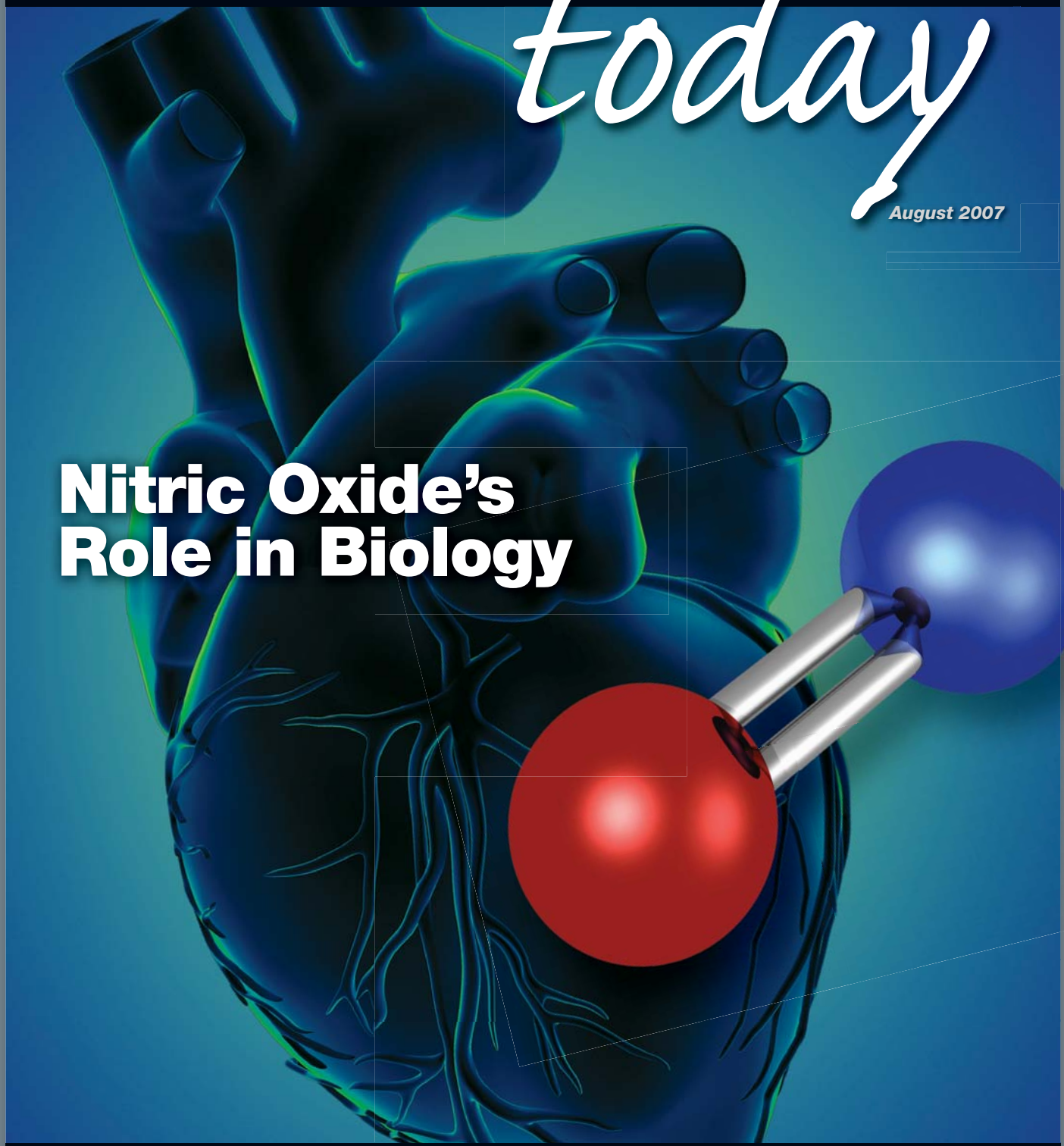
2008 ANNUAL MEETING THEMATIC OVERVIEWS INSIDE

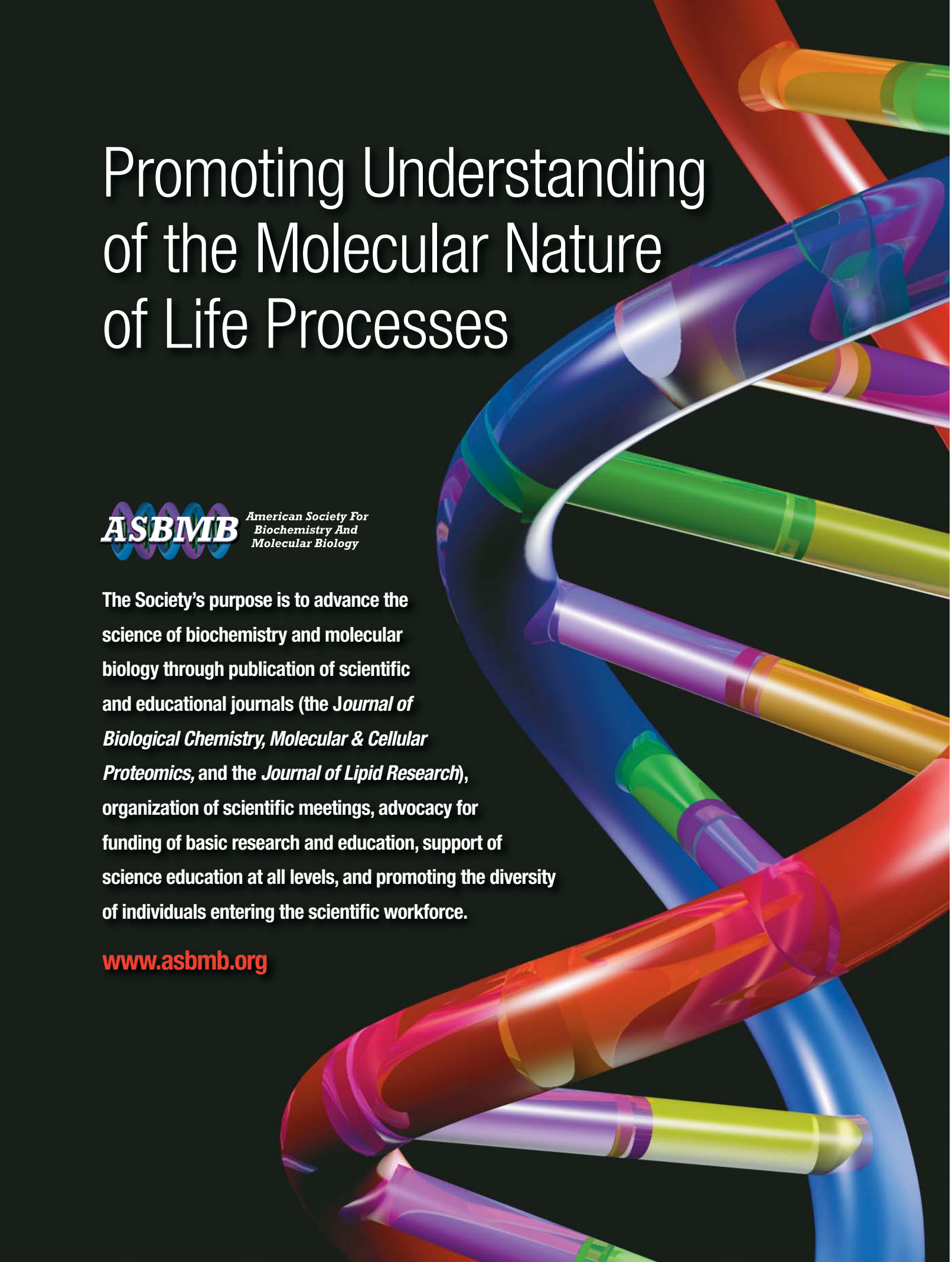
ASBMB today

August 2007



Nitric Oxide's Role in Biology

American Society for Biochemistry and Molecular Biology



Promoting Understanding of the Molecular Nature of Life Processes

ASBMB American Society For Biochemistry And Molecular Biology

The Society's purpose is to advance the science of biochemistry and molecular biology through publication of scientific and educational journals (the *Journal of Biological Chemistry, Molecular & Cellular Proteomics,* and the *Journal of Lipid Research*), organization of scientific meetings, advocacy for funding of basic research and education, support of science education at all levels, and promoting the diversity of individuals entering the scientific workforce.

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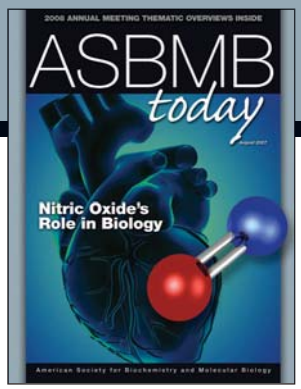

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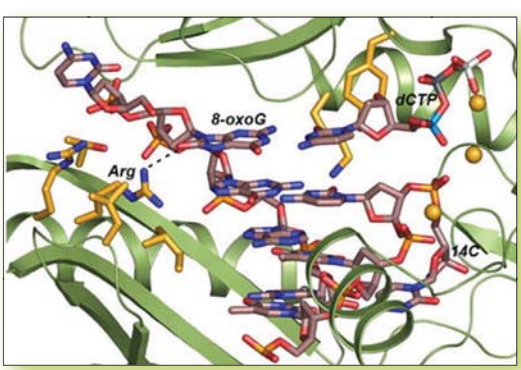

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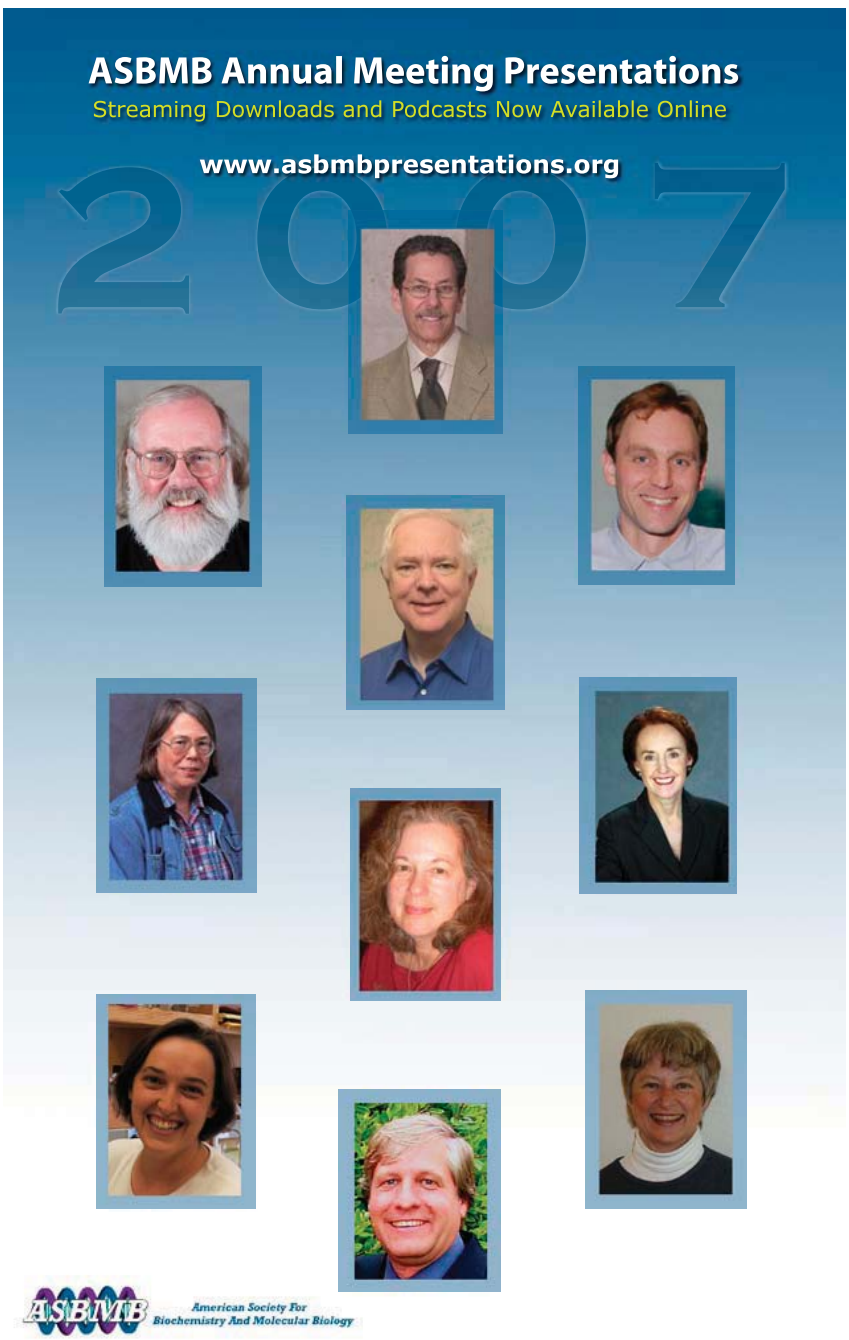
president's message

An ASBMB delegation led by Heidi Hamm is currently in China.

The President's Message will return in the September issue of the magazine.



letters to the editor

Leaving Academic Science

To the Editor:

In the May 2007 issue of *ASBMB Today*, there was a profile of a young woman investigator [Rashmi Nemade, Career Insights, pages 18-19] who, like so many young women, has left academic science for an "alternative career." In the article she says:

"I was disenchanted by the academic lifestyle, i.e. lots of hard work and personal sacrifice for risky gains. I looked around my lab and found that even the brightest, hardest working, dedicated, and well published scientists were, after at least a year or two of interviewing, landing academic positions at institutions that were not their first choices. My colleagues that got academic positions had to work seven days a week trying to prove to their new department members that they were worthy of the appointment. In the long run, I didn't want to work that hard for that long and make so many personal sacrifices, i.e. time with family for a last choice institution and a low salary.

"The real turning point came when I realized that children could, should, and would be a part of my future. Both my husband, who is not a scientist, and I had demanding careers and had not planned on having children, but the feeling was growing, and I was worried about how we would balance family and work. I did a lot of soul searching and looked deeply and seriously into my future and realized a few things: I wanted to have children and enjoy time with them, I wanted to have enough money to send my kids to college and retire at a decent age, and I did not want to work in a profession that required me to work seven days a week."

The young woman who wrote this article identifies several critical points. One is of course the issue we are all familiar with, the issue of balancing family and work.

Second, there is a strong sense of reluctance to embark on a career that requires long hours and poor remuneration. "I want to have enough money to send my kids to college and retire at a decent age," she writes. Now, I will argue that anyone who has achieved a Ph.D. and a postdoc is not afraid of hard work *per se*. But clearly this young woman saw no end to it and no way to accomplish her life goals in an academic setting. Bright people with doctoral education have lots of other ways to make money than on partial-year salaries at a university; the brightest are perhaps the least likely to stay.

Third and most disturbing to me is her perception of academic science as high risk and low return. For long hours and hard work, she sees the likelihood of ending up in a place where she wants to work as low, she sees little financial reward and a lot of financial risk, and she sees funding uncertainty and a never ending instability in an academic career that never stops demanding all of her time. Basically she sees her interest in science as incompatible with academic research.

The National Institutes of Health (NIH) funding crisis, the poor job prospects in academic science, the permanent postdocs, and the family-unfriendliness of the profession are a dangerous combination.

With even senior investigators losing grants and salaries, with jobs few and far between and often distant from family, with the demands of our institutions on our time even greater, really, why would anyone who wants to be involved in science choose academe? I fear that this effect will disproportionately affect under-represented groups in science, making the gap seem more insurmountable. I have already seen an increase in women graduate students deciding against academic postdocs because they feel it is too stressful on top of everything else.

Therefore, I think that the women in science groups need to address the hypothesis that the funding crisis in biomedical science is going to disproportionately affect recruitment and retention of women at all levels in academic institutions.

Susan L. Forsburg
University of Southern California

Tell Us What You Think

We appreciate receiving letters that are suitable for publication regarding issues of importance or comment on articles appearing in *ASBMB Today*. Letters should be sent to the editor at the address found in the masthead. Letters must be signed and must contain the writer's addresss and telephone number.

The editor reserves the right to edit all letters.

2008 NIH Funding Advances in House, Senate

BY PETER FARNHAM

Early July saw progress on National Institutes of Health (NIH) funding for FY 2008 in both House and Senate—but the amount of money involved is not what the biomedical research community had been anticipating.

On July 11, the House Appropriations Committee approved a total of $29.65 billion for NIH, an increase of $750 million (2.6%) above FY 2007 and $1.029 billion (3.6%) above the President's request. But the committee also kept the provision contained in the bill approved by the subcommittee on Labor, Health and Human Services, Education and Related Agencies (L/HHS) to increase the amount of the transfer from NIH to the Global HIV/AIDS fund from $99 million this year to $300 million in FY 2008. NIH thus receives only $549 million under the House bill, less than a 2% increase.

Appropriations Committee Chairman David Obey (D-WI) tried to put the best face on the proposal, commenting that it provides $1 billion more than the President requested and that this will allow NIH to increase (by 545) the number of new and competing research grants funded in FY 2008. He also noted that the $620 million increase NIH received in FY 2007 is allowing NIH to support important initiatives, as well as an additional 992 research grants.

President Bush has said he will veto the L/HHS bill if it reaches his desk in its current form because the House version contains $12 billion more in spending than the President proposed in his FY 2008 budget. The Senate bill is, from the President's perspective, not much better, with $10 billion more proposed spending than he wants. However, most of these increases merely make up for inflationary cuts in the President's budget. (His proposals are well below inflation.) Only a little over $4 billion of the proposed additional House spending is more than restoring inflationary cuts.

The bill faces a difficult House floor fight next week. (It is expected to go to the floor on July 18.) Much of the biomedical research community is supporting the bill. However, neither ASBMB nor FASEB is supporting it because the bill does not even meet the level of NIH funding needed to match biomedical inflation, expected to be 3.7% this year. Other major groups that are not supporting the bill are the American Heart Association, the American Cancer Society, and Research!America.

Meanwhile, in the Senate…

The Senate Appropriations Subcommittee on L/HHS did slightly better for NIH funding during its June 19 markup, recommending that NIH receive an additional $800 million in FY 2008, a 2.8% increase (after a $200 million transfer to the Global AIDS program). The bill was approved by the full Senate appropriations committee on June 21.

Chairman Tom Harkin (D-IA) pointed out during the markup that the House L/HHS subcommittee had $2 billion more to distribute among its programs than he did (due to the vagaries of the appropriations process, which proceed largely on parallel but separate tracks in the House and Senate). Harkin said that he plans to fight for the higher House allocation during the upcoming conference.

Ranking member Arlen Specter (R-PA) remarked that although the bill is almost $10 billion higher than the President's proposed spending for FY 2008, the increase is still inadequate and cited the NIH as an example of an agency that requires additional resources. Harkin agreed and said that he wished he could provide more money to NIH, although he noted that NIH was receiving the largest dollar increase for any agency or program in the bill except for the Title I Education Program.

The biomedical research community is thus faced with a fifth year of no growth in the NIH budget; if this situation holds, it means that NIH purchasing power will have declined by more than 13% since the doubling was completed at the end of FY 2003. Further, the prognosis for

meaningful increases at NIH this year is slim; there simply is no money available to distribute. In addition, the President, as noted above, has indicated he will veto the L/HHS bill because it exceeds his spending recommendations, and it may be sustained—147 House Republicans have signed a letter indicating that they will sustain a presidential veto (146 votes are required).

Open Access Language

Both the House and Senate versions of the bill contain identical language regarding NIH's public access policy. The House changed its initial language to recognize copyright concerns, thus agreeing with the Senate language. Here is the bill language:

"…The Director of the NIH shall require that all investigators funded by the NIH submit or have submitted for them to the [National Library of Medicine's] PubMed Central an electronic version of their final, peer-reviewed manuscripts upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication: Provided, That the NIH shall implement the public access policy in a manner consistent with copyright law."

The effect of this language, if implemented, would be to make mandatory the submission of all "final, peer-reviewed manuscripts" derived from NIH-funded work to the National Library of Medicine's PubMed Central within 12 months of the official date of publication. Currently, NIH requests, but does not require, that researchers submit such manuscripts. NIH wants to make the policy mandatory because so far, under the non-mandatory approach, only about 4% of NIH researchers comply.

Peter Farnham, CAE, is ASBMB's public affairs officer.

NCRR Requests Comments on Strategic Plan

In a July 9 letter to the biomedical research community, Barbara Alving, director of the NIH's National Center for Research Resources (NCRR), asked for comments on its developing strategic plan.

As noted, "NCRR is seeking your input as we develop a new Strategic Plan covering 2009–2013. As a $1 billion-a-year research center, NCRR enables NIH-funded researchers across the country to translate basic discoveries into improved patient care. Therefore, to ensure that NCRR remains responsive to our various stakeholders, we would like input from you and your members on six questions, which were published in the Federal Register on July 6, 2007.

We invite you to complete our user-friendly response form, available at NCRR's Strategic Planning Web site, www.ncrr.nih.gov/strategicplan, by **August 24, 2007**."

The questions are as follows:

1. What are the most significant trends, developments, and/or needs in biomedical research that are likely to materialize over the next 5 years, and what can NCRR do to be prepared to respond to them?
2. From the standpoint of achieving the broadest impact among investigators, what new or expanded research resources and/or animal models should be developed over the next 5 to 8 years?
3. The recently introduced CTSA (Clinical and Translational Science Award) program seeks to transform the local, regional, and national environment for clinical and translational science, thereby increasing the efficiency and speed of clinical and translational research. What considerations will be most crucial to the long-term success of this initiative?
4. Despite significant progress, research institutions serving predominantly minority and underserved populations face stiff challenges. What can NCRR do to most effectively support the long-term advancement of these institutions?
5. NCRR has worked with many Federal and private sector institutions, agencies, and organizations and will continue to do so as we move forward. What organizations should NCRR seek out for future partnerships to most effectively support, expand, and advance its programs and services?
6. Is there anything else you would like to add that would be helpful to NCRR?

The ASBMB Public Affairs Advisory Committee will be preparing a response to these questions. If you have any suggestions or thoughts, please send them to ASBMB's Public Affairs Officer, Pete Farnham, at pfarnham@asbmb.org. You are also encouraged to provide your own comments to NCRR as well, using the contact information above. We would appreciate receiving a copy of any comments you submit.

—Peter Farnham

FASEB Society Leaders Take Message to Congress

BY CARRIE D. WOLINETZ AND JON RETZLAFF

FASEB's third annual "Capitol Hill Day" took place June 4-5, 2007, in conjunction with the biannual FASEB Board of Directors' meeting and the meeting of the Science Policy Committee (SPC). During the course of two afternoons, FASEB's SPC and board members from a dozen states visited the offices of Congressional leaders, appropriators, authorizers, and other members of Congress who have expressed an interest in medical research. In addition, FASEB's Board presented House Energy and Commerce Committee ranking member Joe Barton (R-TX) with the 2007 FASEB Public Service Award for working very closely with FASEB on numerous issues, including helping to promote the importance of investigator-initiated research. Unfortunately, because of the Appropriations Committee mark-ups scheduled for that day, we had to postpone the ceremony for the other recipient of FASEB's Public Service Award in 2007, Appropriations Committee Chairman David Obey (D-WI).

The meetings provided an opportunity for FASEB society leaders to discuss the importance of federally-funded scientific research, provide information about their individual work, share their personal experience on being an extramural researcher (how competitive it is to acquire funding, their involvement with peer review panels, etc.) and share various FASEB resources—such as the state-specific National Institutes of Health (NIH) advocacy, FASEB's *Breakthroughs in Bioscience* series, and the community's recommendation for NIH funding in FY2008—with congressional offices. (These resources are available on the FASEB Web site.)

FASEB past president Leo Furcht (left) and FASEB board member David Bylund (right) present Rep. Joe Barton with the federation's Public Service Award.

The following excerpt from *Nature* summarizes a message that the FASEB society leaders conveyed during their meetings with regard to NIH funding: "Only four years after completion of a historic 'doubling' of the NIH budget, biomedical researchers in the U.S. are experiencing unprecedented competition for research funding, and for many there is deteriorating morale about the prospects for survival in research careers. Three factors, in combination, account for this dramatic change: flat funding for NIH has left funded researchers and their institutions vulnerable to the rising costs of biomedical research; funds for new and competing continuations have been cut; and the increased capacity for research has resulted in a higher demand for funds. Boom and bust cycles are wasteful and inefficient. Steady, long-term growth will provide the optimal conditions for progress in science.

Carrie D. Wolinetz and Jon Retzlaff are with the FASEB Office of Public Affairs.

ASBMB Member Assumes FASEB Presidency

Focusing on a long-term vision for science will resonate as a theme for FASEB President Robert Palazzo, Ph.D., who has been an active member of ASBMB's Public Affairs Advisory Committee. Palazzo took office on July 1 and will serve a 1-year term as head and chief spokesperson for the federation. Recently appointed provost of the Rensselaer Polytechnic Institute, Troy, New York, he also serves as professor of biology and director of Rensselaer's Center for Biotechnology and Interdisciplinary Studies. Within FASEB, Palazzo has chaired the NIH Issues Subcommittee of the Science Policy Committee, a group that played a pivotal role in FASEB's influence on and successful passage of last year's NIH reauthorization legislation. Richard Marchase, Ph.D., vice president of research and senior associate dean for research at the University of Alabama School of Medicine, Birmingham, was FASEB's president-elect.

Assessing Minority Programs

For the past three decades, private and federal agencies have supported programs nationwide aimed at increasing the representation of ethnic minorities in science and technology fields. According to participant testimonials, these programs have assisted many in their choice and pursuit of a career in these areas. However, the percentage of minority scientists, physicians, and engineers in the U.S. workforce do not reflect the demographics of our population. Do programs designed to foster the increased participation of minorities in science, technology, engineering, and mathematics (STEM) disciplines really work for all students? Are alternative strategies needed for different student pools? How does one develop an assessment method to answer these questions? The "Best Practices in the Assessment of Minority Programs" symposium at ASBMB 2007 organized by the Minority Affairs Committee and chaired by Takita F. Sumter of Winthrop University addressed these issues. The symposium was comprised of a series of talks that outlined the best practices in evaluating programs designed to increase the numbers of underrepresented groups who pursue careers in the sciences. The speakers presented suggestions and practical ideas for designing and implementing systems that effectively measure program success.

The symposium was opened by Sumter with the most recent statistics on our nation's current status in diversifying the sciences. In the 2000 report published by the National Science Foundation, ethnic minorities accounted for about 7% of the nation's STEM workforce and that those numbers are even lower for those holding doctorates. However, the numbers of doctorates in science and engineering awarded to those from underrepresented groups has increased 11.4% from 2001–2005 compared to a 0.9% increase for non-minority doctorates during the same period. As a result, it was suggested that programs designed to promote increased representation of minorities in STEM disciplines are likely working and that the community is now poised to methodically analyze these programs and their effects on student success.

The first speaker, A. James Hicks, the director of the Louis Stokes Alliance for Minority Participation (LSAMP) at the National Science Foundation (NSF), discussed the results of an LSAMP evaluation conducted by the Urban Institute. Founded in 1991, the goal of LSAMP is to help students from underrepresented groups overcome various obstacles and facilitate their progression through the pipeline. The program supports pre-college, undergraduate, and graduate programs in which students are typically involved in a research experience and receive financial support. As a result of the evaluation, the summer bridge program, research participation, mentoring, and caring staff were identified as elements contributing to the success of LSAMP. In addition, Hicks discussed the newest LSAMP program—Bridges to the Doctorate. This program provides financial support for institutions to bring in cohorts of minority graduate students who have the option of pursuing advanced degrees in any STEM discipline. The students are provided financial support, all while communing with other ethnic minority students "on the bridge." Although students are only awarded NSF support for two years, 70% of students remain in their graduate programs for five years. Hicks concluded his discussion by recapping the elements of success identified by the Urban Institute's evaluation and emphasizing that the study also reported "a high degree of cooperation between alliance members" although each partner institution maintains its autonomy in program administration.

Turning from a federal to an academic perspective, John Matsui of the University of California, Berkeley (UCB) Biology Scholars Program (BSP) described the long term assessment of their program. In his model, Matsui presented the option of serving students who, based on SAT scores, advanced placement courses, and high school grade point averages, are less qualified. Students in the Biology Scholars Program are selected based on their interest and commitment to success, determined from both an application and personal interview. In his efforts to "serve the underserved," Matsui coordinates study groups and provides paid research experiences, faculty mentoring, and an advisor who is sensitive to the unique challenges of the student participants. Upon graduation, ethnic minority BSP scholars graduate with higher undergraduate GPAs than non-BSP ethnic minorities, and the average BSP GPA is typically comparable to majority UCB graduates.

However, Matsui does not rest on the successful history of this program but continues to rigorously analyze its effectiveness. To further investigate the effectiveness of his program, he has collaborated with social scientists to build an assessment model that mirrors the rigor of basic science research. Matsui and his colleagues have begun to ask, "Would these students have been successful without BSP? Are BSP students simply more motivated than Berkeley students at large? Is there a correlation among research, graduation rates, and final GPA for BSP members and/or nonmembers?" Matsui presented some results that addressed these questions and encouraged others in the field to take diversity work, in which student outcomes are effectively measured and published, as their prime obligation.

In contrast to Matsui's model in which students are selected despite their lower than UCB's average high school records, the Meyerhoff Scholars Program at the University of Maryland Baltimore County (UMBC) selects high achieving high school students with exceptionally high GPAs and SAT scores. From the summer preceding their freshman year, these students join the Meyerhoff family that involves many of the elements of the programs mentioned above—summer bridge, study halls, research experiences, etc. Altogether, there are 14 components that successfully integrate methods to address the social and academic needs of the program participants and are geared toward supporting and encouraging success that will eventually lead to a Ph.D. or M.D. / Ph.D. Lynn Zimmerman of UMBC shared the goals and preliminary findings from a new study currently underway to use qualitative and quantitative tools in analyzing the success of each of the 14 program components. The goal of the study is to methodically address whether the Meyerhoff Program has a greater positive impact on particular groups of participants. Are minority women and/or men more likely to benefit from the Meyerhoff Program than non-minority groups? Which student characteristics are the strongest predictors of success? What components of the program are most essential to the successful outcomes observed? Zimmerman also suggested that many of the lessons learned from the studies being conducted by she and a large team of social scientists will impact the entire UMBC campus. She noted that the elements of the Meyerhoff scholars program found to have the greatest effect on student success could be readily adapted to faculty development programs.

The session concluded with an open discussion of the issues and challenges of evaluating programs designed to increase diversity in science. The audience and panelists provided some practical solutions to those challenges that will hopefully provide a framework for developing informative short and long term evaluation plans.

In general, Sumter thought the session was a huge success. The issues discussed are central to the mission of the Minority Affairs Committee and the future of science and technology. In fact, understanding how to promote and sustain a culturally diverse workforce depends on our assessment of these programs. To adequately assess your program you should: 1) Have several clearly defined objectives based on previously published literature, 2) Build a team of experts (likely to include a social scientist) who can accurately measure progress towards the stated objectives, and 3) Disseminate your findings to others by publishing your results.

Ten ASBMB Members in Academy's 2007 Class of Fellows

This past spring, the American Academy of Arts and Sciences announced the election of 203 new Fellows and 24 new Foreign Honorary Members. Ten ASBMB members were among these 227 scholars, scientists, artists and civic, corporate, and philanthropic leaders.

"It gives me great pleasure to welcome these outstanding leaders in their fields to the Academy," said Academy President Emilio Bizzi. "Fellows are selected through a highly competitive process that recognizes individuals who have made preeminent contributions to their disciplines and to society at large."

The Academy will welcome this year's new class at its annual induction ceremony in October at the Academy's headquarters in Cambridge, Massachusetts.

The newly elected ASBMB members and their affiliations at the time of election are:

Brenda L. Bass, University of Utah, Salt Lake City, Utah
Bonnie Lynn Bassler, Princeton University, Princeton, New Jersey
Bernard G. Forget, Yale School of Medicine, New Haven, Connecticut
Barry Hirsh Honig, Columbia University, New York, New York
Robert Andrew Lamb, Northwestern University, Evanston, Illinois
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Jeremy W. Thorner, University of California, Berkeley, California
Joan Selverstone Valentine, University of California, Los Angeles, California
Susan R. Wessler, University of Georgia, Athens, Georgia

RETROSPECTIVE:

John M. Buchanan (1917-2007)

PHOTO COURTESY OF PROTEIN SCIENCE (3).

John (Jack) Machlin Buchanan was 89 years old when he died on June 25, 2007. In an active career that spanned 50 years, he was a pioneering contributor to the fields of purine nucleotide biosynthesis and nucleic acid metabolism.

Buchanan was born in Winamac, Indiana, in 1917. He attended DePauw University in Greencastle, Indiana, where he received an A.B. in 1938. Buchanan started his graduate studies in the Department of Biological Chemistry at the University of Michigan and earned an M.S. in 1939. He then moved to Harvard University where he worked with A. Baird Hastings studying glycogen synthesis in rats using ^{11}C-lactic acid. This was one of the earliest studies of biosynthetic pathways using isotopic labeling techniques, one that materially contributed to the understanding of the gluconeogenic pathway from lactic acid.

After completing his Ph.D. in 1943, Buchanan joined the faculty in physiological chemistry at the University of Pennsylvania Medical School, rising to full professor by the time he left there in 1953. He was awarded a Medical Research Council Fellowship between 1946 and 1948, which he used to work with Hugo Theorell at the Nobel Institute in Stockholm. During this time he gained expertise in protein and enzyme chemistry, and perhaps more importantly, he met Elsa Nielsen who would eventually become Elsa Buchanan, his wife and inseparable companion of 57 years.

At the University of Pennsylvania, Buchanan and his colleagues embarked on a study of the biosynthesis of purines. Initially, the precursors of the various positions of the purine ring were determined by isotopic labeling methods *in vivo*, using pigeons, which excrete the purine uric acid in large amounts. His subsequent elucidation of purine nucleotide biosynthesis *de novo* stands as a classic example of unraveling metabolic pathways by a combination of labeling and enzymological dissection of the individual steps.

In 1953 Buchanan joined the Massachusetts Institute of Technology faculty as professor of biology and director of the newly established Division of Biochemistry. At MIT, his research interests branched in several new directions. Arising from the purine work and its implication of folic acid cofactors in one-carbon transfer reactions, a subset of his group worked out key steps in the biosynthesis of the methyl group of methionine. Another group investigated the details of nucleotide and nucleic acid synthesis in bacteriophage T4-infected *Escherichia coli* cells, including the means by which the phage subverts the normal DNA synthesis of the cell. Continuing the focus on nucleotide metabolism, Buchanan's laboratory found that up-regulation of DNA synthesis after fertilization of *Arbacia* eggs could be traced to a dramatic increase in the synthesis of ribonucleotide reductase, an essential enzyme for the formation of deoxyribonucleotide precursors of DNA. Interest in regulation of eukaryotic cell growth and the cell cycle was extended in enzymological studies on the transformation of fibroblasts by proteolytic enzymes and oncogenic viruses. Buchanan remained at MIT for the rest of his career, becoming Wilson Professor of Biochemistry in 1967 and Wilson Professor Emeritus in 1988.

Over his scientific career, Buchanan was the recipient of many honors. He received the American Chemical Society's Eli Lilly Award in Biochemistry in 1951 and was named the Harvey Society Lecturer in 1958. Buchanan was elected to the American Academy of Arts and Sciences in 1953 and to the National Academy of Sciences in 1962. He was secretary of the American Society for Biological Chemists (now American Society for Biochemistry and Molecular Biology) from 1969 to 1972 and served on the editorial boards of several journals, including the *Journal of Biological Chemistry* (1961–1967), the *Journal of the American Chemical Society* (1961–1972), and *Physiological Reviews* (1957–1960 and 1965–1971).

Additional accounts of Buchanan's research can be found in his *Journal of Biological Chemistry* "Reflection" and "Classics" articles (1, 2).

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asbmb member spotlight

Please submit news about yourself to asbmbtoday@asbmb.org

Holick Honored by Institute for Functional Medicine

Michael F. Holick was recently awarded the 2007 Linus Pauling Functional Medicine Award from the Institute for Functional Medicine. Holick, an internationally recognized expert in vitamin D and skin research, received the award for decades of pioneering work that elucidated the important role vitamin D plays in a wide variety of chronic health conditions.

The award was presented at the 14th International Symposium on Functional Medicine in Tucson, Arizona this past May. The Linus Pauling Award is given for research that is changing the way people think about a biomedical problem.

Holick is a professor of medicine, physiology, and biophysics and director of the General Clinical Research Center at Boston University School of Medicine and is also Director of the Bone Healthcare Clinic at Boston Medical Center. Since joining the Boston University School of Medicine, Holick has initiated numerous clinical research programs. His psoriasis work with active vitamin D is considered to be on the forefront of research into this complex disease. The results of these programs have led to significant contributions in the basic science of vitamin D and more recently toward a clearer understanding of the calciotropic hormone PTHrP and its uses. This translates into remarkable new therapies for a wide diversity of diseases from psoriasis and hair loss to osteoporosis.

Kolodner Is Landon Awardee

This year's winner of the Kirk A. Landon-American Association for Cancer Research (AACR) Prize for Basic Cancer Research is Richard D. Kolodner, member of the Ludwig Institute for Cancer Research, and professor of medicine and member of the Moores Cancer Center at the University of California, San Diego School of Medicine.

Kolodner was recognized for his fundamental discoveries in the field of DNA mismatch repair and its connection to human cancer.

The Kirk A. Landon-AACR Prize for Basic Cancer Research is one of the largest such awards offered to cancer researchers from a professional society of their peers. Kolodner received an unrestricted cash award of $200,000 and presented a scientific lecture at the AACR Annual Meeting in Los Angeles, California, this past April.

Kolodner's major contribution to cancer biology has been in defining the molecular mechanisms of DNA mismatch repair. His work has demonstrated how inherited defects in mismatch repair are directly linked to human cancer. Kolodner was the first to tackle the study of mismatch repair through a creative combination of bacteria/yeast genetics and biochemistry along with a human genomic approaches.

Lefkowitz, Snyder Share Top Prize in Medicine

Robert J. Lefkowitz and Solomon H. Snyder have been awarded the Albany Medical Center Prize in Medicine and Biomedical Research, America's top prize in medicine. They will share the $500,000 prize with Ronald M. Evans for research on how cells communicate with their environment through the use of signaling pathways.

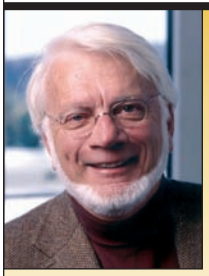
The Albany Medical Center Prize is the largest prize in medicine in the United States and second worldwide to the Nobel Prize in Physiology and Medicine. The annual Prize—announced each spring—was created to encourage and recognize extraordinary and sustained contributions to improving health care and promoting biomedical research with translational benefits applied to improved patient care.

Lefkowitz is James B. Duke Professor of Medicine and Howard Hughes Medical Institute Investigator at Duke University Medical Center. In the mid-1980s he and his colleagues cloned the genes for several adrenergic receptors and showed that all G protein-coupled receptors have a very similar structure and mechanism of action.

LEFKOWITZ

SNYDER

Solomon H. Snyder is Distinguished Service Professor in the Department of Neuroscience at Johns Hopkins School of Medicine. He was the first to identify receptors in the brain that are the targets of opiates and then went on to identify receptors for virtually all of the major neurotransmitters.



Steitz Receives Gairdner Award

Yale biophysicist Thomas A. Steitz has received one of the four 2007 Gairdner International Awards, among the most prestigious awards in science, for his groundbreaking work on the structure and function of the large subunit of the ribosome and the structural basis for the action of antibiotics that target the ribosome.

"The 2007 awards reflect the importance of basic discoveries that lead to a better understanding of human disease and the development of treatments and cures to alleviate them," said John Dirks, President and Scientific Director of the Gairdner Foundation.

Thomas A. Steitz, Sterling Professor of Molecular Biophysics and Biochemistry at Yale and Howard Hughes Medical Institute Investigator, and Harry F. Noller of the University of California at Santa Cruz were honored for their studies on the structure and function of the ribosome, demonstrating that a step in bacterial protein synthesis is an RNA-catalyzed reaction. This step is inhibited by many antibiotics, and understanding the structural basis of the function points the way to the development of new antibiotics.

Steitz established Rib-X Pharmaceutical, Inc., which is using this knowledge of the structures of the large ribosomal subunit and its antibiotic complexes to create new classes of antibiotics. In just five years, Rib-X has moved one potential compound into Phase II clinical trials and hopes that shortly others will enter the Phase I trials pipeline.

Three ASBMB Members Receive ASM Awards

ASBMB members Diana Downs, Susan Gottesman, and Martha M. Howe were honored by the American Society for Microbiology (ASM) during their 107th General Meeting this past May.

Diana Downs of the Department of Bacteriology, University of Wisconsin, Madison, received the 2007 ASM Graduate Microbiology Teaching Award for her excellence in graduate education and as a role model for women in science. According to the ASM, "She has dedicated herself to exemplary teaching and mentoring while maintaining her record as a stellar and productive scientist."

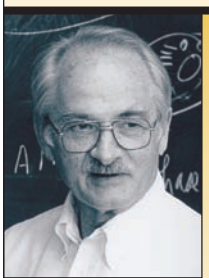
Susan Gottesman, chief of the Biochemical Genetics Section, Laboratory of Molecular Biology, National Cancer Institute, National Institutes of Health (NIH), was honored with the 2007 ASM Founders Distinguished Service Award. Gottesman was recognized for her strong record of work on behalf of the ASM in varied capacities.


DOWNS


GOTTESMAN


HOWE

Martha M. Howe, Van Vleet Professor of Virology, University of Tennessee Health Science Center, Memphis, was presented with the 2007 Alice C. Evans Award for her contributions to the advancement and full participation of women in microbiology.



IN MEMORIAM

Paul Karl Stumpf 1919-2007

Paul Karl Stumpf, a professor emeritus of molecular and cellular biology at the University of California (UC), Davis, who helped build the campus both physically and in scientific reputation, died on February 10, 2007.

Stumpf received his bachelor's degree in biochemistry, magna cum laude, from Harvard University in 1941 and a doctorate in biochemistry from Columbia University in 1945. In 1948, he joined University of California, Berkeley as an assistant professor in the Division of Plant Nutrition, then the Department of Plant Biochemistry—later renamed Agricultural Biochemistry—finally becoming professor and chair of that department at Berkeley. In 1958, Stumpf and another Berkeley colleague, Eric Conn, moved to University of California, Davis to establish the Department of Biochemistry and Biophysics. Stumpf served as chair of the department four times during his career at UC Davis. He retired in 1984, going on to help found the UC Davis emeriti association and serving as its founding president.

Stumpf pioneered the study of the biochemistry of lipids in plants, training many students who went on to become leaders in the field and publishing more than 250 research papers over four decades. Among his achievements was the discovery in plants of the α-oxidation pathway for degrading fatty acids. Genetic defects in the same pathway in animals are linked to rare hereditary diseases.

Lipid Signaling and Metabolism

BY JAMES NTAMBI AND SUZANNE JACKOWSKI

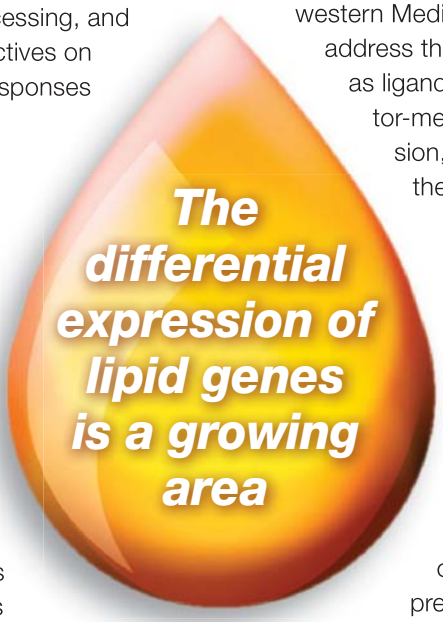
Knowledge of the molecular links between signaling and metabolism is increasing every year, particularly where lipids are involved. Lipid intermediates can be signaling ligands, inducing expression of selected genes to reconfigure metabolic networks. Activation of biological programs that distinguish the structure and function of different cell types also stimulates lipid biosynthetic or degradative pathways. Investigators who are forging the links between these two complex areas of research are featured in four symposia organized under the theme of "Lipid Signaling and Metabolism" at the ASBMB 2008 Meeting in San Diego. Multiple modes of regulation govern lipid interactions and lipid processing, and the speakers will provide their perspectives on the factors that balance the cellular responses to lipids and by lipids.

In the session on "Tissue-specific Regulation of Lipid Metabolism," we will get insight into the unique functions of lipids and their precursors in different specialized organs. James Ntambi from the University of Wisconsin-Madison will describe the role of the stearoyl-CoA desaturase as a mediator of the prolipogenic effects of saturated fatty acids and a regulator of *de novo* hepatic triglyceride synthesis. Dan Lane of Johns Hopkins University will provide an update of his research on malonyl-CoA signaling in the hypothalamus; this signaling is rapidly transmitted to skeletal muscle by the sympathetic nervous system and increases energy expenditure. David Bernlohr, from the University of Minnesota, will report on the link between fatty acid transport in adipose tissue and the activation of AMP-kinase, an important regulator of fatty acid metabolism and flux.

The differential expression of lipid genes is a growing area of interest because it contributes to the variety of cell types in higher organisms. In the session on "Lipids and the Control of Gene Expression," Suzanne Jackowski from St. Jude Children's Research Hospital will present her latest investigations of mouse knock-out models and what they reveal about the roles of phospholipid biosynthetic genes in cell biology and physiological function. Donald Jump, who recently moved to Oregon State University, will describe the fatty acids, their metabolites, and the membrane proteins that utilize them in the regulation of genes of lipid metabolism. And Joyce Repa from the University of Texas Southwestern Medical Center will address the functions of lipids as ligands of nuclear receptor-mediated gene expression, with recent focus on the FXR.

Suzanne Jackowski

James Ntambi



"Stress and Lipid Metabolism" is the focus of the third session and will provide new and exciting information about the involvement of lipids in cellular challenge—both as a cause and as a component of the response. Jean Schaffer from Washington University will update her research findings on lipotoxicity and lipid-mediated endoplasmic reticulum stress. Sarah Spiegel of Virginia Commonwealth University will present the latest data on the bioactive ligand sphingosine phosphate and its role in the response to stress. Jody Brewer, who recently moved to the University of Southern Alabama, will describe the transcriptional activation of the genes of phospholipid synthesis by factors that control the unfolded protein response.

A link is emerging between lipid metabolism and the inflammatory response, both normal and aberrant, and will be covered in the session on "Lipids and Inflammation." Alan Tall from Columbia University College of Physicians and Surgeons will address the relationships between lipoproteins, macrophages, and atherosclerosis, an important area of broad interest. Peter Tontonoz,

Lipid Signaling and Metabolism Thematic Meeting

ORGANIZERS:
James Ntambi,
University of Wisconsin-Madison
Suzanne Jackowski,
St. Jude Children's Research Hospital

Symposium: Tissue-specific Regulation of Lipid Metabolism

Stearoyl-CoA Desaturase and Regulation of de novo Hepatic Lipid Synthesis, *James M. Ntambi*

Malonyl-CoA Signaling and Control of Hypothalamic Control of Energy Balance, *M. Daniel Lane*

Fatty Acid Transport in Adipose Tissue Linked to Activation of AMPK, *David A. Bernlohr*

Symposium: Lipids and Control of Gene Expression

Animal Models and Control of Genes of Lipid Metabolism, *Suzanne Jackowski*

Lipids and Membrane Proteins That Regulate Genes of Lipid Metabolism, *Donald B. Jump*

Lipids as Ligands of Nuclear Receptor Mediated Gene Expression, *Joyce J. Repa*

Symposium: Stress and Lipid Metabolism

Lipid-mediated ER Stress, *Jean Schaffer*

Sphingosine Phosphate and the Response to Stress, *Sarah Spiegel*

Membrane Biogenesis Induced by the UPR, *Joseph W. Brewer*

Symposium: Lipids and Inflammation

Lipoproteins, Macrophage Function, and Atherosclerosis, *Alan R. Tall*

LXR in Lipid Signaling-mediated Inflammation, *Peter Tontonoz*

Fatty Acids, Macrophage Function, and Inflammation, *Gökhan S. Hotamisligil*

University of California at Los Angeles, will describe his productive investigations into the regulation of LXR activity in inflammation that is mediated by lipid signaling. And Gökhan Hotamisligil of Harvard School of Public Health will present his insight into the role of fatty acids in macrophage function and inflammation.

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Signal Transduction Theme

BY KUN-LIANG GUAN

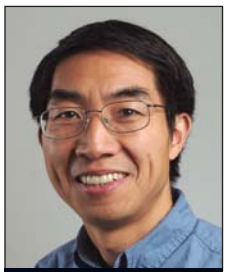
Appropriate cellular response to the microenvironment is a fundamental aspect of cell biology. Cells must properly perceive extracellular and intracellular signals and translate them into their own language to adequately respond. In other words, they must communicate with one another to function correctly

This communication is critically important in the regulation of cell growth, proliferation, differentiation, and development. Understanding the biochemical mechanism of cellular signaling has been a major research topic throughout the past decades. Dysregulation of the signaling pathway is associated with a wide range of human diseases such as cancer, metabolic disorders, and autoimmune diseases.

Signal transduction has had a significant presence in ASBMB annual meetings, and 2008 will be no exception. The Signal Transduction theme of the 2008 annual meeting consists of four sessions covering current topics in the field. Jean Wang from the University of California, San Diego (UCSD) Medical School will chair the first session, titled "Signaling in Disease and Therapy." Wang will discuss Abl tyrosine kinase signaling and its role in cancer development. Gleevec is a specific Abl kinase inhibitor and represents a new generation cancer drug with exciting therapeutic results. This topic will be followed by Melanie Cobb from the University of Texas (UT) Southwestern Medical Center. Cobb will present protein kinases that are implicated in diabetes and hypertension. Mutation of specific protein kinases has been linked to these common diseases. The session will end with Jack Dixon from UCSD. He will present exciting new insights into how pathogens—specifically bacteria pathogens—hijack our signaling systems for their benefit. This session will have a strong focus on signaling and disease relevance.

Understanding the biochemical mechanism of cellular signaling has been a major research topic throughout the couple past decades.

The second session will be devoted to research on the mechanism and regulation of cell growth. Recent studies have established mTOR as a central regulator in cell growth and cell size. The pathway integrates a wide range of intracellular and extracellular signals, and dysregulation of mTOR is frequently associated with human diseases. This session will be chaired by Kun-Liang Guan from the University of Michigan. Guan will discuss the regulation of TSC tumor suppressors and their role in the control of mTOR. Mike Hall from the University of Basel will discuss new developments of the TOR complexes and their cellular functions. Lew Cantley is a professor at Harvard Medical School, and his presentation will focus on lipid kinases such as phosphatidylinositol 3-kinase in the regulation of cell growth and metabolism.


Kun-Liang Guan

Post-translational modifications are extensively utilized by all signaling pathways to regulate cellular protein activities. This session will be chaired by Kim Orth from the UT Southwestern Medical Center. Ubiquitination is involved in not only regulation of protein degradation but also protein function. Ubiquitination and protein degradation ensure that a biological event occurs unidirectionally, such as the cell cycle. Yue Xiong from the University of North Carolina (UNC) at Chapel Hill will discuss protein ubiquitination, especially the large family of E3 ubiquitin ligase, in control of ubiquitination specificity, protein stability, and cell cycle regulation. Orth will continue on with post-translational modification of ubiquitin family proteins. In addition, she will discuss the novel modification of serine methylation and the coordination or antagonism between serine methylation and phosphorylation. Steve Young from the University of California, Los Angeles will lecture on lamin A protein modification, such as farnesylation and its implication in progeria, a disorder with accelerated aging. These presentations will demonstrate how various protein modifications regulate cellular signaling processes.

The last session is on G proteins and protein kinases. This session will be chaired by Ken Blumer from Washington University at St. Louis. G protein coupled receptor (GPCR) signaling and protein phosphorylation are the two main themes in the signaling field. Each of these could be sufficient for a full conference. There has been significant progress in understanding the pharmacology, cell biology,

Signal Transduction Thematic Meeting

ORGANIZER:
Kun-Liang Guan, *University of Michigan*

Symposium: Signaling in Disease and Therapy

Nuclear Abl in DNA Damage Signaling, *Jean Wang*

Kinases in Diabetes and Hypertension, *Melanie Cobb*

Intersection of Host Signaling Pathways by Pathogens, *Jack Dixon*

Symposium: Growth Regulation

Growth Regulated Kinases, *Kun-Liang Guan*

Tor Complexes, *Mike Hall*

Growth and Survival Signaling by Lipid Kinases, *Lew Cantley*

Symposium: Post-Translational Modifications

Ubiquitination and Cell Cycle, *Yue Xiong*

Serine and Threonine Acetylation by YopJ-like Proteins, *Kim Orth*

Lamin A Processing and Inhibition in Progeria, *Steve Young*

Symposium: G Proteins and Protein Kinases

RGS Protein Regulation in Cardiovascular and CNS Signaling, *Ken Blumer*

Structural Mechanisms of G Protein Activators and Regulators, *John Sondek*

Phosphoproteomics and Erk Signaling, *Natalie Ahn*

and physiology of the large family of G protein coupled receptors over the past two decades, and yet we still know very little about the structural basis of GPCR signal transduction. Brian Kobilka from Stanford University will discuss recent progress in characterizing ligand-induced conformational changes and crystal structures of the β-2 adrenergic receptor. Along the same line, John Sondek from UNC will present new studies on small molecule in regulation of G proteins, with an emphasis on structure and function. The proteomics approach has dramatically impacted the research of protein kinases and phosphorylation, and thus in conclusion Natalie Ahn from the University of Colorado at Boulder will discuss protein phosphorylation and ERK signaling in a proteomic aspect. Collectively, these speakers will advance the understanding G protein and kinase signaling.

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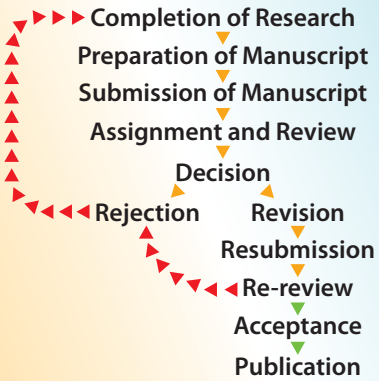

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RNA-Mediated Gene Expression

BY LYNNE E. MAQUAT AND WILLIAM F. MARZLUFF

You know RNA has hit the big time when it makes the cover of the June 14 issue of none other than *The Economist*! These days, its not so much of a surprise when RNA makes the New York Times in articles with cute titles like "RNA Comes out of the Shadow of Its Famous Cousin" or "RNA Trades Bit Part for Starring Role in the Cell." However, when *The Economist* runs an article on RNA entitled "Really New Advances," in which it takes note of the "staggering" diversity of RNA, we know that non-scientists are beginning to appreciate that RNA is something worth learning about.

The growing understanding that RNAs are structurally and functionally more diverse than ever imagined comes with the realization that there is much to discover (and, from *The Economist's* perspective, money to be made). It follows that those of us who work on RNA will be in business for a very long time. Furthermore, the impact of RNA on cellular metabolism makes it a molecule of importance even to researchers who don't study it directly.

ASBMB is pleased to sponsor talks on RNA biology at the 2008 ASBMB meeting in San Diego, a number of which will constitute the theme on "RNA-Mediated Gene Expression."

The first of four sessions that encompass this theme will focus on the "Regulation of Nuclear RNA Metabolism" and, in particular, transcripts synthesized by RNA polymerase II. James L. Manley from the Department of Biological Sciences at Columbia University in New York City will discuss the remarkable coordination of co- and post-transcriptional RNA processes in mammalian cells. Pamela A. Silver from the Department of Systems Biology at Harvard Medical School in Boston will present data demonstrating links between transcription and pre-mRNA splicing in *Saccharomyces cerevisiae*. Brenton R. Graveley from the Department of Genetics and Developmental Biology at the University of Connecticut Health Center in Farmington will discuss how the seemingly daunting process of pre-mRNA splice site selection occurs in *Drosophila melanogaster*.

The impact of RNA on cellular metabolism makes it a molecule of importance even to researchers who don't study it directly.

The second session falls under the broad domain of "Ribonucleoprotein" or RNP. Ever since scientists realized that RNA occurs in complexes with proteins rather than naked in cells, the association and dissociation of RNA binding proteins as a function of RNA biogenesis, processing, function, and decay has been an important topic of study. The first two talks will be by x-ray structural biologists Elena Conti from the Max-Planck-Institute of Biochemistry in Martinsried, Germany, and Jennifer A. Doudna from the Departments of Molecular & Cellular Biology and Chemistry at the University of California-Berkeley. Each has a history of generating beautiful and informative RNA structures that have lent insight into, for example, RNA channeling by the exosome or the basis for double-stranded RNA processing by Dicer, respectively. The third talk, to be given by Marvin Wickens from the Department of Biochemistry at the University of Wisconsin-Madison, will address the mechanisms of cytoplasmic polyadenylation and deadenylation, lending important insight into how proteins recognize RNA.

William F. Marzluff

Lynne E Maquat

The third session is entitled "RNA Transport and Localization." The first speaker, Robert H Singer from the Albert Einstein College of Medicine of Yeshiva University in the Bronx, is known for his impressive ability to track individual RNA molecules in living cells. He will present data on pathways for mRNA localization in the cytoplasm. Anne Ephrussi, who is a wonderful developmental biologist from the European Molecular Biology Laboratory in Heidelberg, Germany, will discuss RNA localization in early *Drosophila* development. Last, Susan R. Wente from the Department of Cell and Developmental Biology at Vanderbilt University Medical Center in Nashville, Tennessee, will speak about the regulation of nuclear mRNA export, which is critical to mRNA function in the cytoplasm.

The final session will pertain to "RNA Turnover." Lynne E. Maquat from the Department of Biochemistry and Biophysics at the University of Rochester Medical Center in Roch-

RNA-Mediated Gene Expression Thematic Meeting

ORGANIZERS:
Lynne E. Maquat, *University of Rochester*
William F. Marzluff, *University of North Carolina, Chapel Hill*

Symposium: Regulation of Nuclear RNA Metabolism

Co-transcriptional RNA Processes, *James L. Manley*
Differential Recruitment of the Splicing Machinery during Transcription Predicts Genome-wide Patterns of mRNA Splicing, *Pamela A. Silver*
Splicing Bioinformatics and Biology, *Brenton R. Graveley*

Symposium: Ribonucleoproteins

RNA Channeling by the Exosome, *Elena Conti*
Structural and Mechanistic Insights into RNA Function, *Jennifer A. Doudna*
Cytoplasmic Polyadenylation and Deadenylation, *Marvin Wickens*

Symposium: RNA Transport and Localization

Pathways for mRNA Localization in the Cytoplasm, *Robert H. Singer*
RNA Localization in Early Development, *Anne Ephrussi*
Nuclear mRNA Export, *Susan R. Wente*

Symposium: RNA Turnover

Nonsense-mediated and Staufen1-mediated mRNA Decay, *Lynne E. Maquat*
Cell Cycle-regulated Histone mRNA Decay, *William F. Marzluff*
Molecular Chaperones and Quality Control in Noncoding RNA Biogenesis, *Sandra L. Wolin*

ester, New York, will talk about nonsense-mediated mRNA decay, which is a quality control mechanism, and the related Staufen1-mediated mRNA decay pathway, which provides a means to conditionally regulate genes encoding mRNAs. William F. Marzluff from the Program in Molecular Biology and Biotechnology at University of North Carolina-Chapel Hill will discuss the intricacies of cell cycle-regulated histone mRNA decay. Last but not least, Sandra L. Wolin from the Department of Cell Biology at the Yale University School of Medicine in New Haven, Connecticut, will describe her exquisite work on molecular chaperones and quality control in non-coding RNA biogenesis.

Additional, shorter talks will be added based on abstract submissions. The organizers, Lynne E. Maquat and William F. Marzluff, hope to see you at the talks and will be happy to answer questions at any point during the meeting.

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Cell and Organelle Dynamics

BY MATT WELCH AND LOIS WEISMAN

One of the major challenges in cell biology is understanding how dynamic cell behaviors arise from the concerted action of intracellular mechanical systems and the regulatory networks that control them. The Cell and Organelle Dynamics theme at ASBMB 2008 will highlight exciting new developments in our understanding of the molecular mechanisms that underlie cell behavior. Sessions will focus on whole-cell behaviors such as division and migration, as well as intracellular processes such as membrane trafficking and organelle transport. Moreover, one session will highlight how pathways involved in cell and organelle dynamics are exploited by pathogens that cause infectious disease. The talks on this theme will emphasize that advances in this area have come from the study of diverse organisms as well as from technological developments in microscopy, genomics, and computational methodology.

Sessions will focus on whole-cell behaviors as well as intercellular processes.

The Cell and Organelle Dynamics theme is organized into four sessions:

- **Cell Division** ***(Chair: Tom Pollard,*** *Yale University)*
- **Cell Migration**
  (Chair: Alan Hall, *Memorial Sloan-Kettering Cancer Center)*
- **Intracellular Dynamics**
  (Chair: Lois Weisman, *University of Michigan, Ann Arbor)*
- **Host Pathogen Interactions**
  (Chair: Matthew Welch, *University of California, Berkeley)*

The **Cell Division** session will focus on advances in our understanding of the mechanical systems that drive cell division and the regulatory circuits that coordinate division with genome replication and segregation. The talks in this session will feature work in diverse organisms to highlight the evolutionary relationships between cell division mechanisms. Tom Pollard (Yale University) will describe work that combines quantitative microscopy and biochemistry methods to dissect the mechanisms of cytokinesis in fission yeast. Lucy Shapiro (Stanford University) will discuss recent efforts in her laboratory to elucidate how chromosome replication is spatially and temporally integrated with cell cycle regulatory circuits in the aquatic bacterium *Caulobacter crescentus*. Karen Oegema (University of California, San Diego) will discuss work using functional genomics and advanced microscopy in *Caenorhabditis elegans* to dissect the mechanisms of centrosome duplication and cytokinesis.

Matthew Welch

Lois S. Weisman

The **Cell Migration** session will feature new advances in our appreciation of how cytoskeletal and adhesion systems that mediate cell migration are coordinated by chemical signals from the environment and intracellular signal transduction pathways. The talks in this session will highlight diverse approaches, including advanced imaging and computational methods. Alan Hall (Memorial Sloan-Kettering Cancer Center) will describe work done in his laboratory to elucidate how migration processes are coordinated by RhoGTPase signaling. Carole Parent (National Institutes of Health, NCI) will discuss work done in her laboratory on the signaling pathways that control cell polarization and migration during chemotaxis. Gaudenz Danuser (The Scripps Research Institute) will describe advanced imaging and computational approaches that reveal how mechanical and chemical signals are integrated during cell protrusion and migration.

Complex cell behaviors are mediated by the underlying dynamic behavior of intracellular organelles. The **Intracellular Dynamics** session will focus on advances in our understanding of the processes of organelle transport and biogenesis, and will feature both diverse organisms and advanced approaches. Lois Weisman (University of Michigan, Ann Arbor) will describe recent work on the mechanisms that coordinate vacuolar transport and inheritance in yeast. Pietro De Camilli (Yale University) will discuss work in his laboratory to understand the molecular mechanisms that control membrane trafficking pathways in the neuronal synapse. David Drubin (University of California, Berkeley) will describe how the dynamic behavior of the actin cytoskeleton is harnessed for endocytic trafficking events in yeast.

The pathways that control cell and organelle dynamics are frequently exploited by pathogens that cause infectious disease. The **Host Pathogen Interactions** session will explore advances in our understanding of pathogen exploi-

Cell and Organelle Dynamics Thematic Meeting

ORGANIZERS:
Matthew Welch, *University of California, Berkeley*
Lois S. Weisman, *University of Michigan*

Symposium: Cell Division

Molecular basis of cytokinesis in fission yeast, *Tom Pollard*

Spatial and temporal integration of chromosome replication with the genetic circuit controlling the Caulobacter cell cycle, *Lucy Shapiro*

Using C. elegans to dissect cell division mechanisms, *Karen Oegema*

Symposium: Intracellular Dynamics

Vacuolar dynamics and inheritance in yeast, *Lois S. Weisman*

Molecular mechanisms in endocytosis at neuronal synapses, *Pietro De Camilli*

Harnessing actin dynamics for endocytic trafficking events, *David Drubin*

Symposium: Cell Migration

RhoGTPase signaling during cell migration, *Alan Hall*

Molecular insight into chemotactic signaling, *Carole Parent*

Integration of mechanical and chemical signals in cell protrusion, *Gaudenz Danuser*

Symposium: Pathogen Exploitation of Host Machinery

Exploitation of the actin cytoskeleton by bacterial and viral pathogens, *Matt Welch*

Modulation of host-cell function by a bacterial pathogen, *Jorge Galan*

TBA, *Julie Theriot*

tation of host cell systems, and will highlight how the study of pathogens has generated new insights into both disease processes and the normal mechanisms that control cell behavior. Matthew Welch (University of California, Berkeley) will discuss strategies used by bacterial and viral pathogens to exploit the host cytoskeleton during intracellular transport and replication. Jorge Galan (Yale University) will describe the work in his laboratory aimed at understanding how bacterial pathogens subvert host cell signaling pathways and functions during infection. Julie Theriot (Stanford University) will discuss the biophysical mechanisms used by pathogens to enable intracellular motility.

The organizers especially encourage students, postdoctoral fellows, and young investigators to submit abstracts for these sessions. We look forward to seeing you at the meeting!

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COLLEEN J. McKEIRNAN: *Thinking Creatively about Science and Law*

I am a patent agent in the Boston office of the law firm Edwards Angell Palmer & Dodge, LLP. I work with clients in both academia and industry to protect some of their most interesting ideas and to plot a path through what can be a crowded field of prior art or other patents. Patent law allows me to think creatively about both science and law, and forces me to continually learn about new areas of science, many of which I would have never been exposed to in a research career.

For me, I think that the hardest part about leaving the laboratory bench was convincing myself that it did not mean that I was no longer a scientist. I had started working in a laboratory at the University of Massachusetts Medical Center before I even went to college. One of the reasons that I went to Wesleyan University was the opportunity to do research as an undergraduate. Graduate school was a wonderful experience. A scientist was not simply what I was, it was who I was.

My ultimate goal had been to return to a place like Wesleyan, a substantially undergraduate liberal arts institute with a strong research program. During my postdoctoral fellowship, I was lucky to have the opportunity to spend a month teaching at Bowdoin College in Maine. I had a wonderful time giving lectures and living the faculty life. However, it became clear to me that it was not what I wanted to do for a full-time position (even if I could ever get one). Now what was I going to do with my life?

As my postdoctoral fellowship progressed, my enthusiasm waned. I was still incredibly excited about science, as long as it was not my own research. Fortunately, or perhaps unfortunately, at The Scripps Research Institute, there is always someone else's research to hear about. I found myself spending more and more time at seminars and less and less time at the bench. It was the research, not science itself, that I was enjoying less. Unfortunately, research was about the only job that I had ever had. At what seemed like a relatively late stage, I needed to figure out what I wanted to do with my life.

With more years of education under my belt than I wanted to count, I started contacting anyone who would talk to me about what they did all day long at work. I talked to people in big biotech, small biotech, consulting, science education, and patent law. I spent months searching the job listings and my soul to try to figure out if I could, or should, make the jump from research to another field. One day a friend from Scripps who had transitioned to patent law about 6 months earlier managed to set my mind at rest: she said that it was not that you could not go back once you stepped away from the bench, it was that once you stepped away, you never *wanted* to go back.

I drafted a cover letter and a resume that looked more like a curriculum vitae and sent them to the friend who was now working in patent law. She sent them back to me and told me to start over, remembering that the people reading my resume would not be scientists.

Colleen J. McKiernan

Colleen J. McKiernan received her B.A. from Wesleyan University and her Ph.D. in Cell and Molecular Biology from the University of Vermont. She was a postdoctoral fellow at the Scripps Research Institute before joining Gordon & Rees, LLP as a patent agent/technical advisor. She then worked as assistant director of patents at Isis Pharmaceuticals, Inc. Currently, Mckiernan is a patent agent with Edwards Angell Palmer and Dodge, LLP.

I was eventually offered a position by a small "boutique" intellectual property law firm in San Diego. I was fortunate to have low billable hours and time to study for the patent bar exam. I could not have been happier with the work. Patent law is science for people with a short attention span. There is always something new to learn, and the range of topics that you are expected to work on may reach beyond your area of scientific comfort.

In sharp contrast to research science, patent prosecution (*i.e.* drafting patent applications and working for their allowance) as compared with

litigation is a relatively non-interactive activity. Time is money in a completely literal way. At the firm, I would spend most of my day sitting in my office reading and writing and then writing some more. Meeting with scientists was the most enjoyable aspect of the work. New data are always exciting, even when they are not your own.

After about 2 years, the opportunity to go in-house to a medium size biotech firm presented itself. I found the idea of being back in a more science-oriented environment appealing, and I was more than happy to no longer have to track my day in billable hours. Being in that environment allowed me to see the process of drug development far beyond the regulatory process. Selection of a compound to develop for testing was not simply a process of finding an active compound. What indication for a specific compound should be pursued first? What were the relative advantages or disadvantages of each? How much would it cost to do a Phase I trial that might be large enough to produce some efficacy data rather than just safety data? Would this allow a compound to be picked up more quickly by big pharma? When would the chemists be able to produce enough compound for a specific purpose? I was able to learn in depth about a few drugs and their potential therapeutic uses. Patent prosecution continued to take much of my time. However, the work was more proactive than reactive, as I interacted regularly with the scientists performing the research rather than being contacted after a university technology transfer office or company identified a "complete" invention for patenting.

Meeting with scientists was the most enjoyable aspect of the work.

My life recently has brought me to Boston. There were advantages to being in-house, but I thought that I had much more to learn in regard to law and that the learning would be best done at a law firm. Being at a firm would expose me more to litigation, which provides a look at patent prosecution from the other side, by looking at issued patents to try to protect them or knock them down. The firm will pay for patent agents to attend law school, and many of the agents attend school at night and work an 80% schedule. Although having someone else cover the tuition for law school is an appealing offer, until I find that the work is not sufficiently interesting or that I lack job security—neither of which I expect to happen—I do not plan to apply to law school. One of the reasons that I left the bench was to have my nights and weekends to myself. I have also been told by my many Ph.D. friends who later went on to get J.D.s that they end up doing more law and less science. I have little interest in that because I am still a scientist.

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Educating Non-scientists

BY ROBERT NEWBURGH

Today's questions about relevance, needs, controversies, and competition for public funds increase the need for a grassroots effort by scientists to reach out to non-scientists to tell them why research is important. The Marian Koshland Museum in Washington, D.C. is a prime example of how this can be done. The museum was founded by Daniel E. Koshland to honor his late wife, Marian, who was a renowned molecular biologist and immunologist. Koshland, along with then-President of the National Academy of Sciences, Bruce Alberts, decided to create a small museum showcasing high quality science that would appeal to scientists and non-scientists alike. The museum's mission is to engage the general public in current scientific issues that impact their lives. The state-of-the-art exhibits, public programs, and educational programs provide information that stimulates discussion and provides insight into how science supports decision-making. What follows is a description of some of the museum's exhibits.

Infectious Diseases: Evolving Challenges to Human Health

This exhibit provides an in-depth view of the viruses, bacteria, fungi, and parasites that surround us, the deadly diseases they cause, and the scientific challenges involved in targeting them. As you walk through the exhibits, you will investigate the extremely rapid reproduction and mutation rates of microorganisms and learn about the challenges they pose to our immune system and to the development of effective vaccines and treatments. In the exhibit "Can You Find What Causes Infectious Disease?" one can explore the wide range of viruses, bacteria, parasites, and fungi that make their homes in our bodies. From the helpful bacteria that colonize our guts to the dangerous organisms of acute and chronic disease, this exhibit introduces visitors to the unseen passengers that inhabit us. The "Global View" contains interactive kiosks in which the distribution of major infectious diseases—such as tuberculosis, HIV, malaria, and cholera—and how factors such as global travel and land-use changes can spread disease worldwide are shown. "Protecting Health" shows how public health in the United States has dramatically improved as a result of clean water, good sanitation practices, and better nutrition, along with the widespread use of vaccines and antibiotics. "Can We Predict How an Epidemic Will Spread?" showcases a computer model that predicts the course of measles or influenza outbreaks based on different vaccination rates, and "Cures From Microscopic Competition" shows that the rapid mutation of bacteria constantly requires searches for new treatments. "The Changing Impact of HIV" explores how HIV attacks the immune system and how antiretroviral drugs fight the disease.

Global Warming: Facts and Our Future

One of the most popular exhibits is a 3-foot-diameter, self-sustaining, sealed biosphere containing brine shrimp, algae, water, and air and demonstrating "The Carbon Cycle." A lifelike model of a cow—one of today's major methane emitters—illustrates the second most significant cause of global warming. A sliding plasma screen displays "A Century of Change" in temperature across the globe. Actual year-to-year temperature and carbon dioxide variations appear on the screen as it is moved along a timeline of the 20th century. Further along on a similar plasma screen are future predictions based on climate models by the National Center for Atmospheric Research, Boulder, Colorado, and Princeton University's Geophysical Fluid Dynamics Laboratory, Princeton, New Jersey. A popular kiosk allows visitors to consider alternative scenarios for responding to climate change and records trade-offs regarding monthly costs, quality of life, and the environment. The data, which are sent to Penn State, include age ranges and sex of participants, to be used as part of a study on ways to improve public policy.

The Wonders of Science

This exhibit looks at how scientists are tackling some of the most mind-boggling questions in the universe. "What Is the Universe Made Up Of?" is an introductory movie showing recent research helping to unravel some of the greatest mysteries of the universe including the physical and the biological. Each section explains what we know, asks key questions, and ends with the challenging statement, "We are not there yet." Then the visitor moves to interactive kiosks that offer more in-depth information on concepts such as dark matter, dark energy, and satellite-based images of the Earth's light at night, as well as an animated depiction of DNA replication.

I encourage you to visit the Marian Koshland Museum and to tell friends going to Washington, D.C. to visit it as well. Group visits include a host to lead the tour. You may also view all of the exhibits at www.koshland-science-museum.org.

Informal and Formal Approaches to Educating Non-Scientists

The second part of this article is an expansion on my "Letter to the Editor" in the May 2007 issue of *ASBMB Today*, in which I indicated ways in which scientists could educate non-scientists about what we do and why it is important.

Scientific societies do an excellent job of interacting with congressional members and people who fund research. However, we may not take the opportunity to tell neighbors, friends, or other groups what we do, why we do it, and why it is significant. I believe there are two approaches one can take to educate non-scientists. The first is informal and involves daily interactions occurring in a variety of settings. When talking to a neighbor or other acquaintance, you can steer the conversation to what each of you does for a living, or perhaps discuss a recent news item that relates to your research. You can also do this in other small social settings. Non-scientists are always interested in the what, how, and why of science, particularly biomedical science because it impinges on their daily and long-term life. At the Marian Koshland Science Museum most of the visitors are non-scientists, and I noticed that they are intrigued by the exhibits and want to learn more about science and its practitioners.

The second approach is more formal and involves scientists offering to speak to various non-science organizations. Depending on the size of the audience, this may mean developing either slides or a computer presentation. Many organizations have regular lunches, dinners, or other types of meetings to which they invite guest speakers. Certainly, topics related to biomedical research are always of wide interest. This is an opportunity to relate how your research contributes to medicine, biotechnology, and other areas that are familiar to the general public. In addition to your own research, you should not hesitate to use examples from other researchers. One suggestion is to begin by picking a general area, and then indicate what is known along with what still is unknown. Allow plenty of time for questions. I believe it best, unless asked, to be careful in addressing funding, because your talk might be regarded as a pitch by someone with a vested interest. However, if the question arises as to what is limiting progress, mention funding along with other technical needs.

What is needed to accomplish this outreach? The first step is to learn the names of program chairs of societies, service organizations, school organizations, and other groups looking for speakers. The Public Relations office in your institution may also be able to help you. You might talk with faculty at other schools, such as schools of business schools or education, which could provide inroads to teachers, pupils, and local businesses. While in no way inclusive, a few other suggestions include Kiwanis, Rotary, women's clubs, PTAs, neighborhood associations, NAACP, chambers of commerce, high schools, church groups, and college and university alumni. Be willing to talk to small groups. If only one person writes to his or her respective member of Congress about the importance of your research, this will have some impact, since it comes from someone without a vested interest. Also, many locals are influential members in their respective communities.

Here are a few suggestions for your talk:

- **Don't "talk down" to your audience or get too technical.**
- **Do a lot of preparation and solicit help from colleagues and non-scientist friends.**
- **Use slides.**
- **Use humor.**
- **Mention that not every experiment is successful.**

For more help, the education program at the Howard Hughes Medical Institute has sponsored several talks that are available on DVDs (at www.hhmi.org/biointeractive). You can also use the information available on the Marian Koshland Science Museum Web site.

I hope these brief comments are valuable and will lead to increased efforts to inform non-scientists of the importance of our efforts in both national and local communities.

Acknowledgment: Amy Shaw, Communications Officer at the Marian Koshland Science Museum, provided some of the descriptive material.

Postdoc Brain Circulation: A Global Affair

BY JONATHAN GITLIN

You only have to take a peek inside the laboratories of your nearest research university to see that science is an international endeavor. In the United States, a significant bulk of the work done in academia is accomplished by postdocs, those of us who have Ph.D.s but don't hold faculty jobs. When the National Institutes of Health (NIH) budget went through a doubling phase in the 1990s, more money translated into more Ph.D.s[1]; however, the supply of faculty positions did not increase at anywhere near the same rate.[2] Prior to this time, when the demand for new scientists matched supply, the postdoctoral position was a 1- or 2-year stepping stone into academia. Following the boom in supply, a postdoc appointment has now become, for many, a holding position for 3 or more years, where researchers continue to work dependently under a principal investigator and occupy a no-man's land between student and staff. Indeed, the average length of postdoctoral appointments in biochemistry is now 3.8 years, according to a recent National Science Foundation survey.[3]

Young scientists are no longer that young when they finally achieve independence; in the 1980s, fully one-quarter of NIH R01 Grants were awarded to researchers under the age of 35. As of 2002, that figure was below 4%.[4] The median age of first faculty appointment for Ph.D.s at U. S. medical schools is 38; the median age for Ph.D.s to first receive an NIH R01 award is 42.[5] Unfortunately for young scientists, and for science itself, these early career years are often the most productive for breakthroughs and advances. At the ages when our forebears made novel discoveries and even won Nobel Prizes (James Watson at 34; Thomas Cech at 42; Frederick Sanger at 40), many of the current generation are still toiling away in someone else's laboratory. As it stands at the moment, the postdoc system for training young scientists in the United States is more than a little broken; the system stems from 19th century German academia and is no longer effective as a pipeline for training young scientists for independent research careers.

Back to my starting point: even a cursory glance around any U. S. campus will show that a significant proportion of postdocs aren't native to the United States. Currently, around 60% are international, and foreign-born scientists continue to make up a significant demographic within the U. S. science base. As described in a recent article in *The FASEB Journal*,[6] foreign-born researchers make up the lion's share of U. S. recipients of Nobel Prizes, and the importance of recruiting and retaining foreign talent as it relates to the U. S. economy has been stressed by William Wulf, past president of the National Academy of Engineering. Dr. Wulf testified before a subcommittee of the U. S. House of Representatives that "Foreign-born scientists and engineers have come to the U. S., stayed in large numbers, and we are more prosperous and more secure, in a large part, because of them!"[7]

These foreign scientists typically spend 2 to 4 years in the United States before returning home or applying for permanent residency. Those in the latter category tend to be from countries like India and China. In contrast to the visiting scholars from Europe and other developed nations, the United States can be an attractive place to settle, with more perceived opportunities and greater freedoms than their home countries. This has fueled fears of a "brain drain" for quite some time, but that concept, along with the assumption that scientists from developing countries come to the United States to settle, is beginning to change.

The brain drain idea is being replaced by that of "brain circulation." This concept was discussed at the Fifth National Postdoctoral Association Annual Meeting held this spring at the University of California, Berkeley,[8] and also was featured in an article in a recent edition of *Cell*.[9] For instance, more and more Chinese postdocs are being lured back to the motherland; China is rapidly expanding its scientific base, and research funding is easier to acquire there than in the United States. Additionally, other nations are following the United States' lead to make themselves more attractive to foreign scientists. Countries like Japan and China that traditionally supplied labor are now wooing foreign talent, and other nations such as Australia and the UK are making it easier for foreign scientists to come and work.

There are both opportunities and challenges for international postdocs working in the United States. The majority of biomedical research in the United States is funded by the Federal government through the NIH. Unfortunately for international scholars, these grants and fellowships are only available to U. S. citizens and

permanent residents. Given that most foreign scientists working in the United States are on J-1 or H1-B visas, they have a much more difficult time obtaining the funding needed to transition into scientific independence. Instead, most are funded directly by their Principal Investigators. This can lead to conflicts of interest in the laboratory, where researchers may be unable to follow their own interests but instead are simply a hired pair of hands. The NIH is aware of this issue, and although the nationality restrictions on Federal funding are put in place by Congress, things are beginning to change slowly. The recently announced K99-R00 awards are available to both residents and non-residents alike and are specifically designed to aid the transition into independent research.

Because of the cracks appearing in the U. S. postdoc system, which is no longer effective at training and placing independent young scientists, along with the increased difficulty of obtaining visas in the current U. S. political climate, fears are growing that the United States will begin to lose out compared with competitors when it comes to the training and retention of the "best and brightest" global scientific talent in the coming decades. If a young, foreign scientist faces the choice of more than 4 years as a postdoc at a U. S. laboratory or a shorter stint followed by their own lab in another nation, fewer will be making the choice to move to America to complete their training

It remains to be seen, however, whether the problem is as bad as some in the United States claim. It is true that the overall share of international postdocs to the United States has decreased, but looking at actual numbers rather than percentages tempers the issue.[8] Other countries have also experienced a boom in the numbers of freshly minted Ph.D.s, increasing the size of the global talent pool. Although it is true that a smaller percentage of foreign-born scientists are coming to the United States, the actual numbers are still slowly increasing.

The idea of a brain circulation, where researchers might spend a few years in one country undertaking to earn a Ph.D., then move to another country for a postdoc, and possibly even go to a third country for a full-time position, has immense appeal. The continuing exchange of scientists around the world helps to spread knowledge that could benefit all of mankind and have an impact on the environment; a rising tide lifts all boats, as they say. Researchers returning to home countries that might have fewer civil liberties or freedoms than the ones they visited would take with them those ideals. As such, postdoc exchange around the world would enhance the globalization of science and freedom of ideas, thereby facilitating technological advancement in all partner countries. Long may the brain circulation continue!

New Postdoc Exchange Programs at HHMI

The Howard Hughes Medical Institute (HHMI) recently announced a variety of partnership programs aimed at international and national postdoc exchange. These programs are intended to provide early career research opportunities and to facilitate cutting edge collaborative science. This past spring, HHMI announced a postdoc exchange program with the Wellcome Trust in the United Kingdom (UK). In this exchange program, postdocs from HHMI labs in the United States (U. S.) will travel abroad for work at Wellcome Trust labs throughout the UK, including the Sanger Institute near Cambridge. Conversely, UK postdocs at Wellcome Trust laboratories will travel here to the U. S. for work at HHMI laboratories throughout the U. S., including Janelia Farm in Virginia. Expenses will be paid for 3-12 months (travel, housing, stipend), and exchange program officers will help with securing visas and work permits. Application details are available at: www.wellcome.ac.uk/node2164.html.

Furthermore, on June 4, HHMI announced postdoc partnership programs with 4 organizations in the United States: the Jane Coffin Childs Memorial Fund, the Helen Hay Whitney Foundation, the Life Sciences Research Foundation, and the Damon Runyon Cancer Research Foundation. Each organization will select 4 fellows annually, awarding research fellowships to be conducted in the laboratories of HHMI Investigators. Each research fellowship includes salary stipend and supply budget for a duration of 3 years. At full capacity, the new HHMI partnerships with U. S. research organizations will fund 48 postdocs per year, at a cost of $3 million annually. For more information, please see: http://www.hhmi.org/news/20070604postdoc.html.

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[2] www.fasebj.org/cgi/reprint/03-0836lifev1.pdf.
[3] depts.washington.edu/coe/cirge/pdfs%20for%20web/maresi's%20postdoc.pdf.
[4] E. Goldman and E. Marshall (2002) NIH grantees: Where have all the young ones gone? *Science* **298**, 40-41.
[5] books.nap.edu/openbook.php?record_id=11249&page=39; grants1.nih.gov/grants/new_investigators/resources.htm.
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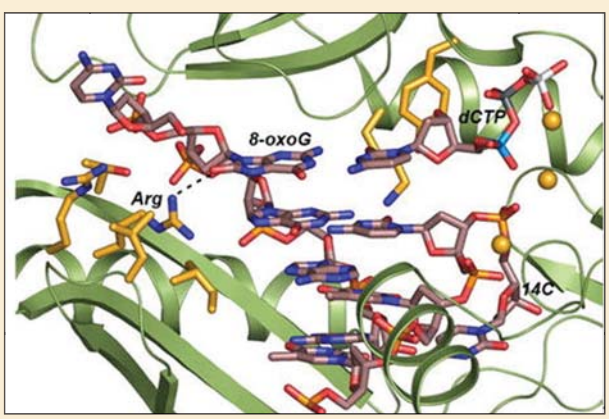
[7] William A. Wulf, Ph.D., Statement before the Subcommittee on Immigration, Border Security, and Claims Committee on the Judiciary U. S. House of Representatives, The Importance of Foreign-born Scientists and Engineers to the Security of The United States, September 15, 2005.
[8] Rajika Bhandari, Institute of International Education, The Future of the Science & Technology Workforce: What can we learn from international mobility data? Presented at the 5th Annual National Postdoctoral Association Meeting, Berkeley, CA, 2007; www.nationalpostdoc.org/site/c.eoJMIWOBIrH/b.2069739/k.8758/Plenary_Session_Abstracts.htm
[9] K. M. Dente (2007) Scientists on the Move. *Cell* **129** 15-17

Replicating Damaged DNA

DNA polymerases assist in DNA replication by catalyzing the polymerization of deoxyribonucleotides alongside a template DNA strand. Based on sequence homology, DNA polymerases can be subdivided into seven different families: A, B, C, D, X, Y, and RT. The Y family polymerases differ from others in that they are able to use damaged DNA as a template. For example, P2 DNA polymerase IV (Dpo4) can bypass 7,8-dihydro-8-oxodeoxyguanosine (8-oxoG), a major lesion arising from oxidative stress. In this JBC paper, the authors looked at the means by which Dpo4 is able to bypass this lesion with high fidelity, thus preventing mutation. Previous crystal structures had indicated that Arg^{332} might play a role in stabilizing the 8-oxoG template base, allowing insertion of dCTP in the complementary strand. The results of the paper confirm that a bond between Arg^{332} and 8-oxoG plays a role in determining the fidelity and efficiency of the Dpo4-catalyzed bypass.



Arg^{332} forms a bond with 8-oxoG during replication.

Hydrogen Bonding of 7,8-Dihydro-8-oxodeoxyguanosine with a Charged Residue in the Little Finger Domain Determines Miscoding Events in Sulfolobus solfataricus DNA Polymerase Dpo4

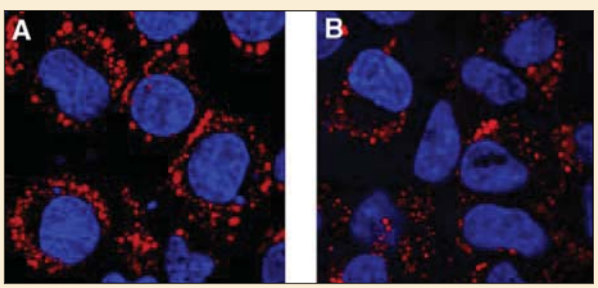
Robert L. Eoff, Adriana Irimia, Karen C. Angel, Martin Egli, and F. Peter Guengerich

J. Biol. Chem. 2007 **282**: 19831-19843

jbc

The Side Effects of CETP Inhibition

Cholesteryl ester transfer protein (CETP) is a plasma protein that facilitates the transport of cholesteryl ester and triglyceride between lipoproteins. The protein picks up triglycerides from very low or low density lipoproteins (VLDL or LDL) and can exchange them for cholesteryl esters from high density lipoproteins (HDL) (and vice versa). Because HDL has a protective function in atherosclerosis and cardiovascular disease, the pharmacological inhibition of CETP has been investigated as a way to raise HDL levels. In this *JBC* paper, the authors use antisense CETP cDNA to suppress expression of the protein in adipocytes and document, for the first time, the importance of intracellular CETP in lipid transport and storage. They show that CETP deficiency affects the translocation of cholesteryl esters and triglycerides from the endoplasmic reticulum to their storage sites. With the extensive recent interest in raising HDL levels through CETP inhibition, the results of this study suggest that an increase in cellular cholesteryl ester storage may be one potential mechanism contributing to the adverse effects of CETP inhibitors such as Pfizer's torcetrapib.



Triglyceride levels in CETP-deficient cells (B) are lower than in wild-type cells (A).

Possible Role for Intracellular Cholesteryl Ester Transfer Protein in Adipocyte Lipid Metabolism and Storage

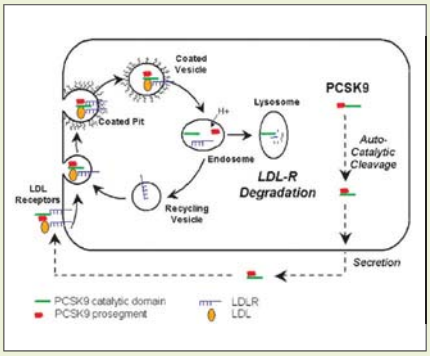
Lahoucine Izem and Richard E. Morton

J. Biol. Chem. 2007 **282**: 21856-21865

jbc

Decreasing Plasma LDL

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a protease that regulates low density lipoprotein receptor (LDLR) protein levels. LDLR, in turn, controls plasma low density lipoprotein (LDL) cholesterol levels. Thus, PCSK9 is a potential pharmacological target for lowering LDL cholesterol levels and consequently reducing risk for atherosclerosis, heart attack, stroke, and peripheral vascular disease. In this JLR paper, the authors shed some light on the molecular pathway through which PCSK9 reduces cell surface LDLR levels and thus controls plasma LDL cholesterol levels. From their data they propose a model in which prodomain-associated PCSK9 is secreted through the endoplasmic reticulum into the plasma environment, where it either exists in free form or may become associated with plasma LDL. PCSK9 then binds to LDLR and is endocytosed to endosomal/lysosomal compartments where LDLR is degraded. These findings provide a framework for the development of novel assays that could be used as a means to pursue potential therapeutic approaches to decreasing plasma LDL.



A model for PCSK9 action.

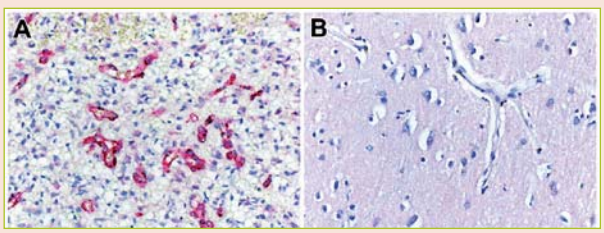
Secreted PCSK9 Down-regulates Low Density Lipoprotein Receptor through Receptor-mediated Endocytosis

Yue-Wei Qian, Robert J. Schmidt, Youyan Zhang, Shaoyou Chu, Aimin Lin, He Wang, Xiliang Wang, Thomas P. Beyer, William R. Bensch, Weiming Li, Mariam E. Ehsani, Deshun Lu, Robert J. Konrad, Patrick I. Eacho, David E. Moller, Sotirios K. Karathanasis, and Guoqing Cao

J. Lipid Res. 2007 **48**: 1488-1498

Proteomics on the Brain

Gliomas are the most common primary brain tumors, with about 25,000 new cases per year occurring in the United States. The growth of gliomas largely depends on their blood supply, the elimination of which results in the destruction of the tumors. Thus, the identification of angiogenesis-related proteins not only provides biomakers for gliomas but is also important for the development of new glioma therapies. The aim of this MCP paper was to identify proteins that are specifically expressed in glioma vasculature but not in the normal blood vessels of the brain. To achieve this goal, the authors used laser microdissection to surgically remove glioma blood vessels for comparison with normal brain vessels. They then used advanced proteomics techniques to compare the expression profiles of the blood vessels and identified four proteins that appeared to be expressed exclusively in the glioma blood vessels. This paper shows for the first time that laser microdissection can be used in combination with proteomics for the analysis of brain blood vessels.



Colligin 2 protein is found in glioma samples (A) but not in normal brain samples (B).

Identification of Glioma Neovascularization-related Proteins by Using MALDI-FTMS and Nano-LC Fractionation to Microdissected Tumor Vessels

Dana A. N. Mustafa, Peter C. Burgers, Lennard J. Dekker, Halima Charif, Mark K. Titulaer, Peter A. E. Sillevis Smitt, Theo M. Luider, and Johan M. Kros

Mol. Cell. Proteomics 2007 **6**: 1147-1157

Jonathan S. Stamler: Revealing the Ubiquitous Role of Nitric Oxide in Biology and Medicine

BY PAT PAGES

Jonathan Stamler, professor of medicine and biochemistry at Duke University, Durham, North Carolina, has spent much of his training and 15-year career explaining how nitric oxide works in biological systems. He has identified a fundamental molecular mechanism that explains how nitric oxide regulates a broad array of physiological processes and has discovered new classes of molecules and enzymes that promote nitric oxide's widespread role in cellular signaling. Stamler has also questioned many widely held assumptions and challenged his colleagues to think differently, ultimately providing a new way to look at the role of nitric oxide in biology.

"Nitric oxide has long been known for dilating blood vessels and for being involved in the immune system and memory, but how it works at the cellular and molecular levels has been a great quandary," Stamler says. "Many early assumptions have now been overturned and new insights are establishing a novel paradigm in cellular signaling that may lead to improved treatments for major diseases, including heart disease, diabetes, cancer, asthma, and neurodegenerative disorders."

An unexpected passion for medicine

Stamler's contributions may not have occurred if he had achieved his early goals. He had wanted to become a professional tennis player and had pursued his passion with some success. "Fortunately," as he puts it, a hand injury at the age of 18 helped to end those ideas. Stamler took a deferral from the University of Oxford in the United Kingdom and went to Brandeis University in Boston "to buy time." In his sophomore year, still unsure of his academic interests, he decided to take a class in chemistry. "The room was full of premedical students," he says. "My interest was piqued. I went to the library for the first time in my life." Medicine quickly became his new passion.

In 1981, Stamler enrolled at Mount Sinai Medical School in New York. "I wanted very much to become a knowledgeable doctor," he says. "I devoted myself wholeheartedly to the task of understanding and memorizing the large body of medical literature that was part of the program."

By the third year of medical school, Stamler was finding his professors' answers to his questions less than satisfying, and the textbooks no longer seemed as complete. His instructor in a medicine rotation, a cardiologist named Ray Matta, offered a new perspective and initiated his interest in cardiology. "He was and remains my role model," Stamler says. "He treated people kindly, gave patients hope, was very caring, and worked tirelessly. He also had an unparalleled breadth of knowledge but knew the limits of his knowledge. He was the type of physician I wanted to become."

Oxygen free radicals and the heart

After graduating from medical school in 1985, Stamler went to Harvard University's Brigham and Women's Hospital in Boston for his internship and medical residency. Like most other interns, he took care of hospitalized patients for an average of 100 to 120 hours a week, but he also found the time to start his own research.

Jonathan S. Stamler

PHOTO: DUKE UNIVERSITY MEDICAL CENTER

Not long after starting his internship, Stamler read an article in the *New England Journal of Medicine* on oxygen free radicals—highly reactive molecules that harmed cells—by Joe McCord, now a professor of microbiology and immunology at the University of Colorado Health Sciences Center, and colleagues. The article, which described how these molecules were involved in heart disease and other organ damage, captivated Stamler. "I was fascinated by the molecules' fleeting nature," he says. "They reminded me of daffodils—William Wordsworth's 'Daffodils'—a brilliant flash, and as quickly, they would be gone."

Stamler decide to do a clinical trial to study the role of free radicals

in the heart. The proposal, involving a drug never used before to treat heart patients, was approved by the Brigham's institutional review board, and Stamler began his trial. There was only one problem: the reviewers had assumed that Stamler was a cardiologist, not an intern. When he was called to perform cardiovascular tests on patients, the trial was quickly—and quietly—terminated.

Undeterred, Stamler contacted Harvard's Department of Chemistry looking for ways to measure free radicals and was given the name of David Singel, a physical organic chemist. And so began what Stamler calls, "by far my most formative and rewarding scientific relationship." "There is no way I could have managed without it," he says. "David had the time for me, taught me when I needed teaching, provided foundation when I needed gravitas, and offered much intellectual input when real problems needed tackling."

Nitric oxide takes center stage

It was 1987, and Stamler was working in two laboratories—Singel's laboratory, where he was examining free radicals in the blood stream, and the laboratory of the Brigham cardiologist Joseph Loscalzo, where he was exploring the effects of the medicine nitroglycerin on blood platelets—when he read an article in *Nature* that would change the course of his work. The article showed that the free radical nitric oxide—the active ingredient of nitroglycerin, a medication used to dilate blood vessels—was also produced by the vessels themselves. Stamler decided immediately to stop his work on oxygen free radicals and focus on nitric oxide instead.

That article, by Salvador Moncada, currently director of the Wolfson Institute for Biomedical Research at University College London, and colleagues, also caught the attention of the scientific community. Within a few years, scientists had shown widespread effects of endogenously derived nitric oxide across the immune system, brain, heart, lungs, and blood.

But such studies provided limited information about how nitric oxide worked at the cellular level. A prevailing view emerged that nitric oxide diffused freely through cells and across membranes and interstitial spaces into neighboring cells. Implicit in this view was the belief that nitric oxide did not react with most cellular proteins and that its effects would not be restricted to a cell of origin or a subcellular domain.

A new biochemical process

How nitric oxide carries out its many effects was not clear. Earlier studies by physician and pharmacologist Ferid Murad and pharmacologist Lou Ignarro had shown that nitric oxide derived from nitroglycerin bound to a heme—an iron-containing group—in the enzyme guanylate cyclase to dilate blood vessels. Nitric oxide produced in blood vessels also apparently relied on guanylate cyclase. Scientists concluded that guanylate cyclase was the only physiologically relevant receptor for nitric oxide.

Stamler saw things differently. Few proteins had hemes and the evidence that all—or even most—effects of nitric oxide could be identified with guanylate cyclase signaling seemed weak. Also, if nitric oxide diffused freely, its control within the body would not be easy, he thought. Instead, he reasoned, nitric oxide might bind to cysteine residues—known to be very reactive—in proteins to elicit its diverse effects.

Unlike hemes, cysteine residues are present in all classes of proteins, and yet their roles were largely unknown. So Stamler tested whether nitric oxide binds to the cysteine residues of three proteins: serum albumin, which is abundant in plasma; tissue-type plasminogen activator (t-PA), an enzyme that destroys blood clots; and cathepsin B, a protein that breaks apart other proteins.

Not only did his results make clear that nitric oxide reacted very selectively with cysteines in each protein to form a stable *S*-nitrosothiol product, but they also showed that nitric oxide could change the function of those proteins and enable them to dilate blood vessels. In articles published in 1992 in the *Proceedings of the National Academy of Sciences*, Stamler and colleagues reasoned that nitric oxide binding to cysteine residues in proteins—a modification they termed *S*-nitrosylation—could be a ubiquitous process to regulate protein function similar to phosphorylation.

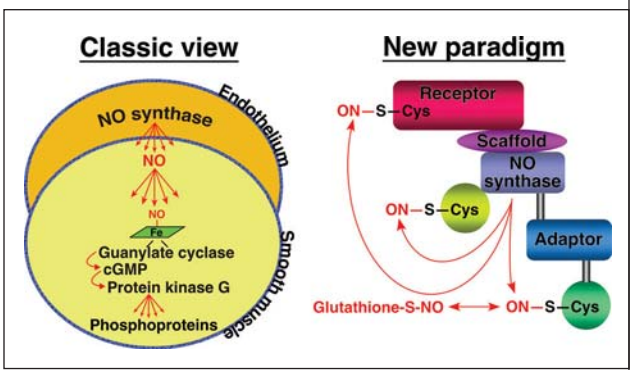


Fig. 1. The classic view (*left*) held that nitric oxide diffuses widely within and between cells and acts principally by binding to heme iron in guanylate cyclase. Under the new paradigm (*right*), nitric oxide and endogenous *S*-nitrosothiols (such as SNO-glutathione) act largely through *S*-nitrosylation of specific cysteines in many proteins.

Persistence in the face of skepticism

Stamler's work was received with much skepticism by his peers, who objected to the idea that nitric oxide could even bind to a cysteine residue—the chemical reaction was viewed as improbable—let alone change protein function. Also, the idea that proteins bearing nitric oxide could dilate a blood vessel seemed unbelievable. Stamler responded that the reaction with cysteine could occur if free radical nitric oxide formed species *in vivo* that have the properties of nitrosonium cation (NO^+) or nitroxyl anion (NO^-).

Chemists argued that this was unlikely. Stamler and Singel countered that, in fact, much of the emerging biology of nitric oxide was far more consistent with these nitric oxide-related species than with nitric oxide itself and laid out the biochemistry of these reactions under physiological conditions. In 1992, nitric oxide was named molecule of the year by *Science*, magazine and Stamler's perspective accompanied the issue as a lead article.

"The backlash was fast and furious and lasted for about six years," Stamler says. "Then, almost overnight, the concepts went from heretical to broadly accepted. But *S*-nitrosylation remained difficult for most scientists to confirm experimentally, and it would be another five years or so before protein *S*-nitrosylation would take firm root."

In 1994, a year after completing fellowship training in both cardiology and pulmonary medicine, Stamler was recruited as an associate professor of medicine to Duke University where his program flourished. "Advocates are crucially important in times of challenge," says Stamler. "Irwin Fridovich, now emeritus professor of biochemistry at Duke, has been instrumental in keeping me on track in the face of opposition."

A ubiquitous process

At Duke, Stamler's team would show that proteins of many classes were susceptible to *S*-nitrosylation, including membrane receptors (establishing that nitric oxide does not need to diffuse through cell membranes to be active), transcription factors, G proteins, cysteine proteases, ion channels, and kinases. Through this work, the researchers established that *S*-nitrosylation played a role in a wide range of cellular and physiological processes.

One of those processes, oxygen transport from the lungs to tissues, is particularly noteworthy. Scientists had believed that hemoglobin, the red blood cell protein that transports oxygen, constricted blood vessels. Vasconstriction was attributed to sequestration of nitric oxide by hemes in hemoglobin. But constriction of blood vessels meant that oxygen delivery to tissues would be hindered, which, to Stamler, seemed paradoxical.

In 1996, Stamler and co-workers revealed in a *Nature* article that nitric oxide could escape binding to hemes in hemoglobin and instead bind cysteine residues, thus preserving nitric oxide's activity. Also, when the researchers conducted experiments under the low oxygen conditions found in tissues—as opposed to room air—*S*-nitrosylated hemoglobin assumed a conformation that allowed nitric oxide to be released to dilate vessels.

"Textbook views on hemoglobin's role in oxygen delivery needed to be revised to include a role for red blood cells in regulating blood flow," says Stamler.

With the list of proteins modified by *S*-nitrosylation growing by the day—well over 100 to date—and essential roles for *S*-nitrosylation established in many aspects of cellular biology and mammalian physiology, Stamler sees the implications of *S*-nitrosylation for human health as the next frontier.

"*S*-nitrosylation goes awry in many diseases, including sickle cell anemia, multiple sclerosis, asthma, heart failure, and Parkinson's disease," Stamler says. "If we can understand how and why this happens, we may be able to develop new classes of therapeutic agents to correct the defects."

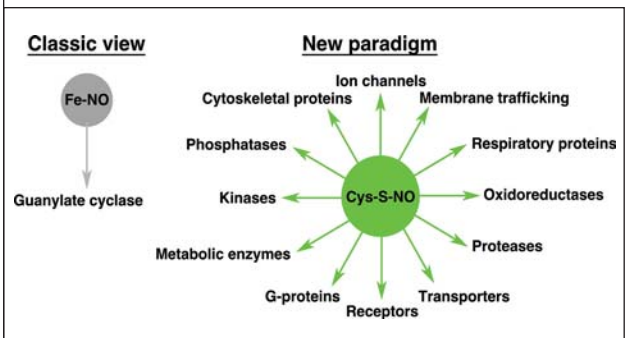


Fig.2. Under the classic view (*left*), nitric oxide relied exclusively on guanylate cyclase and thus largely upon cyclic GMP-dependent phosphorylation of a limited set of targets. Under the new paradigm (*right*), nitric oxide regulates many proteins (over 100 proteins of virtually all classes have been identified to date), which participate in a broad range of cellular functions.

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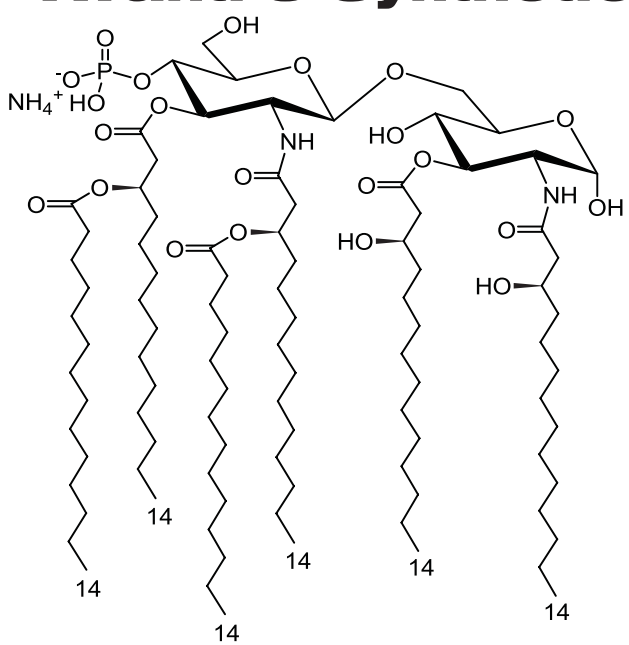

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