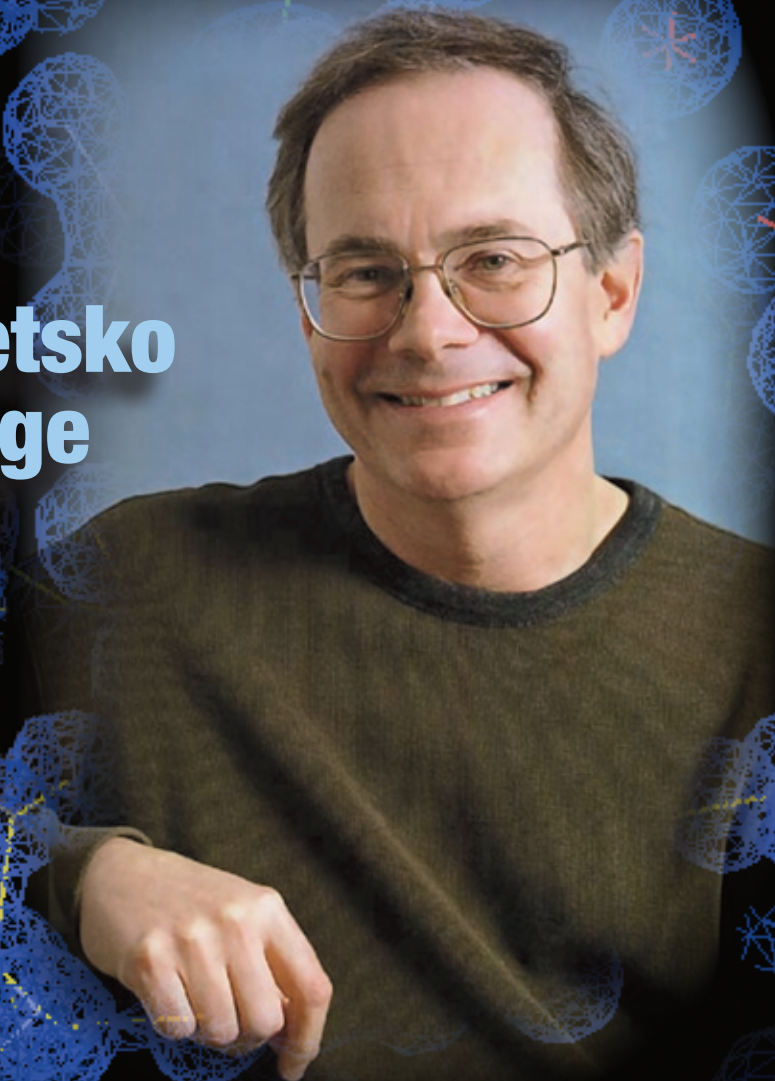


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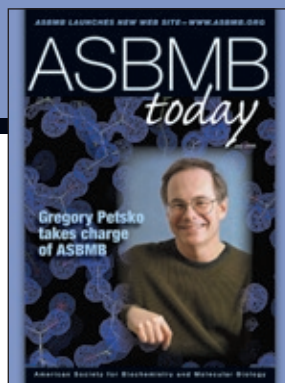
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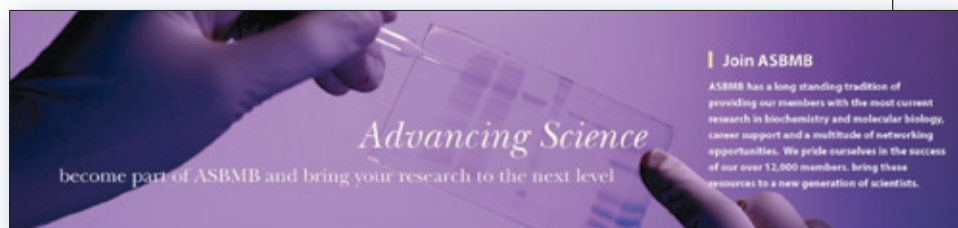
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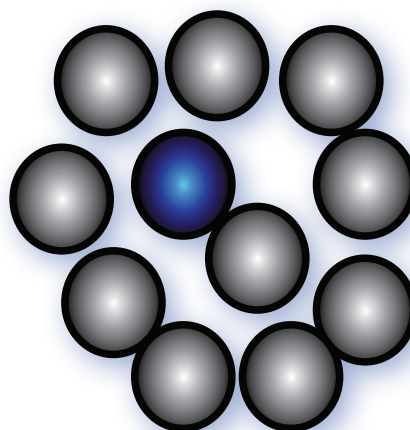
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<http://www.faseb.org/asbmb/media/media.asp>



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ASBMB Today Welcomes New President

BY NICOLE KRESGE

We at *ASBMB Today* would like to welcome new ASBMB President Gregory Petsko of Brandeis University, who officially took office on July 1 following a one-year term as president-elect. This issue contains Petsko's inaugural President's Message, as well as a short profile introducing the man taking over the reins of ASBMB for the next two years. We wish him all the best in his new role, and we look forward to working with him in the future on both his monthly columns and other ideas for the magazine.

ASBMB Today would also like to thank outgoing President Heidi Hamm for all her contributions to the magazine and, of course, the society, over the past two years. We know that in her role as past president she will continue to help ASBMB grow and become a major voice for basic biological scientists, students, and educators everywhere.

This issue of the magazine also marks the first of our three thematic previews for the upcoming 2009 ASBMB annual meeting in New Orleans. As we may have said a few times before, it's never too early to start thinking ahead, so be sure to read our previews to find out about the exciting topics being covered and the speakers who will be presenting research at the meeting next year. This month features overviews of two of the five thematic groups: "Cell Systems" and "Metabolism and Signaling." Over the next two issues we will cover the remaining themes of "Nuclear Transactions," "Molecular Structure and Dynamics," and "Protein Synthesis, Folding, and Turnover." In addition, as part of our efforts to expand into other media, ASBMB will feature podcasts with the organizers of these thematic sessions that will provide more insight into these upcoming symposia. Be sure to go to the ASBMB multimedia section on our newly revamped web site to hear more. ☺







First Things First

BY GREGORY A. PETSKO

I want to begin my two-year sentence—I mean, term—as President of ASBMB by saying to all those who voted for me: “I’ll get you for this if it’s the last thing I ever do.” I mean, I was president-elect for a year, now I’ll be president for two years, and then past president for a year. That’s four years! Convicted felons get paroled in three!

But seriously (and for those of you who don’t know me, let me say up front that I take as few things seriously as possible), thank you for expressing your confidence that I can lead this organization. I would be a lot less confident myself were it not for the fact that Heidi Hamm and the other past presidents have bequeathed me a Society that is in superb shape on all fronts: financially, administratively, and in terms of its mission. I’ll try very hard not to mess it up. That should be easier than you might think, because they have also bequeathed me a superb staff that I’m just getting to know and on whom I intend to rely heavily. So please join me in congratulating Heidi on a magnificent two years as president, in which she showed that this job can be an activist position. I intend to continue that to the best of my abilities.

Although ASBMB is in fine shape, the same cannot be said for American science. These are the toughest times I’ve seen in my 35 years doing independent research. I don’t have to tell you that the funding situation is historically bad; that the influence of science on government has become virtually non-existent under the Bush Administration; that young people face enormous difficulties starting their careers; that mid-career scientists face equally enormous ones staying in their field or moving to a new one; that competition at home and from abroad has never been

tougher; that peer review is in peril; and that research priorities are not being set the way they should be. These and other problems are so severe that they threaten the entire magnificent edifice that is American science, an edifice that I believe has also been the foundation for much of the prosperity that this country has enjoyed in the last 60



years. I intend to try to do something about this, using both the bully pulpit of the ASBMB presidency and the human resources of the society—by which I mean you. I need your advice and support as we try to put things right.

In future columns, I’ll try to address these and other problems. It’s the nature of essays to focus on the difficulties we face and what we ought to do about them. But that focus can give a strident, negative tone to the dialogue, and that’s not the way I want this to begin. So in this letter I want to step back from the things that are wrong with American science and talk about the many things that are right.

It’s easy to forget just how fortunate we are. We live and work in a country where freedom of inquiry is protected by law, and where the public has a high degree of respect for what we do. We are part of a great tradition that stretches back literally thousands of years, to before Euclid and Archimedes, and

that is responsible for nearly all human progress. To put it another way, the reason I’m writing this column at a nice desk in a room lit by an electric light while sitting on a comfortable chair in a cozy house instead of sitting in a tree wondering where my next banana is coming from is entirely due to people like you, who for

Although ASBMB is in fine shape, the same cannot be said for American science. These are the toughest times I’ve seen in my 35 years doing independent research.


centuries have dared to ask questions and pursue ideas. Even those of us who never make that earth-shattering discovery will have contributed some brick or mortar of consequence to the enormous wall that is human knowledge.

Ours is a noble and honorable profession, and it is a profession in the original sense of the word: a service performed for the public good. We live by our wits, to be sure, but we do so for the benefit of mankind. We never have to question the value of what we do; we need no justification for getting up in the morning and going to work. Indeed, most of us work way beyond the traditional 40-hour week, with no overtime pay, because we love what we do and recognize its worth. Most people in the world have jobs; we have a vocation. Sometimes we forget just how lucky we are in that regard. There are aspects of what I do that I could cheerfully do without, but I can honestly say that I would scrub floors if I had to in order to do science.

And most of us don't do it alone. We are fortunate to have colleagues and collaborators and to have them, potentially, in almost every country on earth. Think of it: we can go anywhere and the odds are there will be people who will be interested in what we do and with

whom we can talk about things of mutual interest. We are truly citizens of the world.

Moreover, our friends and colleagues can come from every age group. That's almost unique in this world. In nearly every other line of work there is a hierarchy that is based in large part on age and experience. Upper management tends to be middle-aged and doesn't socialize or even work with much younger junior executives. We can and do both without regard for such artificial barriers. For those of us who teach or train graduate students and postdocs, we have the added pleasure of working daily with extraordinarily bright, dedicated, interesting young people. Just imagine: these smart kids do what we tell them to—and if they are really smart, they do stuff we'd never have thought to tell them. The pleasure of training our successors and watching them grow is something I wouldn't give up for all the gold in Ireland.

So let's work together to try to fix the things that are wrong, but let's also remember to celebrate the things that are right. Science is a great life. We get to explore and discover and at the same time know that what we do is worthwhile. Yes, there are problems, but it sure beats working for a living. 

JBC Online now features Paper of the Week author profiles!



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Hearing on Stem Cells Foreshadows New Legislative Effort for Ethical Guidelines


BY CARRIE D. WOLINETZ

A recent hearing on “Stem Cell Science: The Foundation for Future Cures,” held by the Health subcommittee of the House Energy and Commerce committee, proved to be popular among members of Congress, with more than a dozen in attendance to hear testimony on the current status of stem cell research. Witnesses included National Institutes of Health (NIH) Director Elias Zerhouni and embryonic stem cell scientists George Daley and John Gearhardt, as well as adult stem cell researchers and patient advocates. The hearing was held at the request of Representative Diana DeGette (D-CO), who announced plans to introduce new legislation with Representative Mike Castle (R-DE) that would not only expand the number of human embryonic stem cell (hESC) lines available for federal funding, but would “construct a framework for ethical oversight for all cell-based research.” A similar DeGette-Castle bill, the Stem Cell Research Enhancement Act, has passed both houses of Congress multiple times, but has been unable to garner sufficient votes to override a presidential veto.

Topics at the hearing ranged from details about the state of the science to current NIH funding levels of stem cell research to the feasibility of NIH serving as a regulatory body to ensure ethical oversight of stem cell research. Comments from the members of Congress present generally fell along partisan lines, with the Democrats on the subcommittee supporting all types of stem cell research, including embryonic, and the Republican members emphasizing the importance of adult stem cell research and the newer induced pluripotent stem (iPS) cells. Zerhouni testified that from the scientific standpoint, hESC, adult stem cell, and iPS cell research were all “faces of the same coin.” In response to questions about the clinical merit of adult *versus* embryonic stem cells, Zerhouni pointed out that there is an average of 17 years between a basic science idea and clinical trials, and that hESC technologies were far younger than their adult stem cell counterparts. He later added, “If we had more resources, we could accelerate the research...” Daley and Gearhardt talked at length about the impact iPS cells would have on the future of stem cell research, describing the exciting potential of this new technology while cautioning that it was too soon to tell whether

they could fully replace hESC. They both referred to embryonic stem cells as the “gold standard” against which other cell lines must measure up.

Although no further details of the upcoming DeGette-Castle legislation were forthcoming, there were a number of questions about the current lack of regulatory framework for ethical oversight of stem cell research. Zerhouni enthusiastically supported the enactment of “harmonized and cohesive oversight” that would apply to all stem cell research being conducted in the U.S., stating “I wish common ground could be found...” as well as his belief that NIH is the entity best able to administer such a system. Witness statements and an archived webcast of the hearing may be found at: http://energycommerce.house.gov/cmte_mtgs/110-he-hrg.050808.StemCell.shtml.

The general sense in Washington is that it is unlikely any legislation to overcome the presidential policy restricting federal funding of hESC will move forward in this Congress. However, presidential candidates Barack Obama and John McCain have expressed support for hESC research and have voted to support passage of the Stem Cell Research Enhancement Act. Therefore, it seems highly probable that a new administration would alter the current policy. What remains to be seen is the shape of regulations that would be put into place following removal of the funding restriction. With the *Guidelines for Human Embryonic Stem Cell Research* from the National Academies and the *Guidelines for the Conduct of Human Embryonic Stem Cell Research* from the International Society for Stem Cell Research already being used on a voluntary basis by research universities, it will be interesting to see if the federal government chooses to adopt one of these existing models for its regulatory framework. (For FASEB comments on these two sets of guidelines, please visit: http://opa.faseb.org/pages/PolicyIssues/stemcellscnt_pi.htm) The proposed DeGette-Castle bill could potentially impose a different regulatory scheme and may expand beyond hESC research based on Representative DeGette’s assertion that the ethical framework would apply to “all cell-based research.” If the bill is introduced, it will likely be referred back to the House Energy and Commerce committee of which Representative DeGette is vice chair. 



Some Science Funding Survives in Supplemental Bill

BY PETER FARNHAM

On June 19 the House overwhelmingly approved two spending measures—one a \$162 billion war funding measure, the other a \$95.5 billion measure funding a major veterans education program, unemployment benefits, and, in a small but significant victory for science, about \$337 million in new science funding.

The science funding includes \$150 million for NIH, \$62.5 million for NSF, \$62.5 million for DOE science programs, and \$62.5 million for NASA.

The NIH funding is to be spread on a “pro rata basis” across all NIH institutes and centers, with at least some of it going to the Director’s Common Fund. The NSF money is divided between Research & Related Activities (\$22.5 M) and Education and Human Resources (\$40 M). The Office of Science receives the \$62.5 M in money slated for DOE, and the NASA money is to support the Science, Aeronautics and Exploration program.

The vote in the House for the domestic spending component of the supplemental bill was overwhelming, 416 – 12. Majority Leader Harry Reid (D-NV) indicated that he thinks the bill will pass the Senate by the end of June, and the President, bowing to political reality, has indicated he will sign the bill.

Although the increases for NIH pale in comparison to the need at this agency, the funding in the supplemental does represent some progress and is the first break in the impasse over federal domestic spending that has been going on for months now.

The reasons for the impasse are basically tied to the political situation. This being an election year, everything is contentious. And, up until this bill, the President had had enough political support in the House to enforce vetoes.

In other good news, the House began to mark up the Labor/HHS appropriations bill in mid-June, and the NIH fared well. The Labor/HHS

Subcommittee approved a \$1.2B increase for NIH—4.1% over 2008. While we have a long way to go, this is a very good start. Of course, there is a standing presidential veto threat in place for any spending bill that exceeds his requests; however, as in the maneuvering surrounding the supplemental bill discussed above, it is possible that as we enter the last months of the Bush presidency, his ability to sustain vetoes will continue to diminish.

Everyone Likes NSF, but Will it Suffer from Other Funding Battles?

Finally, in continued good news for science, the 2009 NSF appropriations bill was marked up on June 12, and the relevant subcommittee gave the agency a \$6.9 billion budget for next year, up about \$500 million from the president’s request (which was itself a 13% increase over 2008).

The NSF is a rare point of agreement between the Congress and the President; all players support more money for NSF under the America Competes Act, which passed with great fanfare two years ago and which the President signed. However, the agency got caught up in a budget fight last year having to do with issues beyond its control, and thus last year’s generous increase got vetoed. The proposed increase this year is designed to make up for the veto last year.

It remains to be seen whether Congress and the President can restrain themselves from election-year posturing enough to let NSF and NIH enjoy desperately needed funding increases this year. **W**



Peter Farnham CAE is public affairs officer of the Society, a position he has held since 1985. He can be reached at pfarnham@asbmb.org.

A Renovation for www.ASBMB.org

Over the past couple of months we have been working hard to combine some new technology and a fresh new face for the society's webpage! As the last redesign was about 3 years ago, we decided it was time for a functional overhaul and an updated look.

ASBMB is proud to announce the unveiling of the brand new www.ASBMB.org. The entire site has been redesigned. Not only has site navigation been improved, we've added a few new sections to our site including interactive areas and a special members only section.

ASBMB has always posted society news, but the new version of the site will have a dedicated space for hot news stories, (whether they be journal or society related), enhanced search functionality, and an archive for news stories with a powerful search engine allowing you to easily find that old article you read a

couple months back, but can't remember exactly when.

The interactive area of the new site will include monthly summaries of top research from each of the ASBMB journals, our Audiophiles podcasts, video excerpts, members in the news, supplementary research footage, and other media of interest. This is also the place to come if you want to hear proprietary interviews with leading scientist and journal editors. We are also developing a concept for an "ASBMB Online Lounge" that will include social networking functionality and provide a forum for knowledge

sharing, whether through blogging, or other Web 2.0 technology.

As an ASBMB member, you'll also have access to restricted member-only areas of the website. Your unique member-only space will include personal profile information, the ability to update your contact information online, to monitor event registration, exclusive



access to the digital edition of our monthly member magazine, *ASBMB Today*, and a number of other member-only privileges. Also, take advantage of the opportunity to give us your feedback and thoughts on ASBMB articles through comment posting.

We're excited about the new design look and functionality, and we hope you enjoy the fresh new face of www.ASBMB.org! If you have comments, or feedback as we proceed through the website launch, please feel free to email Jessica Homa, Marketing Manager at ASBMB at jhoma@asbmb.org.


Glimcher Recipient of Mentoring Award



Laurie H. Glimcher, Irene Heinz Given Professor of Immunology at the Harvard School of Public Health and Professor of Medicine at the Broad Institute, received the American Association of Immunologists Excellence in Mentoring Award. The award, given in recognition of her exemplary contributions to a future generation of scientists, was presented to Glimcher this

past April at the 95th Annual Meeting of the American Association of Immunologists.

According to the American Association of Immunologists, "In addition to a distinguished academic career and major scientific contributions to the field of immunology, Dr. Glimcher has had a career-long commitment to the development of scientist trainees and mentoring. Her dedication to trainees' success has resulted in a cadre of successful scientists across the spectrum of the science enterprise and the establishment of lifelong friendships."


Glimcher's laboratory uses biochemical and genetic approaches to elucidate the molecular pathways that regulate CD4 T helper cell development and activation. Specifically, she studies the transcriptional pathways involved in the regulation of Thelper1/Thelper2 (TH1/TH2) responses by interleukin-4 and interferon cytokines. 

Kelleher Granted Pittcon Achievement Award



Neil Kelleher, Professor at the University of Illinois, received the 2008 Pittsburgh Conference Achievement Award. The award, sponsored jointly by The Pittsburgh Conference and the Society for Analytical Chemists of Pittsburgh (SACP), recognizes individuals for outstanding scientific achievements within 10 years following completion of their Ph.D.

Kelleher has three main areas of research: custom instrumentation for Fourier Transform Mass Spectrometry (FTMS), Nuclear Signaling, and Natural Products. More specifically, his interests lie in the enzymology of natural product biosynthesis, mass spectrometric based studies of the histone code, and development of FTMS for top down proteomics (*i.e.* analyzing intact proteins directly; no proteases).


He has received several awards for his research, including the Pfizer Award in Enzyme Chemistry from the American Chemical Society Division of Biological Chemistry, a Presidential Early Career Award, a National Science Foundation CAREER Award, and the Lilly Analytical Chemistry Award. Kelleher is also an Alfred P. Sloan Fellow, a Packard Fellow, a Burroughs Wellcome Fund Young Investigator, a Searle Scholar, and a Fulbright Scholar. 

Katzenellenbogen Given Esselen Award



John A. Katzenellenbogen, Swanlund Chair in Chemistry at the University of Illinois, Urbana-Champaign, has received the 2008 Gustavus John Esselen Award for Chemistry in the Public Interest.

The award, which is presented annually by the Northeastern Section of the American Chemical Society, is one of the section's most prestigious honors. It recognizes a chemist whose scientific and technical work has contributed to the public well being, and has thereby communicated positive values of the chemical profession. The award was established in 1987 to honor the memory of Gustavus John Esselen, past-chair of the Northeastern Section and founder of Esselen Research.


Katzenellenbogen received the award for his work in understanding estrogen receptor structure, function, and dynamics. He developed an extensive series of steroid receptor-based agents labeled with fluorine-18 and technetium-99m for imaging receptor-positive breast and prostate tumors by positron emission tomography. His more recent work involves studies of the estrogen receptor protein and the coregulator proteins of steroid hormone receptors. 

Robinson Receives Christian B. Anfinsen Award



Carol Robinson, of the University of Cambridge, has been selected to receive the 2008 Christian B. Anfinsen Award from the Protein Society. The award, which is sponsored by The Aviv Family Foundation, recognizes significant technical achievements in the field of protein science.

Robinson, who is being recognized for her outstanding pioneering scientific contributions in the fields of mass spectrometry and structural biology, has driven the continual development of novel mass spectrometry approaches and instrumentation that are used in laboratories around the world.


After contributing to the development of a prototype electrospray time-of-flight mass spectrometer that substantially extended the mass/charge range, Robinson designed a more sophisticated machine, a high mass quadrupole time-of-flight mass spectrometer. Using this technology, she demonstrated that macromolecular particles with masses in excess of 2 MDa can transverse the mass spectrometer in an intact state, permitting the recording of their mass spectra. In her exploration of the extent to which solution phase complexes resemble those studied in the gas phase of the mass spectrometer, Robinson used ion mobility measurements of protein complexes to show that the 11-mer protein rings formed by the RNA-binding protein TRAP could not only be retained in the gas phase but their stability could be altered by the addition of cofactors. 



Jordan Honored with Karnofsky Award Lecture




V. Craig Jordan, Vice President and Research Director for Medical Sciences and the Alfred G. Knudson Chair of Cancer Research at the Fox Chase Cancer Center, is the 38th recipient of the highest award from the American Society of Clinical Oncology, the David A. Karnofsky Award and Lecture. The award recognizes clinical research that has changed the way clinicians treat cancer.

Jordan is the first Ph.D. to receive this award that recognizes his seminal laboratory work on the pharmacology of the drugs tamoxifen and raloxifene. He was the first to recognize that these drugs are selective estrogen receptor modulators, *i.e.* they stimulated or blocked estrogen target tissues around the body. He took these laboratory data and collaborated with the clinical community to complete the appropriate clinical testing. For 20 years, tamoxifen was the gold standard for the treatment and prevention of breast cancer, and raloxifene is used to prevent osteoporosis and breast cancer. 

IN MEMORIAM: Richard Abrams

Richard Abrams, a distinguished biochemist, died in Pittsburgh in January at age 90.

Abrams was born in Chicago, obtaining his B.S. (1938) and Ph.D. (1941) degrees in chemistry from the University of Chicago. He was a Research Instructor in the Department of Chemistry at the University of Chicago from 1941 to 1942 and then became a Group Leader in the Biology Division of the Manhattan Project (1942 to 1946). From 1946 to 1951 he held the position of Assistant Professor in the Institute of Radiobiology and Biophysics at Chicago. In 1951, he moved to Pittsburgh, remaining there for the rest of his life. His first appointment was as Associate Director (1951 to 1958) of the Montefiore Hospital Institute of Research, becoming Director from 1958 to 1965. At the same time, he held professorial appointments in the Department of Biochemistry and Nutrition, Graduate School of Public Health (GSPH), University of Pittsburgh. Terminating his work at Montefiore, he became Professor and Chairman of the GSPH Department of Biochemistry and Nutrition in 1965. This department was renamed the Department of Biochemistry in the Faculty of Arts and Science in 1968; he continued as Chairman until 1972. He retired in 1984 with the title of Professor Emeritus.

His research focused on nucleic acid metabolism, and in 1955, with Marian Bentley, he isolated inosine 5'-monophosphate dehydrogenase, the enzyme responsible for converting IMP to XMP, from rabbit bone marrow extracts and demonstrated a requirement for glutamine for the further conversion of XMP to GMP. Moreover, in a collaboration with Mary Edmonds beginning in 1957, he examined animal cell extracts for RNA synthesis leading to the isolation of poly(A) and poly(A) polymerase. 

Mobashery Honored with Astellas Award



Shahriar Mobashery, Navari Family Professor in Life Sciences at the University of Notre Dame, is the 2008 recipient of an Astellas USA Foundation Award by the American Chemical Society. Mobashery received the award for his work on antibiotic resistance and his contributions to the understanding of the bacterial cell wall.

The Astellas Awards were established by the American Chemical Society to recognize individuals or teams who have significantly contributed to scientific research that improves public health through their contributions in the chemical and related sciences. The award carries a \$30,000 prize. Mobashery and the other award recipients will be honored in August at the 236th American Chemical Society national meeting in Philadelphia.


The Mobashery lab has been seeking new approaches to understand the antibiotic-resistant superbacterium MRSA (methicillin-resistant *Staphylococcus aureus*). This variant of *S. aureus* surfaced in the early 1960s and has recently emerged as a serious health problem. By figuring out how MRSA lives and thrives, the Mobashery group has enabled the development of strategies for killing this difficult organism.

IN MEMORIAM: Graham Jamieson

Graham A. Jamieson died in Bethesda, Maryland, this past March at the age of 78. He was a leader and distinguished scientist at the American Red Cross for 38 years.

Born in 1929 in Wellington, New Zealand, Jamieson obtained both his B.S. (1949) and M.S. (1951) degrees from New Zealand's University of Otago. He received his Ph.D. degree in organic chemistry from the University of London, Lister Institute of Preventive Medicine, in 1954.

After doing several research fellowships, Jamieson joined the American Red Cross Blood Services in 1961 as a biochemist in its transfusion blood research and development (R & D) program, and in 1964, he became a senior scientist and the assistant research director. Named research director in 1969, Jamieson oversaw major growth of the program and expanded the effort into new scientific and technical fields. Under his guidance, the R & D program achieved national and international recognition and respect.

While developing this program, Jamieson also conducted a significant research program in platelet biology. His department's research addressed many topics, including the role of platelet glycoproteins in platelet function, identification and characterization of platelet receptors, and the interaction of platelets with tumor cells and extracellular matrix proteins. After 15 years guiding the R & D program, Jamieson resigned his position as director in 1984 to return his full attention to research. He retired in April 1999. 

Legislation on Supporting Women in Academic Science

BY ANGELA HVITVED

Earlier this spring, the House Science and Technology Subcommittee on Research and Science Education held a hearing to receive comments on draft legislation titled “Fulfilling the Potential of Women in Academic Science and Engineering Act of 2008.” The legislation, sponsored by Representative Eddie Bernice Johnson (D-TX), was crafted in response to a 2007 National Academies report “Beyond Bias and Barriers: Fulfilling the Potential of Women in Academic Science and Engineering.” The report discussed obstacles facing women in academic science and engineering careers and provided a list of recommendations addressing these concerns. Several of the report recommendations, including workshops to increase awareness of gender bias and better tracking of federal funding information, would be

implemented by the proposed bill. The May hearing was a follow up to one held in October 2007, during which the NAS report was reviewed and participants discussed how potential legislation could be constructed to address the concerns identified (see *ASBMB Today*, December 2007).

The hearing charter posed several questions of the witnesses relevant to their fields of expertise, but there was a general focus on two major issues:

1. Describe the key elements of effective training and education programs addressing gender bias (and their metrics for success) and
2. What demographic data can or should be collected to assess gender disparities in academic science and engineering.

What Women (Scientists) Want: The National Institutes of Health Announces RFA on Initiatives to Support Women in Science


BY ANGELA HVITVED

Few dispute the numbers on retention rates for women in science and engineering, but there is less consensus about what should be done and, more importantly, what works. To address these questions, the National Institute of General Medical Sciences (www.nigms.nih.gov) issued a notice of intent for a Request for Applications (RFA) on “Research on Causal Factors and Interventions that Promote and Support the Careers of Women in Biomedical and Behavioral Research (NOT-GM-08-126).” The RFA will be published in July 2008 with a receipt date of October 2008; they anticipate funding up to eight R01 awards after September 2009. The aims of the RFA, as described in the notice of intent, are to support research on:

- the causal factors, such as individual characteristics, institutional/departmental environment, organizational structure, and disciplinary culture or practices, explaining the current patterns observed in the careers of women in science and variation across different subgroups,

such as underrepresented minority women and socio-economically disadvantaged women

- the efficacy of programs designed to support the careers of women in science

Investigators are strongly encouraged to collaborate with colleagues in the natural, behavioral, and social sciences, and other fields as needed. The RFA was developed in a subcommittee of the National Institutes of Health Working Group on Women in Biomedical Careers, which was created to consider the recommendations of the National Academies report on women in academic science, “Beyond Bias and Barriers.” The purpose of this group is to develop innovative strategies and tangible actions that promote the advancement of women in research careers in both the National Institutes of Health intramural and extramural research communities. This RFA is one of several initiatives that have come out of the Working Group. More information can be found on their web site, womeninscience.nih.gov. 


The hearing featured testimony by Lynda Carlson, director of the National Science Foundation (NSF) Division of Science Resources Statistics; Linda Blevins, senior technical advisor in the Department of Energy Office of Science; and Donna Ginther, associate professor of economics at the University of Kansas and director of the Center for Economic and Business Analysis. The three witnesses weighed in with their thoughts on the proposed legislation and suggestions for possible improvements.


With respect to improved collection of demographic data for federal funding, most agree that it should be a goal. However, it is clear that current mechanisms could not meet the proposed requirements. Carlson, who is the director of the NSF division that is responsible for collecting demographic data on proposals and awards, plainly stated that this legislation would exceed its current data collection capabilities and that it does not have the authority to require other agencies to maintain such records. Additional obstacles include the fact that principal investigators cannot be required to provide demographic information (due to privacy laws), and the proportion of PIs voluntarily reporting their gender has continually declined over the last 10 years. Despite these difficulties, all three witnesses seemed to agree that better data collection is necessary for better understanding the underlying causes of the disparities.

The topic of workshops received slightly more mixed support. Blevins, who helped coordinate the “chemistry workshop” on gender bias, discussed what she believes are important components of a successful program. For those not familiar with this concept, in 2006 the chemistry community organized a workshop addressing issues of gender bias targeted to the chairs of the top 50 university chemistry departments. This workshop inspired a similar effort by the physics community and serves as a model for proposed programming in the legislation under discussion. Ginther, who studies the issue as an economist, pointed out that with admittedly imperfect data, one cannot conclude that gender bias alone accounts for the gender gap in academic success. Her research suggests that issues of productivity, resulting from marriage and child rearing, may also explain the discrepancy, at least in part. However, until better data on home and family commitments can be merged with productivity and funding success, it will be difficult to make definitive conclusions on the role played by gender bias.

Ginther expressed concern about appropriate

EVOLUTION WATCH: Academic Freedom Legislation: One Step Forward, One Step Back...

There was a spate of “Academic Freedom” legislation this spring but fortunately for science education, little progress has been made in these efforts. For those not familiar with this type of legislation, these bills purport to protect the rights of teachers and students to discuss the controversies and weaknesses of evolution in the science classroom but are generally considered an indirect method of introducing intelligent design. In many states, the language was modeled on draft legislation provided by the Discovery Institute, a pro-intelligent design creationist organization, as part of their “Teach the Controversy” campaign. In the past few months, “Academic Freedom” Acts were introduced in the Florida, Louisiana, Alabama, Missouri, South Carolina, and Michigan state legislatures. There is a bit of good news, though. As state legislative sessions close, many of these initiatives are dying in the process, although proponents promise to revive them next session. As of this writing, time has run out for initiatives in Florida, Alabama, and Missouri but action continues in South Carolina, Michigan, and Louisiana. The National Center for Science Education is closely monitoring these bills and regular updates can be found on their web site, www.ncseweb.org. 

evaluation of outcomes from the proposed workshops. Although changing attitudes is important, the key test of success is whether those changes affect concrete outcomes, and this aspect should be analyzed more rigorously. She went on to conclude that an additional action the federal government could take would be childcare support though direct and indirect funding. Details of witness recommendations can be found in their testimony on the subcommittee web site, science.house.gov/subcommittee/research.aspx. Watch for updates on the progress of the proposed legislation in the months to come. 

PRESIDENTIAL PRIMER: *Gregory Petsko*

Brandeis professor takes over ASBMB leadership on July 1



Gregory Petsko, the Gyula and Katica Tauber Professor of Biochemistry & Chemistry at Brandeis University, offers a simple explanation when asked why he decided to run for president of ASBMB. “Because I’m stupid,” he says. “Heidi Hamm and Susan Taylor approached me about the presidency and suggested I run, but they told me not to worry, because I would lose. And I fell for it.”

With a little more prodding, Petsko does offer other, more serious, motivations for taking up the mantle of presidency. “Frankly, I don’t like what I see: the decreased funding, politicization of science, lack of science education, and the general growth of a society that is replacing ‘reason’ with irrationality. Not many jobs can give you the bully pulpit you need to try to do something about this decay, but ASBMB president could be one.”

And judging by his first answer to the question, we probably already have a good idea of what kind of president Petsko will be: direct, unabashed, and forthright. He provides some more of that honesty when discussing his hopes for improvement during his two-year tenure. “I have no real expectations of change,” he says, “and I’m pretty sure I won’t succeed in many of my efforts, but at the same time, it would be irresponsible not to try. After all, we cannot be afraid of uncertainty or failure.”

This brave front comes from Petsko’s unusual career track in his younger days. While he certainly displayed a strong interest in modern science growing up—“I loved watching Mr. Wizard on television, and blew up my parents’ basement with my first chemistry set like everyone else”—he had an even stronger passion for the ancient world. A devout reader of ancient Greek and Roman authors, he enrolled in Princeton University in 1966 to major in classical literature. To make some extra money, he started working in labs part time, first with inorganic chemist Bill Horrocks then later with Robert Langridge, a structural biologist who had worked in England with Maurice Wilkins, the sometimes overlooked third scientist who helped discover the double helix.

His lab work helped renew his childhood scientific interests, and he eventually graduated Princeton having studied both chemistry and classical literature. Considering the divergent nature of these two disciplines, it may be no surprise that Petsko was unsure which direction to take as graduation neared. “I applied to law, medical, and graduate schools, to give you some idea of my confused mindset,” he says. One thing he was fairly certain of was that he would like to spend some time studying abroad, and that led him in 1970 to apply for and win a Rhodes scholarship, which seemed to present him with a golden opportunity. “Oxford was king when it came to the classics,” Petsko says, “so I set sail to get an advanced degree in classical literature and buy time while I sorted things out.”

And set sail he literally did, as back then Rhodes recipients were transported to Great Britain onboard the *Queen Elizabeth II*. However, during that eight-day voyage across the North Atlantic, Petsko’s would-be mentor at Oxford, noted classical scholar Maurice Bowra, unexpectedly died; Petsko arrived at the university to find himself with nobody to work for.

“I decided to call Bob [Langridge] and see if he had any advice, since he had studied in England, and he told me to go and see David Phillips, the crystallographer,” Petsko says. “Of course, when I went to talk with David, he looked at me as if I had two heads. ‘Why should I take you in?’ he asked me, at which point I replied, ‘Because I won’t cost you anything.’” Taken under Phillips’ wing, Petsko spent the next three years learning more about X-ray crystallography, during which time he helped solve one of the earliest protein structures: triose phosphate isomerase. Thus was a future biochemist and structural biologist born.

But while he has been building an impressive resume as a research scientist over the past 35 years by using structural analyses to tease out the functional aspects of enzymes, Petsko has always striven to broaden his horizons. This includes work at the lab bench (he recently ventured into the realm of yeast genetics to look at cell cycle control) and beyond. That was, in fact, a big reason why he took a position at Brandeis in 1990 following 13 years on the faculty at research powerhouse MIT. "I had wanted to work at a smaller institution where both students and faculty were immersed in a more diverse environment." Brandeis also gave Petsko the opportunity to put his humanities knowledge to use, and over the years he has taught courses such as "Chemistry and Art" (using science to find forgeries), "Scientists in Films and Plays," and even "The History of Detective Novels."

Another reason for choosing Brandeis was that they offered Dagmar Ringe, Petsko's co-principal investigator, a professorship, whereas at MIT she was only in charge of the teaching labs. "Dagmar is one of the best scientists I have ever known, and I'm fortunate to have had her running a joint research program with me for the past 30 years," he says. "It was important that she get some recognition, and she did: her first faculty appointment anywhere was with tenure in the Brandeis University biochemistry department, one of the best in the world."

The combination of these qualities—blunt honesty, valuing a diverse education, recognizing the importance of working with others, and daring to wade into new territory—taken along with Petsko's history of vocal contributions to the cause of science (he has written a monthly opinion column on science and society for *Genome Biology* for the past eight years) make him a fitting candidate for ASBMB's top post.

And while he may jokingly complain about taking this position, he is ready to stop just writing and start doing.

"I'll definitely need a little time to test the waters," he says, "because at this point I don't know enough about the 'power' of the office *versus* the 'powers' of the office. Fortunately, ASBMB has a first-rate staff, and I will lean on them for assistance."

However, once he's comfortable, he does have a few ideas for his agenda.

One is to continue Heidi Hamm's efforts at improving National Institutes of Health (NIH) policy, especially the drift away from funding individual investigator-initiated projects, and he plans to meet with policymakers at both NIH and on Capitol Hill. Petsko will also try to mobilize ASBMB membership to make local differences where possible, as well as coordinate larger efforts with other scientific societies "so that we can speak with one voice." Petsko hopes to address other topical issues like the splintering of big societies into smaller ones and the direction of open access in publishing as well. Still, he wants to leave open a good deal of space for the unexpected, be it new policies or new trends. "There is a lot of reaction involved in this work," he says.

One point that Petsko stresses, however, is that the scientific community needs to take many of its problems, like funding deficiencies, on its own shoulders. "I know we have another new U.S. president taking office soon," he says, "and while I believe whoever takes over will be more receptive to scientists, it will be foolhardy to believe that a change in Washington will produce any immediate changes in funding. No one is coming on a white horse to save us."

And while it may not be a popular thought, Petsko believes the first step to improving funding for science is to

acknowledge that scientists have to share some of the blame as well. "We had a period when NIH funding doubled, but we screwed up our priorities and didn't spend the money the best way possible, such as infusing our R01 pool, so when funds tightened we developed shortages. Once we recognize that, we can begin to correct it."

As is his nature, Petsko is not afraid to include himself in any blame. "We've all made mistakes we need to acknowledge; look at me, I got tricked into running for ASBMB president." ❧



Picture Perfect

This article is fifth in a series on publishing your research in the *Journal of Biological Chemistry*. The series will address a variety of issues that authors may have when writing and submitting articles to the *JBC*. The articles are written by Cadmus Communications, a Cenveo company, which is responsible for the editing, production, and printing of *JBC* articles.

Many authors need some guidance to create artwork that is aesthetically pleasing and relevant to the message of the report or paper. Included in this article are some suggestions for preparing print-ready artwork that will produce high-quality images in the *JBC*.

Image Editing Tips & Tricks

Graphic images processed by a computer can be divided into two distinct categories: vector and raster. Vector images lend themselves to well defined elements composed of lines and curves of specific colors. They are created in programs like Illustrator, FreeHand, and CorelDRAW and saved as EPS files. Vector graphics are “resolution independent” and can be sized without any loss of quality.

Raster (or halftone) images are more suitable for photos requiring complex color variation mapped to a non-flexible grid. The grid density sets the resolution and is expressed in dots per inch (DPI) or pixels per inch

(PPI). When resized, raster images must readjust to the fixed grid so image quality suffers as some dots (or pixels) must straddle an opening in the grid. In addition, a raster image with low DPI appears very jagged when output at the high resolution of commercial printing. Photoshop is the primary program for editing raster images, to be saved in TIF format.

The difference may not be visible on a 72 DPI computer monitor, but the enlarged illustration gives a comparison.

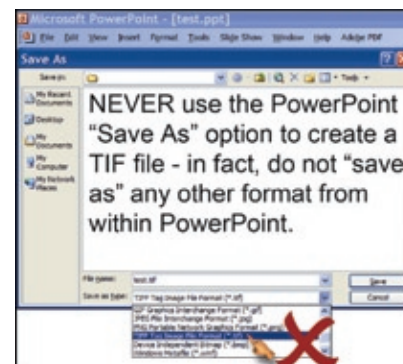


PowerPoint

By far, the most common question from authors is how to take Microsoft PowerPoint source files and convert them into usable digital art files for publication. Because of quality issues, many journals do not accept PowerPoint files for print production. PowerPoint is an application designed to create on-screen computer presentations at 72 DPI resolution. In addition, PowerPoint lacks the capacity for failsafe management of fonts and for seamless cross-platform (Mac/PC) file usage. As a result, PowerPoint images may not reproduce with sufficient accuracy or quality.

If a figure is constructed entirely of text, lines, or charts (in other words, vector elements), the best option is to copy images from PowerPoint and paste them into a program like Adobe Illustrator. This copy-and-paste method will actually give more predictable results without all the resolution, font, color and quality issues found when submitting native PowerPoint files. The full instructions are available by following the PowerPoint link at the Digital Art Support web site.

Fortunately, there are additional user-friendly options and we will share one of the best ones in this article. First, there is one important rule to remember about working with PowerPoint files: NEVER use the PowerPoint “Save As...” option to create a TIF file — in fact, do not “save as” any other format from within PowerPoint.

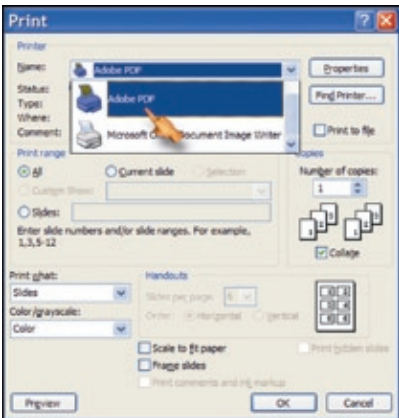


In addition to the aforementioned “cut-and-paste” option, another method is to separate the series of PowerPoint slides into individual PowerPoint files. Each of these files can then be converted into an Acro-

bat PDF file. To create a PDF file from PowerPoint, the system must have the appropriate version of Adobe Acrobat installed. Depending on the configuration, it may be as simple as clicking the Acrobat PDF button on the toolbar.



If there is no button on the toolbar, it should be available as a choice in the “print” dialog window.



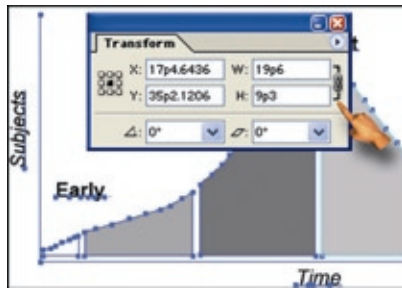
Once a PDF file is created, it should be inspected to ensure that none of the notorious PowerPoint “glitches” occurred during the transformation. These glitches can include the disappearance of special characters (e.g., Greek and math symbols) or rotated text becoming un-rotated. Next, the PDF file can be opened for final editing and refinement in Illustrator or Photoshop, as appropriate.

Illustrator

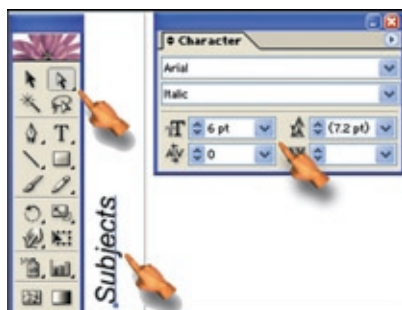
Generally, Illustrator is the best option for editing figures. Among other things, Illustrator retains all the vector information in the final EPS file. There are a few things to remem-

ber when using Illustrator to work on your figure.

Sizing: Go to the “Window” pull down menu, click “Transform” to display the Transform palette if not already visible. Go to “Select” and click on “All” to highlight the entire figure. The small chain-link image at the far right of the palette should have lines connecting the height and width dimensions. Clicking the chain-link will toggle the lines off and on. This is important because it keeps the height proportional as the width is adjusted. Enter the appropriate width for the figure.

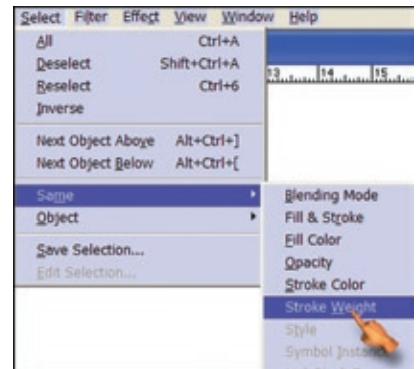


To confirm the figure size is acceptable, check the size of the smallest type. To do this, use the direct selection tool (the white arrow) to select the smallest type in the figure. Under the “Window” pull down menu, click on “Type” and select “Character” from the fly out menu to display the Character palette if not already visible. The smallest type is often ~6 pt (subject to each journal’s standard).

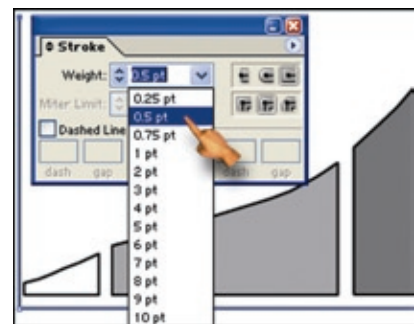


Rule (line) weight: A common issue with PowerPoint files is that rules are often set to “Hairline”; this produces a rule that is too thin for print production.

Under the “Window” pull down menu, click on “Stroke” to display the Stroke palette if not already visible. Using the direct selection tool, click to select one of the thin lines. Under the “Select” pull down, scroll to “Same” and select “Stroke Weight.”



With all strokes with the same weight selected, increase the stroke value. As a general rule, thin rules should not be less than 0.5 pt.



Finish

Finish by converting type to outlines, then save as an EPS file. Converting the PDF to Photoshop 600 DPI TIF files is another option. Detailed instructions are on the web site: http://art.cadmus.com/da/instructions/ps80_win.jsp.

Membrane Dynamics and Organelle Biogenesis

BY FRANCES BRODSKY AND DAVID LAMBRIGHT

How functionally distinct yet highly dynamic membrane-bound compartments form, mature, interact, divide, and exchange endogenous or foreign material remains one of the most challenging problems in eukaryotic cell biology. Our understanding of the mechanisms that control these fundamental cellular processes continues to expand at a rapid rate and is the subject of the talks in the “Membrane Dynamics and Organelle Biogenesis” theme. The talks will highlight new insights into the underlying molecular machinery from a variety of perspectives including functional genomic and molecular biological approaches, structural investigations of trafficking complexes, three-dimensional cryoelectron microscopy reconstructions of membrane remodeling intermediates, phylogenetic analyses of evolutionary relationships, and studies of pathogen subversion.

A major function of intracellular membrane traffic is to generate and maintain organelle integrity in eukaryotic cells and to regulate organelle inheritance upon cell division. The session “Organelle Biogenesis and Evolution” will address conservation and diversity in the pathways for organelle biogenesis and inheritance and include strong consideration of eukaryotic membrane trafficking. Frances Brodsky (University of California-San Francisco) will describe how gene duplication in the vertebrate lineage expanded clathrin function in tissue specific pathways while maintaining critical properties that are required for control of membrane traffic by clathrin. Mark Field (University of Cambridge) will discuss phylogenetic analysis of proteins in the endocytic system and comparative insights from studying endocytosis in protozoa. Janet Shaw (University of Utah) will focus on mitochondria and the mechanisms of membrane remodeling and movement that control their distribution and inheritance.

Dynamic networks of protein-protein and protein-lipid interactions mediate and confer specificity to vesicular trafficking processes. The session “Cargo Sorting and Vesicle Targeting” deals with the molecular mechanisms underlying selective incorporation of cargo molecules into budding vesicles and subsequent targeting of vesicles preceding fusion. David Lambright (University of Massachusetts Medical School) will discuss regulation of vesicle tar-

geting by endosomal Rab GTPases and phosphoinositides. Suzanne Pfeffer (Stanford University School of Medicine) will present analyses of vesicle tethering at the Golgi that highlight the importance of synergism between small GTPase families for localization of GRIP domain golgins. Juan Bonifacio (NICHD, National Institutes of Health) will describe studies on the molecular mechanisms of coat protein, adaptor and scaffolding complexes involved in cargo recognition, and sorting to and from endosomes.

Membrane traffic pathways are subverted by numerous pathogens for infection, propagation and intracellular survival. The “Trafficking Mechanisms and Pathogen Subversion” session will cover membrane traffic pathways that are subverted by virus, bacteria and intracellular parasites. James Hurley (NIDDK, National Institutes of Health) will describe structural studies of the ESCRT (Endosomal Sorting Complex Required for Transport) components of the endosomal pathway that are exploited by the human immunodeficiency virus for virus budding. Mark Marsh (Medical Research Council Laboratory for Molecular Cell Biology) will discuss cellular locations of human immunodeficiency virus assembly and release in macrophages. Norma Andrews (Yale University) will describe how studying pathogens that take advantage of these mechanisms for intracellular survival has elucidated mechanisms of membrane repair.

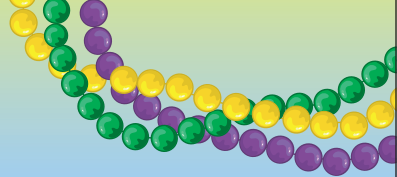
The “Membrane Dynamics and Transport” session will combine mechanistic investigations of membrane dynamics during budding and tubulation with functional genomic analyses of the molecular machinery controlling formation and maturation of transport carriers. Jenny Hinshaw (NIDDK, National Institutes of Health) will discuss the role of dynamins in membrane remodeling, highlighting the application of x-ray crystallography in conjunction with



Brodsky



Lambright



Membrane Dynamics & Organelle Biogenesis

Organizers: Frances Brodsky, University of California-San Francisco, and David Lambright, University of Massachusetts Medical School

Symposium: Organelle Biogenesis and Evolution

- Evolution and function of a novel clathrin isoform, Frances Brodsky
- Origins of the endocytic system: Insights from protozoa, Mark Field
- Mechanisms of membrane remodeling and movement: Lessons from the mitochondrion, Janet Shaw

Symposium: Cargo Sorting and Vesicle Targeting

- Mechanisms for regulation of vesicle targeting, David Lambright
- Molecular analysis of vesicle tethering at the Golgi, Suzanne Pfeffer
- Protein coats involved in sorting to and from endosomes, Juan Bonifacio


Symposium: Trafficking Mechanisms and Pathogen Subversion

- The ESCRT complexes: From lysosome biogenesis to viral budding, James Hurley
- HIV assembly and release in macrophages, Mark Marsh
- Cellular responses to injury: New insights from the study of host-pathogen interactions, Norma Andrews

Symposium: Membrane Dynamics and Transport

- The role of dynamins in membrane remodeling, Jenny Hinshaw
- Caught in the act: Membrane remodeling as seen by electron cryomicroscopy, Vinzenz Unger
- Global analysis of endocytic recycling in yeast, Elizabeth Conibear

cryoelectron microscopy to examine constricted and non-constricted intermediate states. Vinzenz Unger (Yale University) will present three-dimensional reconstructions of FBAR domains on membrane tubules visualized by cryoelectron microscopy. These reconstructions reveal polymeric assemblies with distinguishable mem-

brane binding and bending modalities. Finally, Elizabeth Conibear (University of British Columbia) will describe new transport complexes identified through genome-wide analysis of endocytic recycling in yeast using an approach that features automated phenotypic recognition and novel computational algorithms. 

All New www.ASBMB.org

More Science
More Society News
More Interaction
Come See
What's New!



Principles of Receptor Signaling

BY MARK LEMMON AND ALEX TOKER

Cells can only respond to their environment or communicate with one another because of the existence of an array of receptors for nutrients, hormones, and other cues. Many of these receptors function at the cell surface, transmitting information across the limiting membrane, whereas others in the cytoplasm or nucleus respond to signaling molecules that freely enter the cell and are critical players in orchestrating cellular responses. The wide range of pathological conditions, such as cancers, diabetes, and immune disorders, in which specific receptor proteins are either mutated or otherwise altered highlights the central importance of receptor signaling in biology. Recent advances in understanding the mechanisms used by different receptor classes and the relay pathways that transduce these signals will be highlighted during the four sessions in the “Principles of Receptor Signaling” theme at the ASBMB 2009 annual meeting.

The first session will be chaired by Zena Werb, (University of California San Francisco) and will feature a strong emphasis on mechanisms by which cellular receptors impact disease progression. Alex Toker (Beth Israel Deaconess Medical Center, Harvard Medical School) will discuss the family of matrix proteinases collectively known as ADAMs, and how they modulate breast cancer cell invasive migration. Next, Werb will discuss the large family of conventional matrix metalloproteinases and how they regulate tumorigenesis. Thus, the first two presentations will focus on matrix degradation and ligand release as mechanisms that promote tumor progression. The session will end with a presentation from Bert O’Malley (Baylor College of Medicine) who will discuss proteolysis in the context of nuclear receptors, including recent findings on steroid nuclear receptor coregulators.

The second session will examine mechanisms of signaling through cell-surface receptor tyrosine kinases (RTKs), particularly the epidermal growth factor (EGF) receptor, and will be chaired by Mark Lemmon (University of Pennsylvania School of Medicine). Kathryn Ferguson (University of Pennsylvania) will discuss structural aspects of how EGF binding promotes dimerization of the extracellular part of the EGF receptor as well as how therapeutic antibodies that bind the EGF receptor exert their inhibitory effects. Linda Pike (Washington University School of Medicine) will then provide answers to the long-standing question about the nature of the “high-

affinity” receptors and describe studies about EGF binding to the cell surface that allow translation of structural data to what happens to the receptor in living cells. Finally, Phil Cole (Johns Hopkins University School of Medicine) will illuminate intracellular aspects of RTKs, discussing some surprising mechanisms of tyrosine kinase activation against the backdrop of important disease-related mutations.

The session titled “Transmembrane Signaling by GPCRs” moves to heptahelical receptors, in which a much larger portion of the receptor is embedded in the membrane. Heidi Hamm (Vanderbilt University Medical Center) will chair this session. William Weis (Stanford University School of Medicine) will begin by describing the first structural views of how G protein-coupled receptors (GPCRs) such as the β 2-adrenergic receptor transmit signals across the membrane, a tour de force that prepares the field for more major breakthroughs. Heterotrimeric G proteins play a crucial role as molecular switches in GPCR signal transduction pathways, and these will be the topic of the second talk by Hamm, who will describe how GPCR activation is communicated to the G protein switch. In the final talk, Lakshmi Devi (Mount Sinai School of Medicine) will discuss two other important aspects of GPCR control, intracellular trafficking and GPCR heterodimerization, with a particular focus on opioid receptors.

The final session will be chaired by Fred Hughson (Princeton University) and will focus largely on receptor signaling in unicellular organisms. Hughson will describe his work on mechanisms of signaling in quorum sensing, in which bacterial cells communicate with one another to synchronize certain activities across a population. Mark Goulian (University of Pennsylvania) will then discuss how bacterial cells maintain insulation of distinct signaling pathways, thereby preventing promiscuous cross-talk, while also taking advantage of certain opportunities



Lemmon



Toker

Principles of Receptor Signaling

Organizers: **Mark Lemmon**, University of Pennsylvania School of Medicine, and **Alex Tokor**, Beth Israel Deaconess Medical Center, Harvard Medical School.

Proteolysis and Receptor Signaling

- *ADAM proteases and cancer invasion*, Alex Tokor
- *How matrix metalloproteinases regulate signaling in cancer*, Zena Werb
- *Proteolysis and nuclear receptor coregulator function*, Bert O'Malley

Tyrosine Kinases in Cancer

- *Tyrosine kinase mechanisms and pathways*, Phil Cole
- *Negative cooperativity in EGFR signaling*, Linda Pike
- *Structural aspects of extracellular EGFR signaling*, Kathryn Ferguson


Transmembrane Signaling by GPCRs

- *Structure of GPCRs*, Bill Weis
- *How GPCRs activate G proteins*, Heidi Hamm
- *Opioid receptor dimerization/signaling*, Lakshmi Devi

Signaling in Bacterial Receptor Systems

- *Bacterial quorum sensing*, Fred Hughson
- *Insulation and specificity in bacterial two-component signaling systems*, Mark Goulian
- *Design principles of receptor signaling networks*, Naama Barkai

to integrate the signals from multiple pathways. Finally, Naama Barkai (Weizmann Institute of Science) will discuss new perspectives in a fascinating frontier in cell signaling: biological networks. As our understanding of cellular

signaling networks becomes more sophisticated, it is increasingly clear that they are typically robust systems defined by their organization and system properties rather than the nature of their components. 



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Michael Karin

Moore's UCSD Cancer Center, La Jolla, CA

Lawrence J. Marnett

Vanderbilt University Medical Center, Nashville, TN

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Metabolism and Disease Mechanisms

BY JÜRGEN WESS AND SEAN OLDHAM

The coordinated activity of central and peripheral metabolic processes plays a key role in the proper function of virtually every cell type. Improper signaling through distinct metabolic pathways has been implicated in a variety of disorders including obesity and type 2 diabetes (T2D). Altered metabolism is also known to lead to impaired physiological function associated with senescence and aging. Interestingly, recent studies have led to the identification of many novel metabolic pathways and signaling molecules that play critical roles in health and disease.

In the “Metabolic Signaling in Senescence and Aging” session, the speakers will focus on molecular mechanisms that modulate aging and age-related diseases including T2D. Several laboratories have shown that aging is tightly coupled to nutrient availability and that dietary restriction increases life span. Brian Kennedy (University of Washington) will present studies designed to identify the molecular pathways that underlie the longevity effects of dietary restriction. Nir Barzilai (Albert Einstein College of Medicine) will discuss the physiological actions of a novel mitochondrial peptide, humanin, including its ability to prevent neurotoxicity and its peripheral insulin-sensitizing effects. Peter Elliott (Sirtris Pharmaceuticals, Inc.) will focus on the role of sirtuins in diseases of aging, specifically the consequences of mitochondrial biogenesis in animal models of disease and clinical trials with T2D patients.

T2D is emerging as a major threat to human health worldwide, and the “Signaling Pathways Involved in Diabetes” session will focus on various factors that regulate insulin action and glucose homeostasis. Morris White (Howard Hughes Medical Institute/Children’s Hospital) will talk about molecular mechanisms of insulin signaling in the central nervous system, pancreatic β cells, and liver that play important roles in nutrient homeostasis and growth. G protein-coupled receptors are known to regulate the activity of many cell types involved in glucose homeostasis, and Jürgen Wess (NIDDK, National Institutes of Health) will discuss new strategies aimed at understanding the *in vivo* roles of distinct G protein pathways in modulating β cell function. Susan Bonner-Weir (Harvard Medical School) will describe studies

indicating that carbonic anhydrase II-expressing pancreatic cells give rise to both new islets and acini after birth and injury (ductal ligation), which has implications for a potential expandable source of new islets for diabetes replenishment therapy.

The “Metabolic Signaling and Obesity/Metabolic Syndrome” session will highlight several metabolic pathways and signaling molecules that are of significant pathophysiological relevance. Sean Oldham (The Burnham Institute for Medical Research) will discuss how altered TOR (target of rapamycin) signaling regulates metabolism and contributes to obesity, diabetes, and aging. Laurie Goodyear (Harvard Medical School) will discuss some of the metabolic roles of AMP-activated protein kinase (AMPK) and its upstream kinase LKB1, two serine/threonine kinases that have been proposed to function as master regulators for a diverse array of metabolic processes, particularly examining the putative roles of AMPK and LKB1 in regulating skeletal muscle metabolism. Heidi Tissenbaum (University of Massachusetts) will focus on studies aimed at identifying the molecular connections between lifespan, diabetes, and obesity, using as a model the nematode *C. elegans*, which is endowed with an insulin/IGF-1 signaling pathway that modulates both longevity and fat storage.

The “Metabolism and Nutritional Signaling” session will focus on metabolic/nutritional factors and pathways that might serve as therapeutic targets in various metabolic disorders. Gen-Sheng Feng (The Burnham Institute for Medical Research) will discuss the functions of Shp2 tyrosine phosphatase in orchestrating signaling events downstream of insulin and leptin receptors in glucose homeostasis and energy balance. Laura Bordone (Novartis Institute for Biomedical Research) will talk about a mouse model overexpressing SIRT1 that




Oldham



Wess

shows phenotypes resembling calorie restriction. Her talk will also deal with the role of SIRT1 in regulating insulin secretion. Cristina Rondinone (Hoffmann-La Roche Inc.) will describe strategies, such as the use of different enzymatic regulators of triglyceride synthesis that are aimed at reducing the exaggerated plasma-free fatty acid and triglyceride levels usually associated with obesity for obesity therapy, insulin resistance, and other components of metabolic syndrome.

These incorporated sessions will highlight many important advances in the field of metabolism, bringing together researchers who are using a wide range of experimental approaches. The increasing integration of biochemistry and molecular biology with cellular and organismal physiology promises exciting times ahead for metabolic research. 

Metabolism and Disease Mechanisms

Organizers:

Jürgen Wess, *NIDDK, National Institutes of Health*, and Sean Oldham, *The Burnham Institute for Medical Research*

Metabolic Signaling in Senescence and Aging

- *Conserved links between nutrient signaling, translation, and aging*, Brian Kennedy
- *Central regulation of peripheral glucose metabolism: Target therapy for aging*, Nir Barzilai
- *Sirtuins: Novel metabolic targets for disease of aging*, Peter Elliott

Signaling Pathways Involved in Diabetes

- *IRS signaling and diabetes*, Morris F. White
- *GPCR signaling pathways in β cells*, Jürgen Wess
- *Pancreatic regeneration: Role of pancreatic progenitors*, Susan Bonner-Weir

Metabolic Signaling and Obesity/ Metabolic Syndrome

- *TOR in metabolism and aging*, Sean Oldham
- *AMPK: A critical metabolic signal*, Laurie Goodyear
- *Regulation of lifespan and fat storage by *C. elegans* *tubby**, Heidi Tissenbaum

Metabolism and Nutritional Signaling

- *Shp2 and molecular signaling in obesity/diabetes*, Gen-Sheng Feng
- *SIRT1, calorie restriction, and metabolism*, Laura Bordone
- *Targets affecting lipid metabolism to treat metabolic diseases*, Cristina Rondinone

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Lipid Signaling and Metabolism

BY SUZANNE SCARLATA & RUSSELL DEBOSE-BOYD



Debose-Boyd

The lipid field has been established as one of the most prominent in biochemistry and cell biology, and new concepts and mechanisms continue to emerge. The “Lipid Signaling and Metabolism” theme at ASBMB 2009 will encompass the ways in which lipids are maintained and stored in the cell, the role they play in cell signaling, their ability to organize protein complexes and mediate protein signals, and the ability of a specific family of lipids, inositol phospholipids, to regulate key events in the cell.

The first session will be devoted to the role of membrane domains in lipid signaling. Although the existence of protein and lipid domains in the plasma membrane is well known, the ability of these domains to affect cellular functions through their composition and organization is just beginning to be uncovered. Presentations will focus on the effect of domains on functions such as G protein signaling, membrane-cytoskeletal adhesion, and phagocytosis. Speakers in this session will be Suzanne Scarlata (Stony Brook University), Michael Sheetz (Columbia University), and Sergio Grinstein (Hospital for Sick Children, Toronto, Canada).

The second session will explore signaling through phosphatidyl inositol (PI) lipids. It is known that PI lipids are coupled to both growth factor and G protein agonists to raise intracellular calcium levels that can generate a host of intracellular responses. Additionally, these lipids appear to be involved in other cellular processes. Shamshad Cockcroft (University College London) will talk about the role of these lipids and their transporters in the

dynamics of internal vesicles. Bertil Hille (University of Washington School of Medicine) will discuss the affect of PI lipids on the properties of certain ion channels, and Peter Devreotes (Johns Hopkins University School of Medicine) will describe how PI lipids regulate the dynamics of chemotaxis and cytokinesis.

In the third session, the mechanism for lipid storage and transport will be discussed. Storage and transport of lipids play important roles in metabolism, membrane synthesis (cholesterol and phospholipids), and steroid synthesis. Abnormalities in these processes are associated with obesity, fatty liver, cardiovascular disease, and neurological disorders. Karen Reue (UCLA) will talk about lipin proteins, which participate in triglyceride and phospholipid biosynthesis as phosphatidate phosphatases and also act as inducible transcriptional coactivators in conjunction with peroxisome proliferator-activated receptor- γ coactivator-1 α and peroxisome proliferator-activated receptor- α . Dawn Brasaemle (Rutgers University) will discuss the importance of lipid droplets in lipid metabolism and disease. John Dietschy (University of Texas Southwestern Medical Center) will discuss cholesterol metabolism in the brain.

The final session will look at the various lipid-mediated signaling events. Some of these signaling cascades control feedback regulation of lipid synthesis and guard against

Lipid Signaling and Metabolism

Symposium: Role of Membrane Domains in Cell Signaling

- *Regulation of G protein Signals by Membrane Domains*, Suzanne Scarlata
- *Membrane-Cytoskeleton Adhesion; Mechanical Controls and PIP2 Dynamics*, Michael Sheetz
- *Lipids dictate surface charge and direct signaling during phagocytosis*, Sergio Grinstein

Symposium: Novel Lipid-Mediated Signaling Events

- *Sterol-accelerated ubiquitination and degradation of HMG CoA reductase*, Russell DeBose-Boyd
- *New insights from lysophospholipid receptor-null mice*, Jerold Chun
- *The Role of Phospholipid Synthesis in Lipid-Mediated Signaling and Regulation in Yeast*, Susan A. Henry

Symposium: Phosphatidylinositol Signaling and Metabolism


- *Co-ordination of vesicle delivery and signaling by phosphatidylinositol transfer proteins*, Shamshad Cockcroft
- *Dynamics of PIP2 regulation of Kv7 (KCNQ)K channels*, Bertil Hille
- *Signaling Networks in Chemotaxis and Cytokinesis*, Peter Devreotes

Symposium: Mechanisms for Lipid Storage and Transport

- *The Role of Lipin Proteins in Lipid Storage and Metabolism*, Karen Reue
- *Control of Triacylglycerol Metabolism by Lipid Droplet Proteins*, Dawn Brasaemle
- *Mutations in NPC1 and cholesterol metabolism in the brain*, John M. Dietschy

lipid overaccumulation, whereas others mediate cell-cell communications. Russell DeBose-Boyd (University of Texas Southwestern Medical Center) will discuss feedback regulation of the cholesterol biosynthetic enzyme, 3-hydroxy-3-methylglutaryl CoA reductase. Jerold Chun (The Scripps Research Institute) will present the latest findings on lysophospholipid-mediated signaling pathways. Susan Henry (Cornell University) will describe the role of phospho-

lipid synthesis in lipid-mediated signaling events in yeast.

These primary presentations will be complemented by short talks selected from abstracts submitted within these areas. The organizers encourage students, post-doctoral fellows, and young investigators to submit abstracts for these sessions. We look forward to fruitful discussions in the ever-expanding field of lipid cell and molecular biology. 


US Alters Conditions on Visa-Free Travel

The ASBMB Annual Meeting is an international event, and our foreign members and guests planning on attending next year's meeting should take note of an important travel change:

The U.S. State Department, in an effort to boost security, has announced that visitors traveling to the U.S. from visa waiver countries (such as Great Britain, Australia, and Japan) will soon have to register online 3 days in advance of travel. Currently, such visitors fill out paper forms on route and are screened by customs agents upon entry. The U.S. will begin implementing

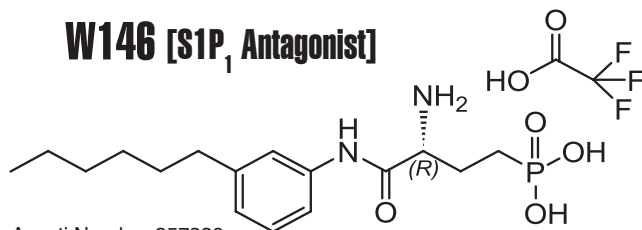
this rule in August 2008 and it will be **mandatory by January 12, 2009**. This online registration, however, need only be completed once every two years, and not during every trip.

In addition, our U.S. members should also take note as travel agreements are typically made on a reciprocity basis; therefore, U.S. visitors to visa-free countries, such as those in western Europe, will likely have to start registering in advance of travel as well.

For the official announcement about the new system, called the Electronic System for Travel Authorization (ESTA), as well as a full list of visa waiver countries, please go to: http://travel.state.gov/visa/temp/without/without_1990.html 

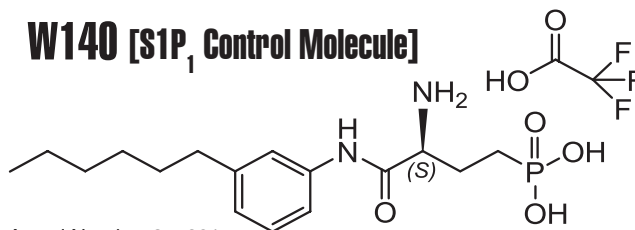
W146 THE NEW SELECTIVE ANTAGONIST

W146 [S1P₁ Antagonist]



Avanti Number 857390

W140 [S1P₁ Control Molecule]



Avanti Number 857391

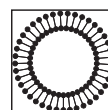
Enhancement of capillary leakage and restoration of lymphocyte egress by a chiral S1P₁ antagonist *in vivo*.

Sphingosine 1-phosphate (S1P₁) regulates vascular barrier and lymphoid development, as well as lymphocyte egress from lymphoid organs, by activating high-affinity S1P₁ receptors. We used reversible chemical probes (i) to gain mechanistic insights into S1P systems organization not accessible through genetic manipulations and (ii) to investigate their potential for therapeutic modulation. Vascular (but not airway) administration of the preferred R enantiomer of an *in vivo*-active chiral S1P₁ receptor antagonist [W146] induced loss of capillary integrity in mouse skin and lung. In contrast, the antagonist did not affect the number of constitutive blood lymphocytes. Instead, alteration of lymphocyte trafficking and phenotype required supraphysiological elevation of S1P₁ tone and was reversed by the antagonist. *In vivo* two-photon imaging of lymph nodes confirmed requirements for obligate agonism, and the data were consistent with the presence of a stromal barrier mechanism for gating lymphocyte egress. Thus, chemical modulation reveals differences in S1P-S1P₁ 'set points' among tissues and highlights both mechanistic advantages (lymphocyte sequestration) and risks (pulmonary edema) of therapeutic intervention.

M Germana Sanna, Sheng-Kai Wang, Pedro J Gonzalez-Cabrera, Anthony Don, David Marsolais, Melanie P Matheu, Sindy H Wei, Ian Parker, Euijung Jo, Wei-Chieh Cheng, Michael D Cahalan, Chi-Huey Wong & Hugh Rosen.

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Where Is the Equity in Education and Can ASBMB Help?

BY THOMAS D. LANDEFELD

It has been decades since *Brown v. Board of Education* and the Civil Rights Movement. Where are we now relative to those efforts made to achieve equality in education and elsewhere so many years ago? Unfortunately, not very far.

Historically, W. E. B. Du Bois stated: "The problem of the 20th century is the problem of the color line." We are now almost a decade into the 21st century and the color line is still a major problem, as illustrated by the changing demographics of our country and the not-so-changing demographics of education. For example, the percentage of black and Hispanic faculty has hovered around 4-5% for the past few decades. Similarly, under-represented minority students receiving graduate and professional degrees has increased ever so slowly. For example, in 2006 the total number of black, Hispanic, and Native American students who obtained a Ph.D. in the sciences represented only 10% of the total Ph.D.s awarded. Similarly, under-represented minorities comprise less than 10% of health professionals (M.D.s, nurses, pharmacists, dentists, etc.), a distressing number when one considers that this group comprises almost 30% of the population!

The significance of these low numbers is exacerbated by the impact that minority health disparities is having and will continue to have on our country. For example, the incidence of diabetes is 1.5 times greater in Hispanics than in whites and two times greater in blacks than in whites, whereas the prevalence of diabetes in Pima Indians has been reported to be as high as 80%. In addition to diabetes, a plethora of other disorders affect minority populations disproportionately, e.g. obesity, hypertension, prostate cancer, glaucoma, and cardiovascular disease. Considering these disparities in combination with the leaky pipeline of minorities to the graduate and professional levels and the lack of attention that these areas have received in the past, the health status of our future society is at great risk. Professional scientific societies such as ASBMB can help make a difference; however, things must change for this to happen.

So what needs to change? I will focus on just a few of the many problems. First, the anti-affirmative action movement, as demonstrated by Proposition 209 in California

and Proposition 2 in Michigan, has been devastating. Ever since Proposition 209 passed in California in 1996, minority enrollment in professional schools, particularly in the health professions, has fallen and never recovered. As a result, fewer minorities are attaining professional degrees, severely thwarting efforts to address health disparities. It is expected that similar declines will soon be seen in Michigan and other states that are considering such propositions. The efforts by groups that support these propositions, such as the Center for Equal Opportunity and Center for Individual Rights, have also had deleterious effects on programs targeting under-served individuals in the educational system, e.g. summer research programs for minorities. The playing field when these groups started their attack was far from level, and since then it has become even more unequal.

A major obstacle in fighting these groups has been the fact that they have received government support all the way to the top levels, including from the Department of Justice and the Office of Civil Rights. For this to change, government priorities have to change. This certainly could begin with a new administration that is responsive to these needs, much like the Clinton administration and the then-Office of the Surgeon General under David Satcher. Change also requires legislature at both the local and national level with similar commitments. Certainly we as scientists, ASBMB members, and citizens can assist by supporting candidates that stress equality in their platform. Also, as a professional society of over 10,000 scientists, we can work to inform and educate legislators about the importance of this issue, not only to science but to society as well. This can be done as individuals, but more importantly it can be done through ASBMB groups such as the public affairs group.

Are we doing that? If one examines the important issues that have been taken to Congress by the ASBMB public affairs group (referenced in President Hamm's column in the June issue of *ASBMB Today*) one does not see the issue of under-represented minorities in science. Why is that? One only has to look at graduate programs across the country, national scientific conferences, and committee



and board meetings everywhere to see that this should be high on the list of issues to be addressed by societies like ASBMB. Along these lines, the May issue of *ASBMB Today* featured an article by Minority Affairs Committee (MAC) member Jerome Nwachukwu and reported on a meeting on diversity cosponsored by FASEB. In fact, that meeting focused specifically on the role of professional societies in enhancing diversity, and it included society executives and representatives with an interest in diversity. Who represented ASBMB at this retreat? Were any members of the MAC involved? If not, why not? To make strides in this area we need to do it as a well informed and committed group. If not, how can we expect the message to be relayed with the compassion and experience necessary?

Another major problem, in fact the one I consider most significant, is “white privilege,” defined as the social inheritance of rights, advantages, power, and opportunities by those who are white. Interestingly, despite this being the source of most of these problems, this issue is talked about least because those who have white privilege do not want to acknowledge it, and those that do not have it are extremely vulnerable when talking about it. Moreover, those that have it seem constantly threatened by the fact that they may lose it, whereas those that do not have it seem to think they can never really obtain it. The presence of white privilege is seen in essentially every poll regarding color, *i.e.* whites see no problem, people of color do. Does this mean the problem doesn’t exist? To the contrary, it exists but individuals who are in positions to address it simply choose not to because of their privilege. An excellent example in academia is the approval of legacy admissions, which are almost always for those white and privileged, *versus* affirmative action programs, which almost always target people of color.

This problem is harder to address because folks who are part of the white privilege group have to be willing to speak out and take action against it, even though it would mean sacrificing some of that privilege. Few are willing to do that, and that is exactly why so much of the talk about diversifying an organization or an institution is just talk. It is stated or written because that is the “right thing to do,” but those in the power positions see the possibility of losing some of that power, and subsequently, many diversity programs never leave the paper they are written on. Will these programs only materialize if the person in charge is not someone who enjoys white privilege and therefore not at risk for losing it? Not necessarily; however, that person in charge has to be willing to make sacrifices that many in those positions are not prepared to make.

Some may even question whether someone who is not of color can truly be effective in making progress for those of color. To answer that, one simply has to read Carter G. Woodson’s *The Mis-education of the Negro*, first published in 1933, in which he states: “It is alright to have a white man as a head of a Negro college or a red man at the head of a yellow one, if in each case the incumbent has taken out his naturalization papers and has identified himself as one of the group which he is trying to serve. It seems that the white educators of this day are unwilling to do this, and for that reason, they can never contribute to the actual development of the Negro from within. You cannot serve people by giving them orders as to what to do. The real servant of the people must live among them, think with them, feel for them, and die for them.”

And how does this relate to ASBMB? Simple: how many white scientists within ASBMB are willing to do what Woodson states? Very few, I would guess. So until such a time when more individuals are willing to make this sacrifice, we will continue to make efforts piecemeal that cannot ultimately make a difference at an organizational, institutional, or society level. This should not be surprising because as Frederick Douglass stated, “there is no progress without struggle.” Why would one expect changes of this magnitude to occur without a major effort or significant sacrifices, especially if *status quo* is really not that bad, at least from the “privileged” perspective?

So what’s the bottom line? Can ASBMB make a real difference in this area? Certainly applying pressure and providing information to governmental representatives including state or national congresspersons, governors, and mayors is critical. And although individuals can do this, doing it as a 10,000+-member society is even more effective. But when will ASBMB choose to make this an issue?

As for actually choosing to give up some of the white privilege to embrace the cause, this has to be an individual decision. But if the person making such a decision is an ASBMB president or a council member, then who knows? ASBMB could truly make a difference in changing the face of science and academia so as to parallel the face of the Society in this century and, in doing so, help to ensure the color line is no longer a problem in the 22nd century! ❧

Thomas D. Landefeld is Professor of Biology and Pre-health Advisor at California State University Dominguez Hills. He is a member of the ASBMB Minority Affairs Committee and can be reached at tlandefeld@csudh.edu.

Scientists and Lawyers: More in Common Than Meets the Eye

BY JOHN J. EMANUELE

I am an attorney and concentrate my practice on prosecuting patents, providing legal opinions on the value of U.S. patents, and supporting litigation involving patents. Although trained as a scientist, I decided to enter law after I became interested in patents while I was working as a research scientist. Reasons that people with science backgrounds give for becoming attorneys are as varied as the people themselves. To make this article of interest to a wider audience, I decided to write about what I see as similarities between the two professions. Many, if not most, people think that scientists and attorneys are worlds apart; however, in my opinion this is not necessarily the case. For example, both scientists and lawyers believe in the existence of objective reality and that we can uncover it if we work hard enough. In addition to this fundamental similarity, there are many other qualitative parallels as well.

Honesty

Both scientists and lawyers value diligent information gathering and a dispassionate analysis of the facts. Whether testing a hypothesis in the laboratory or the validity of someone's story told under oath, the facts and how they can best be interpreted are of primary interest to people in both professions.

I have always held scientists in the

highest regard; after all, how many among us have the courage to try to prove ourselves wrong every time we go to work? Moreover, while many attorneys are paid to tell one side of a story best (*i.e.* their client's), it is necessary to know as much as possible about both sides of the story to do the most effective job. In the practice of law, as in science, diligence matters. In the practice of law, as in science, you may not lie. One of the greatest misconceptions about lawyers is that they lie. In reality, a lie can get an attorney fired and cost them their license. Again, like scientists who publish results that they know to be false, deliberately telling tall tales to a court or to opponents can result in the loss of reputation and professional standing.

Law School and Graduate School: Learning a New Language

Lawyers, like scientists, speak in their own language, and a big part of gaining admittance to either group is learning the jargon. If you don't believe this is true, think back to the first time that you tried explaining your research project to your non-scientist friends or family members. On the flip side, read the fine print on the agreement that you have with your credit card company and then tell the rest of us what it means. The ability to communicate



Emanuele

in both technical and legal terms helps scientists who practice law to stand out from their peers.

Writing Is Essential to Both Professions

Most attorneys spend most of their billable time writing. You cannot draft strong patents, persuasive briefs, or even memos or letters explaining the law to senior attorneys or to your clients unless you develop good writing skills. A very big part of the practice of law, like science, is communicating in writing with your peers and, increasingly, with the uninitiated. Explaining patent law to a scientist who is a novice inventor or an invention to a judge with a BS degree in English present opposite sides of the same coin. Similarly, a major component of being a successful (*i.e.* well funded) research scientist is being a good writer. Journal articles, like legal briefs and memos, are only as good as their endnotes. No judge cares what an attorney thinks. Each statement in a legal brief or motion, just like each statement in a peer reviewed journal article, must be supported by proper references or pinpoint cites to data. Both the style and frustrations of scientific writing provide excellent training



for law school and the practice of law.

If you are considering attending law school, my best advice is to learn how to write effectively, especially under a tight deadline. Grades in law school depend directly upon how well you write under pressure, and your success and happiness as a practicing attorney are very likely to be tied closely to how well you write and how much you enjoy writing.

Uses of a Science Degree in the Practice of the Law

Like many attorneys with a technical background, I have concentrated my practice in the area of patent law. Great potential exists in many areas of the


film prints and journal articles to MP3 files. Trademarks are actually about protecting consumers; someone asking for a Coke® has the right to receive a Coke® and not a Pepsi®. Any licensed attorney may practice copyright, trademark, and trade secret law and litigate patents. But only a registered patent agent or patent attorney may represent clients before the United States Patent and Trademark Office (PTO).

To become a registered agent you must pass the patent bar exam, a test administered by the PTO. To take the exam you must have studied either science or engineering. In practice, most patent attorneys and agents have degrees in either engineering or one

to examine patent applications and determine which applications warrant patent protection. The rationale for patents is that they promote economic growth by allowing investors that fund the development of an invention the right to monopolize the invention long enough to allow the investors to recoup their investments plus an incentivizing profit. Patents also serve the common good by encouraging inventors to share their knowledge with the general public. In order to qualify for a patent, inventors must describe their inventions and teach (enable) their competitors how to use them as well. When the patent term expires, anyone may freely use the invention.

Currently, there is considerable debate among economists and law school professors as to how well this system works. Most experts agree that patents are essential to the pharmaceutical industry. This fact means that people with degrees in both the life sciences and the law still have decent job prospects, although the number of opportunities varies by region. Jobs are more plentiful in areas of the country with large investments in the pharmaceutical and biotech industries.

Closing

For me, the practice of law has been a great experience because I am paid to learn something new almost every day. If you are interested in becoming an attorney, I urge you to seek out someone in the profession and offer to take that person to lunch. Lawyers love to talk about their work and themselves like most folks do, so you will likely get some great insight into both the field and the job market in your region. If you look like a prospective client, the attorney will very likely pay for your lunch! 

“If you are considering attending law school, my best advice is to learn how to write effectively, especially under a tight deadline.”

law for people who possess a technical background, including environmental law, regulatory affairs such as representing clients before the Food and Drug Administration or the Environmental Protection Agency, medical malpractice, toxic tort liability, product liability, and transactional work involving the possession or use of intellectual property such as patents and technical trade secrets.

Intellectual Property: Technical Writing and the Law

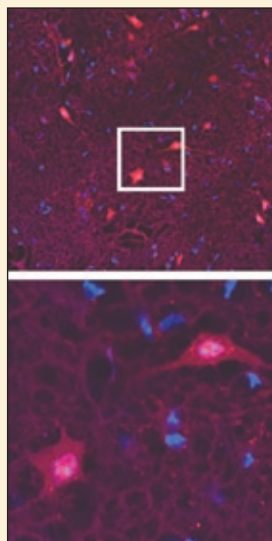
For most technical people, intellectual property means patents. To lawyers, intellectual property includes patents, trade secrets, copyrights, and trademarks. Copyrights govern the right to reproduce and distribute materials from

of the natural sciences. As a marketing tool, an advanced degree in some technical field is very helpful, but it does not guarantee success as an attorney. A registered patent attorney (in contrast to a registered patent agent) is someone who is admitted to at least one state bar and who has also passed the patent bar exam. In most states, you must graduate from an accredited three-year law school and then pass the bar exam of that state to be admitted to bar.


The U.S. Constitution gives Congress the authority to create copyrights and patents: “Congress shall have power . . . To promote the progress of science and useful arts, by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries” (U.S. Const. Art. 1 § 8). Congress created the PTO

Silencing Superoxide Dismutase

The use of small interfering RNA (siRNA) to silence mutant genes that possess unwanted functions holds promise for treating disorders such as Parkinson disease or amyotrophic lateral sclerosis. One big roadblock, however, is developing stable siRNA molecules that can effectively treat such chronic degenerative conditions. In this article, the authors designed and tested a chemically stabilized siRNA (modified on the 2'-hydroxyl position of the nucleotide) for human Cu,Zn superoxide dismutase (SOD1) in a mouse model of ALS, infusing the siRNA through an osmotic pump implanted near the spinal cord. The molecule demonstrated remarkable stability, lasting



Fluorescence microscopy revealing wide distribution of modified SOD1 siRNA in mouse spinal cord.

for at least one month at body temperature. The authors also showed that their approach met many other criteria for therapeutic effectiveness, including widespread siRNA distribution, intracellular uptake, and most importantly the ability to knock down SOD1 and slow disease progression without adverse side effects. Although clinical trials are still far in the future, this study does bring siRNA therapy one step closer to that goal. 

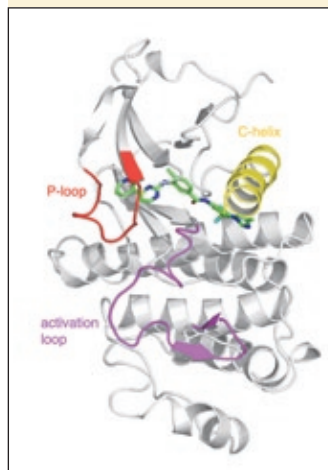
Therapeutic Gene Silencing Delivered by a Chemically Modified Small Interfering RNA against Mutant SOD1 Slows Amyotrophic Lateral Sclerosis Progression

Hongyan Wang, Animesh Ghosh, Huricha Baigude, Chao-shun Yang, Linghua Qiu, Xugang Xia, Hongxia Zhou, Tariq M. Rana, and Zuoshang Xu

J. Biol. Chem. 2008, **283**, 15845–15852


jbcb

ABL Bodied Structures



Ribbon diagram of ABL kinase bound with the inhibitor nilotinib (in green).

The ABL protein kinase is an important drug target in the treatment of chronic myelogenous leukemia (in the form of the BCR-ABL fusion protein). However, current structural understanding of ABL is largely based on x-ray crystallography of the solid state that may not capture the full ensemble of available conformations. Now, the NMR structures of the ABL kinase in complex with three clinically used

drugs (imatinib, nilotinib, and dasatinib) have been solved, providing the first detailed solution structures of a kinase-inhibitor complex. These structures provide insights into the dynamics of ABL protein kinase and help clarify its physiologically relevant binding modes. For example, residual dipolar coupling data on the imatinib and nilotinib complexes show that the ABL activation loop adopts the inactive conformation, whereas the dasatinib complex preserves the active conformation, contrary to the predictions based upon molecular modeling. These structures should enhance our understanding of multiple inactive conformations observed in some kinases and may also shed light on how point mutations in BCR-ABL lead to drug resistance, enabling the rational design of more potent inhibitors. 

Solution Conformations and Dynamics of ABL Kinase Inhibitor Complexes Determined by NMR Substantiate the Different Binding Modes of Imatinib/Nilotinib and Dasatinib

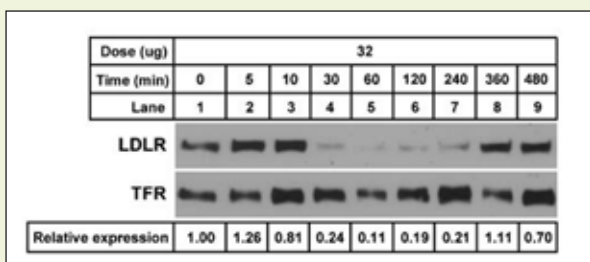
Navratna Vajpai, André Strauss, Gabriele Fendrich, Sandra W. Cowan-Jacob, Paul W. Manley, Stephan Grzesiek, and Wolfgang Jahnke

J. Biol. Chem. 2008, **283**, 18292–18302

jbcb

PCSK9 Reduces LDL Receptors

Proprotein convertase subtilisin/kexin type 9 (PCSK9) has been gaining attention as a regulator of the low density lipoprotein receptor (LDL-R) protein; gain-of-function mutations in PCSK9 cause hypercholesterolemia, whereas loss-of-function mutations result in lower plasma LDL and reduced risk of coronary disease. Several studies have been teasing out the therapeutic potential of PCSK9, but so far treatments require doses over 100-fold higher than normal circulating levels to be effective. In this article, the authors successfully reduced LDL-R levels in mouse liver with normal plasma concentrations of PCSK9 (0.05–0.60 µg/ml). They obtained large quantities of purified recombinant human PCSK9 from stably transfected HEK293S cells and directly injected the protein into mice. A single injection could reduce liver LDL-R by ~90% in less than an hour, and receptor levels returned to normal after six hours. Treatment with a gain-of-function PCSK9 mutant (D374Y) accelerated the process, whereas a catalytically inactive form of PCSK9 (S386A) also proved effective, suggesting the mode of action of this protein is not dependent on its catalytic activity.



Immunoblot analysis of LDL-R levels in liver membranes of wild-type mice 5–480 minutes after the injection of 32 mg of recombinant human PCSK9.

Plasma PCSK9 Preferentially Reduces Liver LDL Receptors in Mice

Aldo Grefhorst, Markey C. McNutt, Thomas A. Lagace, and Jay D. Horton

J. Lipid Res. 2008 **49**, 1303–1311



Comparing CFTR Repair Strategies

Cystic fibrosis is a recessive disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) that disrupt protein folding, causing



Functional connectivity map of the CFTR-interacting proteins during chemical rescue or genetic repair (red ovals).

degradation, and that also provoke an inflammatory response in the lungs. Two approaches to alleviate CFTR degradation are chemical rescue with agents like sodium 4-phenylbutyrate or gene transfer therapy. In this study, the authors looked for CFTR-interacting proteins that act in common during chemical rescue or genetic repair of cultured $\Delta F508$ -CFTR bronchial epithelia to identify therapeutic networks. Their CFTR interactome revealed that both repair avenues produced changes in a subset of HSP70 chaperones associated with endoplasmic reticulum-associated degradation; these regulatory changes occurred at both the cell surface and in subcellular compartments. These HSP70 system proteins could not only mark therapeutic interactions, but may themselves be useful targets to correct CFTR ion transport and restrain the inflammatory phenotype.

Chemical Rescue of $\Delta F508$ -CFTR Mimics Genetic Repair in Cystic Fibrosis Bronchial Epithelial Cells

Om V. Singh, Harvey B. Pollard, and Pamela L. Zeitlin

Mol. Cell. Proteomics 2008 **7**, 1099–1110



John Denu: *The Importance of Reversible Protein Acetylation*

BY NICK ZAGORSKI

Protein phosphorylation is unquestionably a critical cellular process, but the focus given to the attachment and removal of phosphate groups from proteins sometimes leaves the impression that it's the be-all and end-all method of regulating proteins. However, an abundance of reversible chemical modifications for proteins exist, each serving their own purpose in carefully controlling the countless activities occurring inside cells.

One such emerging modification might be reversible acetylation (not to be confused with irreversible N-terminal acetylation that caps many proteins during translation). True, most researchers consider acetylation an important event, but typically only in relation to histones, the protein spools that compact our DNA thread into form-fitting chromatin. Altering the pattern of acetyl groups can change which portions of chromatin are exposed to DNA-binding proteins, making them essential for proper gene expression, replication, and repair.

"But there's so much more to acetylation than one protein class," says John Denu, Professor of Biomolecular Chemistry at the University of Wisconsin-Madison School of Medicine and Public Health. "And only recently have we gained a greater appreciation for this modification." A goodly amount of credit for this new

appreciation stems from the work of Denu, who switched over from the bustling phosphorylation field to work on this "other" modification.

Through his studies, we've found that proteins throughout a cell—nucleus, cytoplasm, even mitochondria—can be modified by acetylation and learned more about the sirtuins, proteins whose deacetylation of metabolic enzymes might hold the key to a longer life span. He's also begun to branch out to other modifications, examining how all of them come together to form the enigmatic "histone code."

Here's Looking at You, Kid

Denu has always been interested in the living world; a large part of that stemmed from his upbringing in the southern Wisconsin town of Beloit. His house backed along a wooded creek, which, better than any large screen TV, gave Denu a first-hand glimpse into the wonders of nature. "I spent a lot of time as a kid in my backyard, just observing the creatures and other natural events." As he grew a bit older, he shifted his wonder to a deeper level, trying to understand what elements were behind all these natural things he had been enamored by in his youth.



Denu

In high school and later college at Wisconsin, that reasoning would lead Denu toward biochemistry, and particularly enzymology. "I figured, to really satisfy my desire about how biology works at the molecular level, why not try and understand the enzymes that carry out biology. To this day the minute details about enzymatic processes still fascinate me."

After completing his undergraduate biochemistry degree in 1988, Denu moved on to Texas A&M University for his doctorate. And if you're wondering what convinced a small town Wisconsin boy to relocate to Texas, he quotes one of his all-time favorite movies, *Casablanca*: "I went there for the waters," Denu says in an impressive Bogart tone. "I was misinformed."

In all seriousness, Denu sought to take advantage of his Ph.D. years. "This was a prime opportunity for me to get away, find a warm place to study, and experience life in a different culture. And Texas certainly fit that bill." He notes that Texas A&M also contained a large and strong biochemistry department, giving him plenty of options for his graduate

studies; he ended up joining the lab of Paul Fitzpatrick, where he studied the mechanisms of flavoproteins (enzymes that use the riboflavin derivative FAD and/or FMN as a cofactor).

After completing his dissertation, Denu moved on to a post-doc with Jack Dixon at the University of Michigan, a position that would let him apply the enzymology skills he learned as a student to the field of reversible protein modifications. "It had become such a fascinating concept to me," he says. "Add just one tiny chemical group to a protein, and that can completely change its structure or function." Denu specifically chose that lab because Dixon was one of the leaders in protein phosphorylation, specializing in the phosphatase enzymes that remove phosphate groups.

For his project, Denu got to work on an unusual subset of this

family known as dual specificity phosphatases. Phosphatases generally act on one of two amino acid groups, with most recognizing serines/threonines, whereas a minority recognizes tyrosine. The dual specificity phosphatases, first identified by Dixon in 1991, could recognize both groups equally. Not much was known about them, except they were regulated by mitogens and thus central players in cell growth and cancer, but Denu helped uncover both the structure and catalytic mechanism of these enzymes before venturing off to start his own lab at Oregon Health Sciences University (OHSU) in 1996.

The Beginning of a Beautiful Friendship

Denu initially continued his phosphatase studies at OHSU but soon decided to take a slight detour and pursue a different type of reversible modification: the addition and

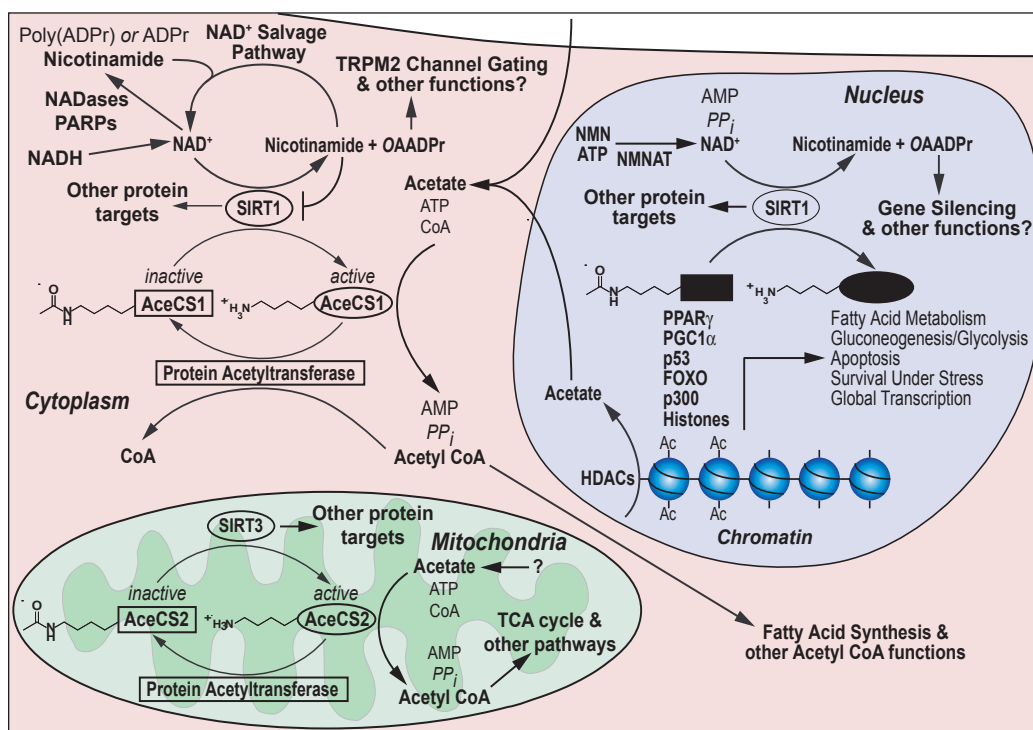
removal of acetyl groups. "Going to acetylation didn't seem like a major intellectual jump," he says. "It gave me a way to explore an exciting new area but remain within the confines of reversible modifications."

The excitement of acetylation had sprung from David Allis' discoveries in the mid-90s of the first histone acetyltransferase (HAT) enzymes in *Tetrahymena*, "a discovery that opened the floodgates of chromatin research," Denu says. Scientists soon discovered that many of the co-activators for the transcription factors they studied were in fact histone acetyltransferases, revealing the importance of these enzymes in gene expression. Not long after, it was discovered that several transcription factors themselves, proteins like p53, were also targets of acetylation.

Denu, though, believed that these findings still represented just the tip of the iceberg. After all, the side chain

target of acetylation is a positively charged lysine (although some recent studies suggest that serine and threonine can also be acetylated by pathogenic bacterial proteins), a common residue in many enzyme catalytic sites. Converting that positive charge into a neutral group would be a logical way to shut an active site down.

In 2006, Denu, after following many leads, found an example, the metabolic enzyme acetyl-CoA synthetase, which joins acetate



More than just chromatin: sirtuin deacetylases regulate many important pathways throughout a cell.

and coenzyme A. His study, demonstrating that an acetyl group on a key lysine (the one that binds ATP) needed to be removed for proper function, provided the first evidence of a mammalian enzyme being controlled by reversible acetylation. “I knew it could only be a matter of time before we saw other proteins, not just those involved in gene expression, with acetylation modifications,” Denu says. “And now that we’ve escaped the nucleus (acetyl-CoA synthetase has two isoforms, one in the cytoplasm and the other in the mitochondria), I think we’ll find many more.” Denu points out that a recent proteomics study suggests that over 200 proteins can be acetylated in mammals.

For Old Times’ Sake

The search for a non-histone-related acetylation took a while as Denu found himself transported to a strange new world a little over 8 years ago. He had begun his studies characterizing the structure and function of HATs when he read about some unusual proteins called sirtuins. Originally identified as transcription silencers

that played a role in life span (at least in lower organisms), these proteins—officially named the SIR2 (silent information regulator 2) family—could deacetylate histones, but apparently they required the NAD⁺ cofactor.

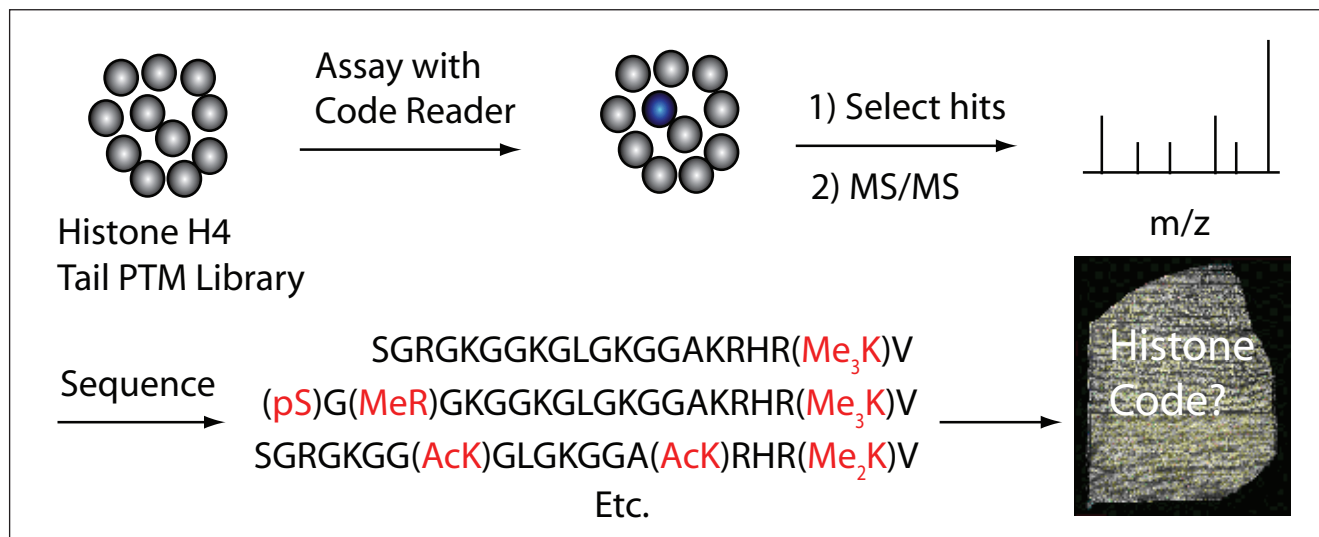
“And this was just too bizarre,” Denu says, “as all other known deacetylases only needed water to remove the acetyl group. So I decided I had to characterize this reaction; from my background as an enzymologist, this was too interesting not to pursue further.” Denu found that in the case of SIR2, the NAD was actually a substrate in the deacetylation reaction; following removal, the acetyl group was transferred onto the ribose ring of NAD, generating an acetylated ADP-ribose molecule (*O*-acetyl-ADP-ribose (OAADP)).

“Of course, this begs the question of why Mother Nature would go through the trouble of consuming NAD to perform a reaction that can easily be done by other means.” Although several researchers proposed that sirtuin activity might be closely linked to the NAD concentration in cells, Denu wondered if at least part of the reason might be to generate this

novel metabolite of largely unknown function. “Maybe some of the phenotypes associated with sirtuins are because of the actions of this ADP-ribose molecule and not protein deacetylation.”

To find out if his idea might be correct, Denu has been further exploring this unusual metabolite. “We don’t know what OAADP ribose does, so our best approach to understanding this chemical is to go after the proteins or enzymes that bind it, metabolize it, or degrade it,” he says. Along with Andrew Scharenberg at the University of Washington, he showed that TRPM2, an ion channel that is involved in cell death, is one potential target (and, interestingly, TRPM2 can bind both the acetylated and non-acetylated ADP-ribose). Other researchers have found that OAADP ribose can bind to a histone H2A variant known as macro-H2A, as well as a complex in yeast responsible for silencing certain regions of the genome, thus working in synergy with sirtuins. “There are definitely some interesting targets out there.”

In addition to the metabolite, the sirtuins themselves have some



Cracking the histone code: a chromatin-binding protein (the “code reader”) is passed over a peptide library containing the ~800 possible modification states of the H4 tail; positive interactions are then analyzed by mass spectrometry, revealing the modification sequences that promote binding for each protein.

interesting targets, as Denu notes they are an enzyme class that's been found to act on non-histone proteins. In fact, SIRT1 and SIRT3 are enzymes that deacetylate the cytoplasmic and mitochondrial acetyl-CoA synthetases, respectively. This connection is especially promising because it ties in to that most tantalizing of sirtuin properties, aging. "SIRT1 has gotten a fair amount of press as a protein that promotes increased life span through caloric restriction or resveratrol, the chemical in red wine that harbors many health benefits," he says. It's possible that sirtuins may extend life span through their direct regulation of metabolic and mitochondrial enzymes, and one of Denu's major initiatives is finding more direct links between deacetylation to metabolism.

Denu's aspirations to unlock the mysteries of sirtuins eventually brought him back to his home state in 2003. "OHSU was a wonderful place, but as a smaller medical institute with a limited number of departments, it would have been difficult to continue our research, which was going down a chemistry road," he says. As it happened, the University of Wisconsin had the opportunities and the opening. It also gave him new collaborators like Richard Weindruch and Tomas Prolla, who have been studying aging and calorie restriction in mice; the three of them have recently begun some new "metabolomics" studies with sirtuin knock-out mice.

Go Ahead, Tell It...

The "genetic code" may have been a tough nut to crack, but it pales in comparison with the "histone code," the arrangement of modifications on histone proteins that dictates how they interact with the DNA wrapped around them as well as other proteins. The complexity arises because histones apparently have yet to meet a protein

Out of Focus: Love and Basketball

Next to science and family, one thing that John Denu loves is basketball. He's been playing it since his youth, and one of his big childhood dreams was making it to the professional ranks. "But of course, this was not reality," he says. Today, he settles for his twice weekly pick-up basketball group with other faculty and staff from the University—but lest you think biochemistry professors have no skills, Denu notes it's a fairly competitive affair. "It's been a real love of mine, and I use many basketball analogies to help describe science and life: leadership, competition, excellence, teamwork, and camaraderie. Not everybody understands my analogies, but I use them anyway."


modification that they don't like; besides phosphorylation and acetylation, methylation and citrullination (removing a side chain nitrogen from arginine) also occur on histones—just to name a few.

"Even the short tail of histone H4, which is about 22 amino acids long, has over 800 possible modification permutations," says Denu, "although the tail of histone H3 ranges in the millions."

No histone is too big for a modification buff like Denu, though, who has decided to take on this challenge. His approach is to develop a combinatorial peptide library that contains all 800 possible states of the histone H4 tail. By passing a specific protein over the library, he can see which peptides elicit the strongest binding. "In essence, we're asking chromatin proteins what modifications they prefer." Denu has tested his library with human JMJD2A histone demethylase and found that binding affinity could range over 1000-fold depending on the modifications, demonstrating that this strategy should be useful to decode the optimal patterns for histone-binding proteins.

And much like Bogart and Bergman from his favorite film, Denu has also been reunited with an old flame, the HAT enzymes he began characterizing nearly a decade ago.

"My HATs were on hold for a little bit after all the sirtuin studies took off," he says, "but now I've managed to get the resources to pursue both with equal fortitude." HATs typically occur as multisubunit complexes, and Denu is trying to figure out what job the other proteins in the complex have. "Do they enhance catalysis? Do they restrict substrate access? Or, is it even some other function we're not considering?"

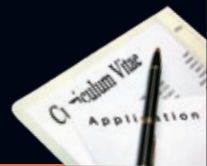
He doesn't know the ending yet, but as someone once said: "Maybe one will come to you as you go along." 

Nick Zagorski, Ph.D., a graduate of Johns Hopkins and Cornell Universities, is a science writer for ASBMB. He can be reached at nzagorski@asbmb.org.

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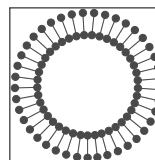
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FEBRUARY 22–25, 2009

SAN DIEGO, CA
<http://www.ushupo.org>
E-mail: ushupo@ushupo.org
Tel.: 505-989-4876

APRIL 2009

3rd International Congress on Prediabetes and the Metabolic Syndrome—Epidemiology, Management, and Prevention of Diabetes and Cardiovascular Disease

APRIL 1–4, 2009

NICE, FRANCE
www.kenes.com/prediabetes

ASBMB Annual Meeting

APRIL 18–22, 2009

NEW ORLEANS, LA
www.asbmb.org/meetings

MAY 2009

57th ASMS Conference on Mass Spectrometry

MAY 31–JUNE 4, 2009

PHILADELPHIA, PA
<http://www.asms.org>
E-mail: office@asms.org
Tel.: 505-989-4517

JUNE 2009

VIII European Symposium of the Protein Society

JUNE 7–11, 2009

ZURICH, SWITZERLAND
Organizer: Andreas Plückthun (University of Zurich)
www.proteinsociety.org

3rd EuPA Meeting—Clinical Proteomics

JUNE 14–17, 2009

STOCKHOLM SWEDEN
<http://www.lakemedelsakademin.se/templates/LMAstandard.aspx?id=2529>

APRIL 2010

ASBMB Annual Meeting

APRIL 24–28, 2010

ANAHEIM, CA
www.asbmb.org/meetings



2008 ASBMB Special Symposia Series



Glycobiology of Human Disorders Symposium

OCTOBER 9-13, 2008

Emory University Conference Center, Atlanta, GA

ORGANIZER: Richard D. Cummings, *Emory University*



Transcriptional Regulation by Chromatin and RNA Polymerase II

OCTOBER 16-20, 2008

Granlibakken, Lake Tahoe

ORGANIZER: Ali Shilatifard, *Stowers Institute for Medical Research*

PLENARY LECTURER: Robert G. Roeder, *The Rockefeller University*



Cellular Lipid Transport: Connecting Fundamental Membrane Assembly Processes to Human Disease

OCTOBER 22-26, 2008

Radisson Hotel & Conference Center, Canmore, Alberta, Canada

ORGANIZERS: Dennis R. Voelker, *National Jewish Medical Research Center, Jean Vance, University of Alberta, Edmonton, and Todd Graham, Vanderbilt University*

PLENARY LECTURER: Robert Molday, *University of British Columbia*



Post Translational Modifications: Detection and Physiological Evaluation

OCTOBER 23-26, 2008

Granlibakken, Lake Tahoe

ORGANIZERS: Katalin F. Medzihradszky, and Ralph A. Bradshaw, *UCSF*

PLENARY LECTURER: M. Mann, *Max Planck Institute of Biochemistry, Martinsried*

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