

**Registration required.*

For more information:

- Times and locations for annual meeting events: www.asbmb.org/meeting2010
- A podcast interview with Larry Shapiro, the subject of "Naturally Obsessed": www.asbmb.org/audio.aspx

Jerry Lingrel: Pumping Out Great Science

BY NICK ZAGORSKI

For Jerry B. Lingrel, a distinguished professor in the department of molecular genetics, biochemistry and microbiology at the University of Cincinnati and an associate editor for the Journal of Biological Chemistry, great science is in the blood.

Not that Lingrel comes from a strong scientific pedigree — to the contrary, he was just a small-town Midwestern boy whose desire to pursue a career in science was encouraged by his parents — but rather that Lingrel has made a living studying this vital fluid. From his early breakthrough in isolating and characterizing globin messenger RNA to his subsequent work sequencing the sodium-potassium pump (Na,K-ATPase) and studying its role in regulating blood pressure to his discovery of Krüppel-like factor 2, a transcription factor that, among other things, maintains blood vessel integrity; Lingrel's science revolves around blood.

And, it all began not by design but simply by convenience.

In 1968, shortly after Lingrel, an Ohio native, had returned home to begin a professorship at the University of Cincinnati after a postdoctoral fellowship at the California Institute of Technology, he decided to focus on the messenger RNA that encoded the proteins involved in protein synthesis.

As he recalls, mRNAs were sort of a "black box" at that time, about a decade after their initial discovery. "They had been identified in bacteria," Lingrel says, "and everyone believed they were present in eukaryotic cells as well. But, it was still a lot of theory because no one had managed to isolate an individual mRNA that coded for a specific protein."

Lingrel wasn't sure if it would be feasible to isolate mRNAs, but he figured, "If I want to give myself a chance, I might as well find a system where mRNA is abundant."

That's where blood came in to the picture. During his postdoc at Caltech with Henry Borsook, a pioneer in protein synthesis studies, Lingrel had worked extensively with reticulocytes (immature red blood cells), which were an ideal model system: As hemoglobin factories, all they basically do is churn out globin chains all day long.

By that same token, Lingrel figured reticulocytes should contain a vast amount of α and β globin mRNAs. To isolate these mRNAs, he thought that using an *Escherichia coli* cell-free translating system, similar to that employed by Marshall Nirenberg to crack the genetic code, would be a reasonable approach; Lingrel would add different fractions of total mouse reticulocyte RNA to extracts of *E. coli* translation machinery and see which ones produced globins.

Of course, his initial attempts didn't bear fruit, and he jokes, "It was not the most ideal way to discover that there are significant differences between bacterial and eukaryotic protein synthesis."

However, when he changed his approach and used a cell-free translation system from rabbit reticulocytes, he achieved success and identified a 9 S RNA that resulted in the synthesis of both α and β globin. In doing this, he identified and translated the first mammalian messenger RNA.

Over the next few years, Lingrel and his lab would further characterize globin mRNA, uncovering many of the key features we know about these transcripts, including their 5′ CAP structure and 3′ poly-A tail as well as the fact that mature mRNAs in the cytoplasm arose from larger precursor RNA molecules in the nucleus. Through his approach, which he shared with many colleagues, globin synthesis became the model in which to study mRNA structure and translation.

No Tension Here

As the 1970s progressed, Lingrel continued his work with globins. Having made complementary DNA to his isolated mRNA, he was able to identify and clone globin genes from a variety of mammalian cells and study both the changes in globin expression during development and

Jerry Lingrel's science revolves around blood.
PHOTO BY DAN DAVENPORT, UNIVERSITY OF CINCINNATI AHC.

the evolution of the globin gene family.

Then, in 1976, the University of Cincinnati's microbiology department hired a new faculty member, Dennis Lang, who ended up becoming one of Lingrel's neighbors. Given their similar destination, the two ended up carpooling on numerous occasions. And through this ridesharing, Lingrel was introduced to another molecular black box: the Na,K-ATPase, which pumps potassium into and sodium out of a cell.

"Lang had done his graduate studies under Efraim Racker at Cornell, who was a leading expert on the Na,K-ATPase," Lingrel says, "and, during our rides, he kept telling me how important this enzyme was in biology. So, one day I asked him what they knew about the ATPase structure, and he responded that they didn't even know the amino acid sequence yet."

That sparked an idea: Lingrel admittedly knew very little about transport proteins, but what he did know was molecular cloning.

"I thought to myself: Oh, our lab could handle that; and if this ATPase is as important as Lang believes, then sequencing and characterizing it would be a tremendous advance to science."

Working with membrane proteins would be tricky, but Lingrel always has operated with a simple belief: If you take the time to think about a problem and pick the right system to work on it, there's no reason a project should not work. So, he picked sheep kidney cells, an abundant source of Na,K-ATPase, and, together with a very talented postdoc, Gary Shull, he managed to isolate ATPase mRNA, make cDNA clones, decipher the amino acid sequence for the α and β subunits and identify important residues for pump activity.

"It ended up that we published our ATPase sequence in the exact same issue of Nature that David MacLennan reported his sequence for the calcium ATPase," Lingrel says. "So, in one day, we managed to open up a whole new era in the study of ion transport proteins."

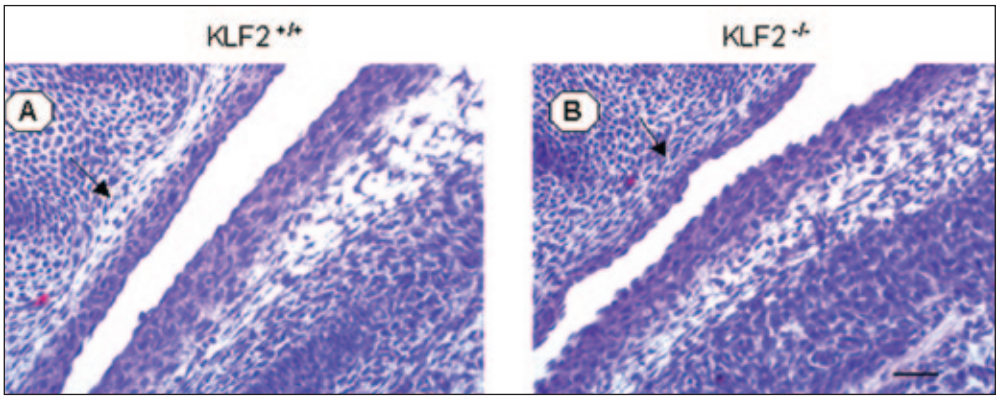
Lingrel would go on to make countless more discoveries regarding Na,K-ATPase, including showing that the catalytic α subunit had four separate isoforms which contributed to the numerous functions the pump had throughout the body. For example, the α4 isoform is found exclusively in sperm and helps sperm cells move, whereas the α2 and α3 isoforms are highly expressed in brain cells and produce learning deficiencies when knocked out in mice.

Some of his most valued work, however, involves the central role of the ATPase in sodium transport in hypertension.

It long had been known that steroid-like compounds like ouabain and digitoxin (both derived from plants) could block the Na,K-ATPase and, thus, force increased heart contractions, a fact that was used to develop similar compounds as treatments for congestive heart failure (though they are no longer widely used, as better drugs such as angiotensin-converting enzyme (ACE) inhibitors have come along).

However, some controversy also developed, as evidence seemed to suggest that animals produced their own ouabain-like steroids to modulate Na,K-ATPase activity (so-called endogenous ouabains). As Lingrel notes, while several studies had shown the presence of ouabain in normal blood samples, it was extremely difficult to prove that they had been synthesized in the body. "And, from a logical standpoint, people wondered why the human body would want to synthesize ouabain, which is a toxic molecule," Lingrel says.

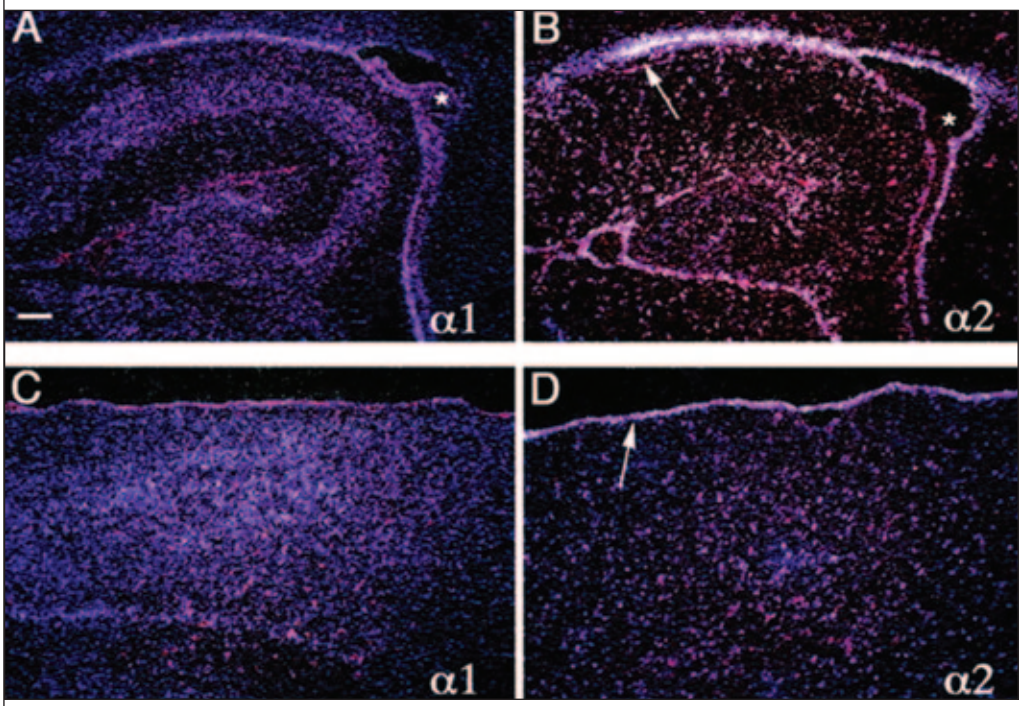
On the other hand, comparative work done by Lingrel's team found that the binding site for ouabain and similar drugs in the Na,K-ATPase α subunit was heavily conserved from fruit flies to humans, which would support a physiological role, and, by extrapolation, a physiological ligand.



Jerry Lingrel's group recently has shown that KLF2 is involved in making blood vessels. Here, stained sagittal sections of wild type (A) and knock-out (B) mouse aorta highlight the vascular defects that occur when KLF2 is deficient. Wu, J., Bohanan, C. S., Neumann, J. C., and Lingrel, J. B., *J. Biol. Chem.* (2008) **283**, 3942–3950.

"So, we decided to work on this mystery, but, rather than focus on the compounds, we decided to focus on the binding site." His reasoning was based on the interesting observation that one of the four mouse α subunit isoforms (α1) happened to be resistant to ouabain. So, he mutated two amino acids in the α2 isoform (the major vascular form), so it resembled α1 in one group of mice and altered α1 so it resembled α2 in another group. He then induced stress in the mice to see what happened.

"Sure enough, the mice that contained the mutated α2 were resistant to hypertension," Lingrel says, "whereas the animals that had the altered α1 almost blew up because they became so hypertensive." That seemed to confirm that the ouabain binding site was physiologically important in regulating blood pressure, and something in the blood was interacting with it. Lingrel is currently collaborating with some colleagues at the University of Cincinnati to try to find that elusive endogenous ligand.



Jerry Lingrel recently has discovered a role for Na,K-ATPase in the brain, as highlighted by this in situ mRNA hybridization analysis of the ion transporter's α1 and α2 isoforms in developing mouse brains; A and B show sections through the hippocampus, with the star highlighting robust expression for α1 but not α2 in the choroid plexus, whereas the arrow highlights the more intense α2 presence in the ependymal lining. C and D show sections through the cortex, with the arrow highlighting the strong expression of α2 in the pia mater. Moseley, A. E. et al, *J. Biol. Chem.* (2003) **278**, 5317–5324.

Low-stress Levels

In some ways, Lingrel is still the curious, small-town Midwestern boy who was fascinated with science and nature. Some of it may arise from the fact that he never really left Ohio. Except for his two-year postdoc at Caltech and a one-year sabbatical at the MRC laboratory in Cambridge, England, Lingrel has been a steady fixture in the Buckeye state, from growing up in Byhalia, to his college years at Otterbein College in Westerville, to his graduate studies at The Ohio State University and finally his long and impressive professorship at the University of Cincinnati.

It's that continued connection with his youth,

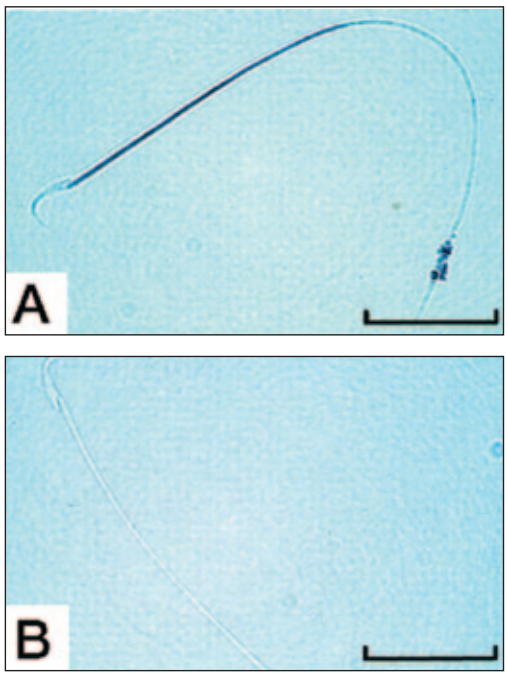
spending countless hours trying to understand how things work, that has shaped his research path, be it his globin or Na,K-ATPase studies, or even his more recent foray into KLF2 (Krüppel-like factor).

These studies began as an offshoot of his research with globin expression, but, as in the case of the Na,K-ATPase, Lingrel notes, "I've managed to make second careers out of what I thought would just be side projects."

Other researchers had discovered a transcription factor, called the erythroid Krüppel-like factor, that was critical in orchestrating the switch from fetal to adult hemoglobin expression, and Lingrel used some cDNA from EKLF as a clone to screen for other proteins that bound to hemoglobin genes.

What he uncovered was not just a protein that shared a similar gene-binding region, but one that closely resembled EKLF, ushering in a new Krüppel-like protein family.

He named this new transcription factor LKLF (for lung Krüppel-like factor, although it was later renamed KLF2) and began pursuing its role. He found that it was vital for proper development of the lung and other tissues in embryos but also had a role in the formation, maturation and integrity of blood vessels.



One of Jerry Lingrel's many discoveries regarding Na,K-ATPase was uncovering the sperm-specific α4 isoform, revealed in A as being localized to the midpiece region of the flagellum. B shows a control sperm with only secondary antibody staining. Woo, A. L., et al. *J. Biol. Chem.* (2000) 275, 20693–20699.

The most interesting aspect of KLF2 function, though, was that it was induced in endothelial cells by fluid shear stress. "That caught my eye," Lingrel says, "because it's in areas of low-shear stress, like bifurcations, where you get plaque buildups and atherosclerosis; so KLF2 might be an atheroprotective agent." His group is currently developing transgenic mice that overexpress KLF2 in low-stress areas and testing their resistance to plaque buildup when fed a high-fat diet.

Lingrel is thrilled that his work has helped so many other scientists. Although he's focused primarily on the vascular system, both KLF2 and the Na,K-ATPase are fairly ubiquitous, and his fundamental discoveries are applicable to areas like muscle activity, neuroscience and development. And, not surprisingly, he's been flooded with requests for advice or one of his many transgenic mouse lines, which he's always happy to oblige.

One cannot help but wonder whether it's perfectly fitting or somewhat ironic that this calm and contented man is revealing the mechanisms of atherosclerosis and hypertension.

Out of Focus: A Little Less Conversation, A Little More Science

Jerry Lingrel's sabbatical with John Gurdon at the MRC laboratory was a fantastic experience, although it did take a while to adjust to local customs. "The scientists there loved to socialize," he says. "They talked over morning coffee, lunch and afternoon tea." At first, Lingrel didn't join the fun – "I thought I was here to work not talk" — but he eventually got hooked. "I had so much fun talking to all the great scientific minds at the MRC about ideas and techniques, and soon I understood why experiments never seemed to fail there." However, Lingrel ended up becoming such the social butterfly during the day that he had to come back to lab every night to do the actual experiments.

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Teaching "From Proposal to Publication"

BY J. ELLIS BELL

There is no one way to teach science; what works in one setting may not work in another. In the past four or five years, there has been much talk about "teaching science the way you do science." In a policy forum article published in the journal Science in 2004 (1), Jo Handelsman and co-authors wrote, "There is mounting evidence that supplementing or replacing lectures with active learning strategies and engaging students in discovery and scientific process improves learning and retention of knowledge." Since then, many scientific societies have included sessions with similar titles in their annual meetings, but little has been written about how to translate this approach into formal courses. For a while now, it has been recognized that undergraduate research opportunities play a crucial role in undergraduate education, but only a few colleges and universities give their students real research experiences by requiring full-time, year long laboratory research and a senior thesis.

> **"'There is mounting evidence that supplementing or replacing lectures with active learning strategies and engaging students in discovery and scientific process improves learning and retention of knowledge.'"**

So, how do we "do science," and what is a "real research" experience? And, how can we realistically teach science the way we do science in the context of a four-year undergraduate education?

Searching for Scientific Teaching

I recently Googled "How do we do science?" and found an interesting site (http://bit.ly/bL6DbC) that listed things we can do to teach children about science. I also Googled "What is real research?" and found another site (http://bit.ly/94epsx) that explained that research begins with questions, not answers. While both Web sites contained some information that was potentially useful, neither provided me with much satisfaction. So, I went to PubMed and tried various combinations of the terms I was looking for. I found some information about teaching medical and nursing school, but still no luck. Finally, I looked at two major education journals in molecular life sciences — CBE Life Sciences Education (http://www.lifescied.org) and Biochemistry and Molecular Biology Education (http://bit.ly/9dTntB) — and found some decent answers.

Interestingly, during my searches, I was not able to find the Science article referred to at the beginning of this article. Even a PubMed search with the paper's title turned up 54,943 results, which effectively buried the actual reference I was looking for. The only easy way for me to find the article was with an advanced search using the author's name and the article's title. My conclusion: It's not easy to find the answers to the questions "How do we do science?" and "What is real research?" if you don't know where to look.

Doing Science

So, how do we do science, and what is a real research experience?

1. The Question.

Students need to learn that, to do science, they have to build on what they already know. Knowledge may come from an observation or from reading scientific literature. Either way, this knowledge leads to a question, and one of the first things that scientists do is find out whether anyone else has asked (and possibly answered) the question. If the question has been answered satisfactorily, the scientist moves on and lets his or her curiosity loose again. If it hasn't been answered, then he or she develops a hypothesis and starts thinking of experiments to investigate the hypothesis.

2. Designing Experiments.

In designing experiments, it is important that students understand the limitations of their approaches and how

to interpret their data. They also should understand that writing a proposal is an integral part of doing science. In the "real" world of research, the proposal both convinces people that the scientist knows what he or she is talking about and allows him or her to get the resources necessary to do the experiments. If done right, proposal writing involves drafts, feedback and revisions. Most undergraduates, however, never get to do this in a meaningful way. Often you hear faculty advisers saying, "I don't want them wasting their time writing a proposal when I need them to be in the lab doing experiments."

3. Doing Experiments.

Doing the experiments is, of course, an important part of the whole process, and, for undergraduates, it is an exciting part of their education which could act as motivation for further work in the sciences. A critical part of this is, of course, analyzing and interpreting the data appropriately. Depending on the experiment, this will involve statistical analysis, the use of a variety of computer programs and an understanding of the limitations of what the data can tell. Real data are the only type of data that can accomplish this — much of the "data" that we provide to students in the classroom as problem sets are not real data; instead, they are often simulated data designed to illustrate a point and not let a student struggle with the analysis and interpretation that is an integral part of research.

Once the experiments are finished and the data analyzed and interpreted, presenting the project is a very important part of the scientific process, and plays a central role in "doing science." The time it takes to put together a good presentation or report is, in many ways, the counterpoint to putting together a good proposal. The ultimate "presentation" is publication in peer-reviewed literature. Increasingly, undergraduate students do put together poster presentations and occasionally are invited to give short talks at professional meetings, but this is a privilege reserved for a few students and not something that is incorporated into everyone's educational experience. Very few undergraduates even get to write the first drafts of papers that will be submitted to peer-reviewed journals, despite the fact that such an activity would provide a tremendous education.

Teaching Real Science

Many of the things that are central to real research are not the things we are getting undergraduates to do. If we want to use "real" research in teaching and also "teach science the way we do science," we need to radically rethink how we involve undergraduates in research activities and how we incorporate research activities into formal class work. We need to think creatively about how we can meaningfully incorporate primary literature into our courses and how we can engage students in hypothesis building and testing and proposal writing. Perhaps we could teach courses with titles like "From Proposal to Publication" to our first-year biology and chemistry students and focus on research skills rather than memorizing facts. Or, we could at least downplay memorization and introduce the facts in a research environment rather than classroom context. If we taught courses this way, our students would have a better chance of acquiring the skills essential to "real" research and a better understanding of how we "do science."

For more information:

- The University of Montana's Integrated Biological Science Courses Organized around Research Experience Project (IBSCORE) (http://ibscore.dbs.umt.edu)
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Mentoring Is a Primary Responsibility

BY PHILLIP ORTIZ

The American Society for Biochemistry and Molecular Biology's Minority Affairs Committee has several missions. One of them is fostering the development of scientists. We think this is important for a number of reasons.

First, funding often is directed toward research areas where there is "interest." For too long, too little money has been allotted to topics of interest to women and people of color — for example, hypertension, breast cancer and diabetes. By enhancing education and increasing the number of women and people of color who are professionals, we hope that these topics will begin to receive the funding they merit. Second, we believe in social justice — for too long, too few people controlled the gates of higher education. This has led to patterns in which only a subset of America has access to education and professional employment.

One of the ways the MAC fosters the development of scientists is by engaging in and encouraging mentoring. For example, at the ASBMB annual meeting in April, we will be hosting a symposium on mentoring, during which four speakers will address such issues as mentoring women and nontraditional students, mentorship from undergrad until tenure and working with mentees at a distance.

Along those lines, I'd like to use this column to do some mentoring. In my experience, many graduating students will be unprepared for the challenges that lie ahead. This problem is not new or unknown, but, it is too often ignored.

The Education System

Science education in the United States is in need of repair. From primary through graduate education, there is a shortage of excellent science teachers. Is it any wonder that scientific literacy rates are low and that "magical thinking" abounds? Try this experiment: Ask a science teacher at a local K-12 school to explain evolution by natural selection. I have found that many can't do this well, but will avow to "believing in it." Similarly, the students who matriculate from our graduate programs enter the professoriate with little or no training in how to teach. As an example of this, ask a graduate student to define "pedagogy." When he or she can't, track down his or her faculty mentor and ask him or her if that's the legacy he or she wants to leave.

The graduate education system is also a mess. The present system is one that allows some graduate schools to admit far more students than they will matriculate. This tremendous attrition is often ascribed to failure of the students, but we all know this is not the case. Graduate students are among our brightest and hardest working, but their programs are neither "rewarded" for retaining them nor "punished" for losing them. All too common is the faculty mentor who is holed up in his or her office writing grants and papers while the graduate students are farmed off on postdoctoral fellows. Little, if any, training or supervision of those postdocs is expected, as they too will be judged solely by the length of their publication record. I believe that, at too many institutions, too little attention is paid to a faculty member's mentoring skills and expertise, and institutional resources are not directed at promoting the development of these skills. Mentees and students (and the requisite mentoring and teaching) in such settings are an afterthought rather than an essential focus. The students who do get to graduation often have learned nothing more than how to succeed in that type of environment. And, as many of them will ultimately not be academic researchers, those skill sets may not be useful.

So what can we do? It is no secret that the behaviors we reward will be the behaviors we encourage. I suggest that we begin rewarding students for taking chances and asking insightful questions. The current system is one that rewards students with a degree once they have completed their research project, and those who finish with a minimum of delay are those who have chosen (or been given) a "clean" project. Students who chose complex problems that require massive amounts of development may find their degrees delayed, if they are ever finished. Sadly, it is exactly these students, the ones who are driven by curiosity and challenge, who are discouraged by our system.

This situation is not unique to graduate schools. How many of your grade school teachers rewarded the students who had the right answer, and how many rewarded the students who asked the right questions? We foster this in our own children by asking them to work hard and

be attentive and doing nothing to encourage their curiosity. In my own case, each night over dinner, I would ask my daughter to tell me three things that she had learned that day. Now, I ask her to tell me three good questions she asked that day. That subtle shift resulted from expecting her to be a passive learner to being an active one. What do you — as a teacher, mentor or parent — do to reward the curiosity of those in your charge? How do you help your students learn and understand the processes of science? Which is more important for a graduate student — finishing a simple problem or understanding a complex one? What is more important for success — "finishing" one's education or being a life-long learner? In one form or another, we are all mentors, and mentoring well is our responsibility.

What You Can Do

So, what is my mentoring advice to you? I suggest you make a five-year plan: Identify what you want your life to be like in five years, and start working toward that goal. If you want to teach, identify the skills, knowledge, abilities and experiences necessary to reach that goal. For example, if you want to teach at elementary or secondary school, learn about your state's teacher certification requirements, determine what gaps exist in your education and experiences and create a road map to get from where you are now to where you want to be. For the most part, excellent teachers, scientists, parents and [fill in the vocational worker of your choice] are made, not born. Identify what you want to excel at and work toward it. The path won't necessarily be easy, and you are likely to make mistakes along the way, but, never forget that anything worth achieving is worth working for, and what you learn on the journey ultimately will inform your understanding and future decisions.

Many colleges and universities have career development centers that can help by providing career counseling, aptitude analysis and other resources. One of the exercises you can undertake is identifying the lifestyle you would like, and working backward from there. Speaking for myself, although I find my career very satisfying I never have forgotten the sage advice given to me by a senior postdoctoral fellow at the National Institutes of Health. She said, "You will probably never hear someone utter with their last breath, 'I should have spent more time in the office.'" Similarly, I realized long ago that no one can ever be paid enough to do a job they don't enjoy. For that reason, I have worked to build my career around my life — I have made my career one in which I can serve my passions. In my case, I take more personal satisfaction in helping mentees identify their goals and then work toward those goals than I ever did preparing a manuscript. And, in my evaluations of my peers, I emphasize successful mentoring and leadership in my justification for their reappointment, tenure and promotion.

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Minority Doctorates: The Numbers

The number of minorities receiving doctoral degrees has increased over the past several years. The table below shows the breakdown of doctoral degrees awarded to U.S. citizens and permanent residents from July 1, 2007 to June 30, 2008.

The data were compiled from three sources — two National Science Foundation reports, which show the breakdown of degrees by specialty, and the American Society for Biochemistry and Molecular biology graduation survey, which shows degrees awarded in biochemistry and molecular biology.*

Ethnic Classification	Degrees Awarded: Biochemistry and Molecular Biology[1]	Degrees Awarded: Science and Engineering[2]	Degrees Awarded: Non-Science[2]	Degrees Awarded: Biological/Medical Sciences[3]
Native American	3.5%	0.3%	0.5%	0.4%
Asian	20.0%	10.4%	5.2%	11.7%
Black	5.0%	4.5%	9.9%	3.7%
Hispanic	7.9%	5.9%	5.6%	6.1%

1. American Society for Biochemistry and Molecular biology graduation survey. ASBMB Today, December 2008, p. 25.
2. National Science Foundation (2009) Numbers of U.S. Doctorates Awarded Rise for Sixth Year, But Growth Slower. NSF 10-308, Table 2. (http://bit.ly/cBgmkD)
3. National Science Foundation (2009) Doctorate Recipients from U.S. Universities: Summary Report 2007–08. NSF 10-309, Table 9. (http://bit.ly/cNy16N)

**Data courtesy of James Zimmerman.*

Systems Biology for Biochemists

Merging the Experimental and Theoretical

BY VALERIE DE CRECY-LAGARD AND ALEXANDRE V. MOROZOV

De Crecy-Lagard

Morozov

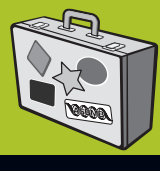
In October 2009, approximately 60 scientists met for the first "Systems Biology for Biochemists" American Society for Biochemistry and Molecular Biology Special Symposium at Granlibakken resort in Lake Tahoe, Calif. As biology is now fully in the post-genomic era, the question of how the availability of more than a thousand genome sequences changes the way biochemists design and conduct their experiments is a pressing one.

Arcady Mushegian of Stowers Institute for Medical Research organized the meeting to allow experimental and theoretical scientists to come together and see how biochemistry is now integrated at several levels with many other fields. This integration was apparent during the first evening, when Gregory A. Petsko of Brandeis University presented his work that combined yeast genetics and three-dimensional structures to rapidly identify drug targets and drug candidates in Parkinson's disease. Another "big picture" presentation was given by Eugene V. Koonin of the National Center for Biotechnology Information, who showed that evolutionary principles can be extracted from whole genome sequences as evolutionary biology goes from "stamp collecting to physics."

The emphasis of the next day's session was on reconstructing ancestral and minimal biochemical pathways. In the morning, Vadim Gladyshev of Harvard Medical School and Valérie de Crécy-Lagard of the University of Florida emphasized the power of using comparative genomic approaches to discover new pathways and physiological trends. Gladyshev presented an impressive analysis of players in metal trace-element metabolism in 700 genomes (1). De Crécy-Lagard showed that in silico data-mining approaches can be used to identify many missing tRNA modification genes. The field of synthetic biology was represented by Mikkel Algire of the J. Craig Venter Institute. He described a general method that eliminates ligation steps in gene, operon or plasmid assembly that was used to assemble a whole *Mycoplasma mycoides* genome in yeast and transplant it into *Mycoplasma capricolum* (2). Eric Gaucher of the Georgia Institute of Technology combined phylogeny reconstruction with gene synthesis to express "ancestor proteins." Using EF-Tu as a molecular thermometer, he analyzed the melting temperature of specific reconstituted ancestor proteins, which pointed to a possible thermophilic origin of life.

The afternoon continued with an "origin of life" theme as Armen Mulkidjanian of Universitat of Osnabruck presented evidence for his "zinc world hypothesis," in which photosynthesizing ZnS precipitating around primeval hot springs in high-pressure environments could have driven the synthesis of organic molecules (3). Other afternoon talks covered a range of topics: Frederic F. Pio of Simon Fraser University talked about automated long range homology algorithms, network analysis and experimental methods used to identify the "inflammasome," and Georgy P. Karev of the National Institutes of Health presented a modification of the Eigen "error catastrophy" model that would allow biological systems to evolve. Literature mining was at the core of the Medscan platform Ilya Mazo of Ariadne Inc. designed to infer relationships between genes and/or compounds using scattered and non-homogeneous literature sources. The afternoon ended with Peter D. Karp of SRI International presenting the Pathway Tools platform.

The focus of the next day's morning session was the progress of the structural genomics initiative. SG is a large-scale structure determination program with an emphasis on previously uncharacterized protein families. Nick Grishin of the University of Texas Southwestern, John-Marc Chandonia of Lawrence Berkeley National Laboratory, Aled Edwards of the University of Toronto and Alexey G. Murzin of the MRC Laboratory of Molecular Biology described the role of SG in improving protein classification schemes and providing new functional insights. In particular, Chandonia used bioinformatic analysis



based on the SCOP structural classification database (4) to argue that new SG structures have greatly enhanced our knowledge of protein families while at the same time decreasing the average cost of solving a protein structure. Edwards discussed SG contributions to characterizing structural and chemical biology of human proteins, with a focus on epigenetic targets such as histone methyl transferases which have been implicated in various human diseases. Murzin described how structure-guided analysis can be used for protein function prediction.

The afternoon session started with a talk by Alexandre V. Morozov of Rutgers University on the theoretical principles of protein folding and evolution. Morozov argued that many evolutionary phenomena (such as increased evolvability of more stable proteins) can be understood using a simple model in which organismal fitness is proportional to the probability of a protein to be folded and therefore functional. The next speaker, Warren DeLano* of DeLano Scientific LLC, provided a brief introduction to the main features of a popular open-source molecular visualization software PyMOL. Other speakers in the session discussed how structural and functional genomics can be used to benchmark large-scale predictions of protein function (Ambrish Roy of the University of Kansas), catalog structurally uncharacterized protein families (Mensur Dlakic of Montana State University), employ mass spectrometry in proteomics (Vlad Petyuk of the Pacific Northwest National Laboratory) and study diversity of polyamine biosynthesis pathways with comparative genomics methods (Anthony J. Michael of the Institute of Food Research).

On the final day of the meeting, the focus shifted from large-scale protein structure determination to studies of genetic and protein networks. Frederick Roth of Harvard University spoke about a systems biology approach to deciphering genetic interactions in Saccharomyces cerevisiae— a useful technique for identifying protein complexes, ordering genes in pathways and finding synergistic drug combinations. Andrey Rzhetsky of the University of Chicago described information overload in modern molecular biology caused by an avalanche of new data and ideas and showed how text-mining techniques could be used to extract both active and forgotten knowledge from vast scientific literature. Arcady Mushegian described the state of the art in creating similarity metrics for biological networks starting from vectors of experimental data assigned to each gene or protein. Mushegian also introduced a novel iterative algorithm, PSI-SQUARE, designed to search for similarities between network nodes. Finally, David Sprinzak of the California Institute of Technology presented a time-lapse microscopy study of the Notch-Delta signaling pathway — the canonical pathway for communication between neighboring cells during development. He found an ultra-sensitive protein-level switch between mutually exclusive sending and receiving signaling states and argued that the biochemical mechanism of the Notch-Delta switch could serve as a new design principle in many other intercellular networks.

This meeting, hopefully, was the first in a long series of workshops, as it clearly fills an urgent need of integrating biochemistry with systems biology.

** It is with a great sadness that the meeting participants and the scientific community learned that on Nov. 3, 2009, Warren Delano, 37, passed away unexpectedly. In honor of his work in bioinformatics, ASBMB has created the Delano Award for Computational Biosciences. See p. 11 for more information.*

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For more information

- To see the meeting program and slides from several of the lectures, go to http://bit.ly/bWzN9o.
- To learn more about systems biology, check out the Journal of Biological Chemistry thematic minireview series, "Computational Biochemistry: Systems Biology," at http://bit.ly/a6lj1G.

DID YOU KNOW?

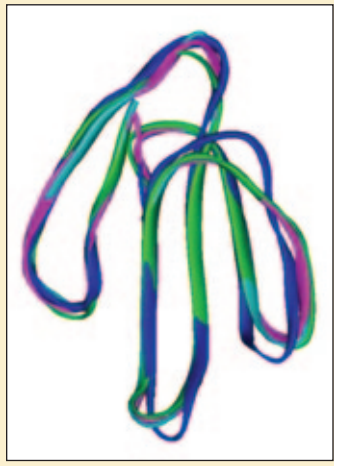
Ninety-seven American Society for Biochemistry and Molecular Biology members have been the recipients of Nobel Prizes.

Otto Meyerhof was the first ASBMB Nobel Prize recipient.

- Thirty-five of the prizes were in chemistry, and 62 of the prizes were in physiology or medicine.
- The first ASBMB member to receive the prize was **Otto Meyerhof** in 1922, for his discovery of the relationship between the consumption of oxygen and the metabolism of lactic acid in muscle.
- In both 1962 and 1972, five ASBMB members received Nobel prizes. **John C. Kendrew** and **Max Perutz** were awarded the 1962 Nobel Prize in Chemistry, and Francis H. Crick, **James D. Watson** and **Maurice H. Wilkins** shared the 1962 Nobel Prize in Physiology or Medicine. In 1972, **William H. Stein**, **Christian B. Anfinsen** and **Stanford Moore** were honored with the Nobel Prize in Chemistry, while **Rodney R. Porter** and **Gerald M. Edelman** shared the Nobel Prize in Physiology or Medicine.
- Four of the ASBMB laureates were women:
  - **Gerty Theresa Cori** *was awarded the 1947 Nobel Prize in Physiology or Medicine for her discovery of how glycogen is broken down and resynthesized in the body to be either used or stored as a source of energy.*
  - **Dorothy Mary Crowfoot Hodgkin** *received the 1964 Nobel Prize for Chemistry for determining the structures of several biologically important compounds using X-ray crystallography.*
  - **Gertrude Belle Elion** *was the recipient of one-third of the Nobel Prize for Physiology or Medicine in 1988 for her development of drugs used to treat several major diseases.*
  - **Carol W. Greider** *received one-third of the 2009 Nobel Prize in Physiology or Medicine for the discovery of how chromosomes are protected by telomeres and the enzyme telomerase.*

For more information about ASBMB Nobel laureates, go to http://bit.ly/bTbwER.

A Novel Neurotoxin



Haditoxin subunit A (blue) superimposed on erabutoxin-a (magenta), erabutoxin-b (cyan) and toxin-α (green).

Snake venoms contain a rich cocktail of pharmacologically active peptides and proteins that have contributed greatly to scientific advances, such as understanding receptor activity and developing new therapeutics. The authors of this paper have now added another member to this class of valuable peptides, providing a detailed structural and functional characterization of a novel neurotoxin from the venom of the King cobra. Their 1.5-Å crystal structure revealed that this new toxin, called haditoxin, exists as a homodimer, similar to the κ-neurotoxin family. Interestingly, however, the monomeric subunits of haditoxin, which consist of a three-finger protein fold, closely resemble short-chain α-neurotoxins, unlike κ-neurotoxin monomers, which resemble long-chain α-neurotoxins. Perhaps more interestingly, while haditoxin could antagonize several classes of nicotinic acetylcholine receptors (nAChRs) in neurons and muscle, its greatest potency is against α7-nAchRs, which are recognized by neither short-chain α-neurotoxins nor κ-neurotoxins. Given this diverse and unique pharmacology, haditoxin might have many future uses in developing molecular probes and therapeutic agents.

Structural and Functional Characterization of a Novel Homodimeric Three-finger Neurotoxin from the Venom of Ophiophagus hannah (King cobra)

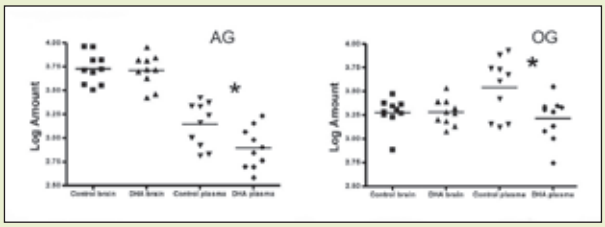
Amrita Roy, Xingding Zhou, Ming Zhi Chong, Dieter D'hoedt, Chun Shin Foo, Nandhakishore Rajagopalan, Selvanayagam Nirthanan, Daniel Bertrand, J. Sivaraman and R. Manjunatha Kini

J. Biol. Chem., published online Jan. 13, 2010

jbc

A Little DHA Goes a Long Way

Endocannabinoids are fatty-acid-derived signaling lipids that are physiologically important in many mammalian systems, particularly the brain. In this study, the authors report on how two-week docosahexaenoic acid (DHA) supplementation affects the physiological state of 15 endocannabinoid-related metabolites in the plasma and brain of mice. Their lipodomic analysis revealed that a DHA-rich diet markedly elevated the DHA, eicosapentaenoic acid (EPA), 2-eicosapentanoylglycerol (EPG) and docosahexanoylethanolamine (DHEA) concentrations in both plasma and brain, while regulating other metabolite species in a compartment- and/or metabolite-selective manner; in general, DHA supplementation shifted the balance to favor docosahexaenoic and eicosapentaenoic species compared with arachidonoyl and oleoyl derivatives. Overall, the endocannabinoid metabolome exhibited greater responsiveness to DHA in plasma, perhaps reflecting that the brain maintains its lipid population within a more stringent homeostatic range. This analysis suggests that even short-term DHA enhancement can affect select constituents of brain and plasma endocannabinoids.



Dietary DHA-supplementation does not affect the concentrations of 2-arachidonoylglycerol (AG) or 2-oleoylglycerol (OG) in the brain, but decreases them significantly in plasma.

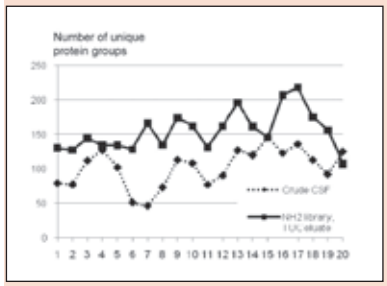
Dietary Docosahexaenoic Acid Supplementation Alters Select Physiological Endocannabinoid-system Metabolites in Brain and Plasma

JodiAnne T. Wood, John S. Williams, Lakshmipathi Pandarinathan, David R. Janero, Carol J. Lammi-Keefe and Alexandros Makriyannis

J. Lipid Res., published online Jan. 13, 2010

Exploring Cerebrospinal Fluid

Cerebrospinal fluid (CSF) contains many proteins of neural origin and is often known as a biochemical window into the brain. Therefore, CSF is an ideal source in the search for biomarkers of neurological diseases, if the proteomic challenge of characterizing a biological fluid with a very wide concentration range of proteins can be overcome. In this study, the researchers used a combinatorial peptide ligand library bound to porous beads to reduce the dynamic range of protein concentrations in CSF and progressively enrich minor protein species.



Unique protein groups identified in a series of one-dimensional gel fractions from either crude CSF (dotted line) or the first eluate from samples treated with the NH2 library (solid line).

With this approach, they managed to uncover a host of previously hidden CSF proteins; of the 1,212 CSF proteins they identified from pooled samples using liquid chromatography-tandem mass spectrometry, only 745 were detected after peptide library treatment. When the protocol was optimized to work with individual low-volume samples, as would be the case in any clinical application, the researchers found that this miniaturized approach was still reproducible and effective at enriching low concentration proteins, making it a feasible strategy for analyzing neurological diseases.

In-depth Exploration of Cerebrospinal Fluid by Combining Peptide Ligand Library Treatment and Label-free Protein Quantification

Emmanuelle Mouton-Barbosa, Florence Roux-Dalvai, David Bouyssié, François Berger, Eric Schmidt, Pier Giorgio Righetti, Luc Guerrier, Egisto Boschetti, Odile Burlet-Schiltz, Bernard Monsarrat and Anne Gonzalez de Peredo

Mol. Cell. Proteomics, published online Jan. 21, 2010

Chance Favors the Prepared Mind

How to Shape Your Future as a Science Administrator

BY SHAWN R. DREW

More than a century ago, Louis Pasteur said, "Chance favors only the prepared mind." By this he meant that sudden flashes of insight don't just happen — they are the products of preparation. Preparation, therefore, is the key to a successful and fulfilling scientific career. Whether you take the "traditional" academic route and become a professor or the "non-traditional" route and become a science writer, policy analyst, venture capitalist, etc., you should identify your career niche and prepare for it.

My Transition from Bench to Desk

I trained as a graduate student and postdoctoral fellow at the National Institutes of Health, but, at the same time, I did a lot of volunteer work. Because I enjoy doing outreach, especially to underrepresented groups, I gave presentations to middle and high school students, taught science courses at area colleges, wrote science curricula for my local church, provided laboratory supplies and gave presentations to students in Nigeria and mentored undergraduate students in my laboratory. One day, while I was a postdoctoral fellow, I read an advertisement for a science administrator position at the NIH and realized that many of the required duties and responsibilities were similar to the activities I already was doing. Thus, I decided to leave the lab and focus on science administration, incorporating my love of science and passion for training young scientists.

Currently, I work as a program official in the Minority Opportunities in Research Division at the National Institute of General Medical Sciences. We administer research and research-training programs aimed at increasing the number of underrepresented minority biomedical and behavioral scientists. I get enormous satisfaction when speaking with students, postdoctoral fellows, faculty members and individuals in leadership positions at academic institutions across the country about our programs and their benefits. I often think, "I can't believe I get paid to do this!"

An Example: The Health Scientist Administrator

A career as a science administrator can take place in academia, industry or government. The NIH employs numerous science administrators to meet its mission of supporting research and training in the biomedical and behavioral sciences. The primary responsibility for planning, directing and managing the evaluation of these activities rests

Shawn R. Drew earned her bachelor's degree from Spelman College in 1991 and her doctorate in biology from Howard University in 1998. She conducted her postdoctoral research at the National Institute of Diabetes, Digestive and Kidney Diseases. In 2003, Drew joined the National Institute of General Medical Sciences at the National Institutes of Health as a program director in the Minority Access to Research Careers Branch. She also serves as the institute's program director for the Biostatistics Research Training Grant program and is the chairwoman of the Committee to Maximize Representation for research-training grant programs. Prior to her appointment, she served as director of the NIH Academy, an intramural post-baccalaureate research training program, and was an adjunct professor of biology at the University of Maryland and Prince George's Community College.

with health scientist administrators (HSAs). Typically, HSA duties include:

- organizing and managing peer-review groups to evaluate research proposals on the basis of their scientific merit;
- managing extramural research and research-training programs and identifying gaps in research and research training areas warranting either increased or decreased funding emphasis;
- developing funding opportunity announcements designed to elicit research and research-training grant proposals from the scientific community;
- providing technical assistance to applicants and grantees;
- conducting site visits to applicant and grantee institutions to determine the adequacy of research and research-training facilities;
- serving as a spokesperson for agency programs dealing with the scientific community, Congress and other federal agencies.

Typically, HSAs attend graduate school, do postdoctoral training, obtain faculty positions and create well-established laboratories before transitioning to science administration. Thus, they have both an appreciation for and the ability to work with faculty applying for research and training support. However, there are other means, albeit much less common, of transitioning to an administration job at the NIH. For example, I did not have a faculty position before entering program administration. Instead, my first-hand knowledge of the NIH helped me to land the job. However, people coming from outside the NIH with only postdoctoral research training experience may find it more difficult to transition to a HSA position before establishing a lab. Furthermore, regardless of the type of organization you join, the likelihood of getting a position increases with postdoctoral research training, as the experience, in part, is designed to develop your independence and leadership skills.

The Skills

The first step to preparing for an administrative career in science is conducting a self-assessment to determine the activities you enjoy, the skills you possess and the skills you lack. This information can help you determine whether a science administration position is right for you. You may want to ask family members, friends, colleagues and mentors to describe your strengths and weaknesses to help facilitate your assessment. Armed with this information, look at the position descriptions in science administration career postings. Are the duties and responsibilities appealing? Do you currently perform or have you performed some of the required duties?

You may surprise yourself and find that you posses the skills employers are seeking. First, science acumen is paramount: You must demonstrate competence in science and have proof of what you have contributed to your field of study. Other desirable skills that science administration recruiters seek include the ability to communicate effectively, leadership and management skills and the ability to work effectively and cooperate with others. Do you have these skills? Well, you may have them and simply not realize it. For example, if you've mentored people in the lab, ordered and organized lab supplies and equipment, organized data clubs, journal clubs or other seminars or worked with collaborators on research projects, you probably possess leadership, management and team-player skills. Other ways to obtain these skills include taking leadership or management classes, teaching science courses, editing research papers or grant proposals, attending career advice workshops and speaking with science administrators about their job duties.

Now that you know what a scientific administrative position might entail and you know the skills involved, conduct your self-assessment to see if that career is for you. If so, try to acquire the training and skills you need to transition to a science administration position. The shift in focus from your specialized research area to guiding decisions that affect the allocation of research and research-training support is definitely achievable if you prepare yourself.

The Unmasking of Plasmalogens: Chlorinated Lipids

BY DAVID A. FORD

Cells of the innate immune system can be compared to cannons poised to release a diverse arsenal of oxidants that kill invading organisms but can frequently cause collateral damage through the oxidation of host cell molecules, including lipids. One of the oxidants produced in vivo is bleach. Yes, neutrophils, monocytes and some macrophages are enriched with myeloperoxidase, which acts to amplify the oxidant potential of these cells by converting hydrogen peroxide to hypochlorous acid and its conjugate base, hypochlorite (or bleach). These reactive chlorinating species (RCS) can chlorinate lipids, and the masked aldehyde of plasmalogens has proved to be the biggest (most reactive) target for the RCS projectile thus far.

Early studies demonstrated that RCS attack esterified and non-esterified fatty acid alkene groups and the primary amines of phosphatidylethanolamine and phosphatidylserine, leading to the production of lipid chlorohydrins and chloramines (1, 2). My lab focuses on RCS-targeting plasmalogens, and we found that RCS target the vinyl ether bond of plasmalogens, releasing the masked aldehyde as an α-chlorofatty aldehyde with a residual lysophospholipid by-product (3, 4). Our recent studies have shown that chlorinated fatty aldehyde is metabolized, giving rise to other chlorinated lipids, including α-chlorofatty acid and α-chlorofatty alcohol (5, 6). It is likely that these chlorinated lipid building blocks may be incorporated into complex lipids. Thus, through the initial volley of RCS attack on plasmalogens, a chlorinated lipidome is born!

These chlorinated lipids are novel molecules that are produced in response to the chemical arsenal released during inflammation, and it is quite possible that they may have important mechanistic roles in host tissue injury. Members of this chlorinated lipidome accumulate in activated neutrophils and monocytes and in infarcted myocardium and human atherosclerotic lesions (4, 7, 8). The primary plasmalogen-derived RCS products, α-chlorofatty aldehyde and unsaturated lysophosphatidylcholine, may propagate localized inflammatory responses because they are chemoattractants and elicit the surface expression of the phagocyte tethering molecule, P-selectin (4, 8). Also, HDL-associated α-chlorofatty aldehyde inhibits protective and vasoregulatory-important eNOS-derived NO production (9). These examples represent the beginning of our understanding of the role of these newly discovered lipids.

In addition to the chlorinated lipids derived from the arsenal of RCS produced by MPO, humans accumulate chlorinated lipids from environmental exposure to RCS (e.g., cleaning with bleach and exposure in swimming pools). Eosinophils also fire an "oxidant cannon" filled with hypobromous acid derived from brominated vegetable oil found in many soft drinks. Thus, not only do we produce these halogenated lipids as a result of the cannons of the innate immune system, but we are likely marching through this battlefield with self-inflicted daily environmental and nutritional exposure to reactive halogenating species and their halogenated lipid products.

David A. Ford (fordda@slu.edu) is a professor in the department of biochemistry and molecular biology and director of the Center for Cardiovascular Research at Saint Louis University.

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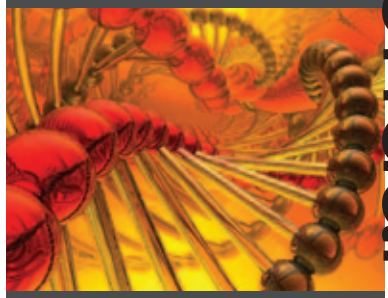

September 30 – October 4, 2010

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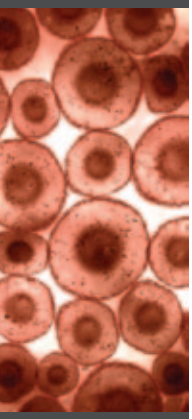
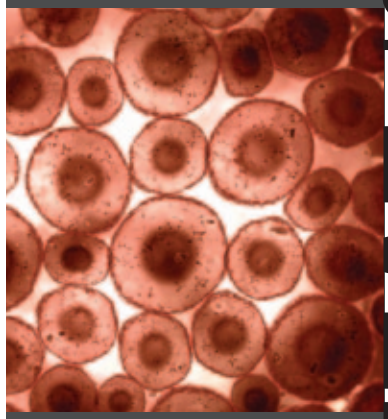
Stowers Institute for Medical Research





October 14 – October 17, 2010

Biochemistry and Cell Biology Of ESCRTs in Health and Disease

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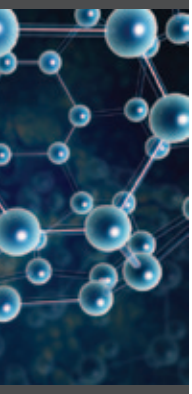
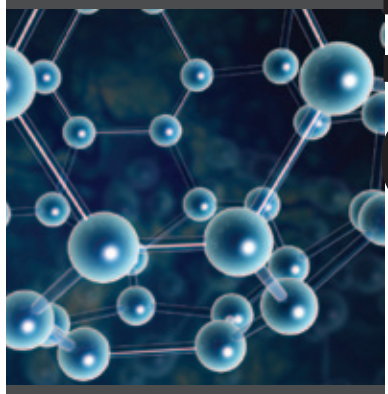
Organizer: James Hurley
National Institute of Diabetes and Digestive and Kidney Diseases

Phyllis Hanson
Washington University School of Medicine





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Post Translational Modifications: Detection and Physiological Evaluation

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Organizer: Katalin Medzihradszky
University of California, San Francisco

Gerald Hart
Johns Hopkins University School of Medicine

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Organizer: Suzanne Pfeffer
Stanford University School of Medicine

Vivek Malhotra
Center for Genomic Regulation, Barcelona, Spain

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