ASBMB TODAY GOES DIGITAL

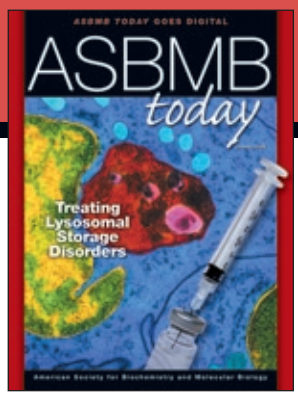
ASBMB today

January 2008

Treating Lysosomal Storage Disorders

American Society for Biochemistry and Molecular Biology

contents



JANUARY 2008

ON THE COVER: Elizabeth Neufeld is working towards new therapies for lysosomal storage disorders by developing therapeutic enzymes. 26

society news

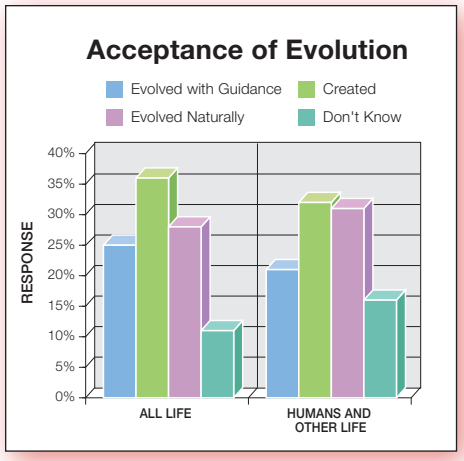
special interest

2008 meeting overview

science focus

departments

resources



Educating the public about evolution 14

HIV/AIDS Education in Tanzania. 22

podcast summary

This month's ASBMB AudioPhiles Podcast includes an interview with Vince Hascall who was featured in a December *JBC* classic titled "Proteoglycans and Orchids: The Work of Vincent Hascall."

Download the podcast at: http://www.faseb.org/asbmb/media/media.asp

ASBMB today

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ASBMB Today

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from the editor

Happy New Year!

BY NICOLE KRESGE

With this new year, we are ushering in a big change in the way in which you receive your advance copy of the magazine. Previously, in advance of your print copy of *ASBMB Today*, we sent you an electronic Table of Contents (eTOC) with links to a PDF of the magazine that was posted on our Web site. Now, we have a new digital platform, provided by Texterity, which produces an interactive, vivid replica of the print edition, offering you an experience very much like an ink-and-paper magazine delivered electronically. The platform requires no applications, plug-ins, or downloads, meaning no additional hassle for you, the reader.

This change is the result of our ongoing commitment to improving *ASBMB Today*. Needless to say, this electronic version offers endless opportunities for us to provide additional content to you. In future issues, we plan on linking articles to podcasts, videos, and online discussions. But don't worry; you'll still receive your print edition of the magazine in the mail.

So please, if you haven't done so already, take a look at the online version of the magazine at www.asbmbtoday-digital.com/current and tell us what you think! You can write to us at asbmbtoday@asbmb.org.

Nicole Kresge

letters to the editor

ASBMB and Peer Review Reform

To the editor:

In *Science Observed*, Jevons in 1973 noted that asking a researcher about the funding system is like asking a bird about aerodynamics [1]. This is well illustrated by recent commentaries on the peer review system[2]. Nowhere is there recognition that peer review as it currently operates is highly error-prone. Nowhere is there recognition of a need for system redesign taking error-proneness into account.

Despite lip service to the contrary, the grant agencies assess projects, not people. In the final analysis, the grant agencies consider that it is better that a less able researcher carry out an approved project, than a more able researcher carry out an unapproved project. Indeed, they hope with the funding carrot to coerce more able researchers to carry out approved projects. For the less able researchers this is not a problem. They just have to write an honest application stating what they want to do and why they want to do it. On the other hand, the more able researchers, who can see beyond the conventional wisdom, have serious difficulties. Grant writing is a marketing exercise that, more often than not, requires that their "best" ideas be discarded because, by definition, these ideas are difficult to understand and communicate (if not, the less able researchers would have already thought of them). Thus, the more able researchers are tested not on their abilities to come up with innovative ideas, but on their abilities to tune into the conventional wisdom and write a proposal with an appropriate degree of marketing spin. Many able researchers, and especially the most able, find this not only distasteful but impossible.

...asking a researcher about the funding system is like asking a bird about aerodynamics.

People find this difficult to understand. Why can't the most able researchers just write a simple application and then, when they have the money, use it to do the work they really want to do? Unfortunately (or fortunately, depending on your perspective), the most able researchers have one common attribute, integrity. They can no more discard this than a tortoise can discard its shell, a giraffe its neck, or an elephant its trunk!

In summary, the peer review system as it currently operates discriminates against the most able researcher, thereby achieving the very opposite of what is desired. If true, this means that over past decades peer review has progressively "dumbed down" the Professoriat, thus impairing the process of scientific discovery and, more seriously, decreasing the quality of "expert" advice available to governments (*e.g.* on bioterrorism). A possible solution has been on the table for some decades, but it would appear to play no role in current discourse[3].

Donald R. Forsdyke,
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Canada K7L3N6

REFERENCES

1. Jevons, F. R. (1973) *Science Observed.* Allen & Unwin, London.
2. Hamm, H. (2007) ASBMB's ongoing activities in peer review. *ASBMB Today* December, pp. 2-3.
3. Forsdyke, D. R. (2000) *Tomorrow's Cures Today? How to Reform the Health Research System*. Harwood Academic, Amsterdam.

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 for clarity and length. Opinions expressed in letters do not necessarily reflect ASBMB policy.

Errata: In the December 2007 issue of *ASBMB Today,* Jack Preiss of Michigan State University was mistakenly omitted from the list of ASBMB members who were elected AAAS Fellows.

Taking an Exam Later—Does It Make a Difference? You Bet!

BY HEIDI HAMM

Many a student can tell you that being able to take an exam later can sometimes make a big difference in the outcome. For one thing, taking an exam later can often give a student more time to prepare, which usually results in an improved grade.

But not all postponements are beneficial. A good example is the National Board of Medical Examiners' apparent intent to move back the date when medical students take the Step 1 Exam by a full year. The Step 1 Exam tests the students' knowledge and understanding of the basic science that they have been studying for the first two years of medical school.

Until now, the Step 1 exam has been given at the end of the second year of medical school. The NBME, however, is conducting a review of medical education and the review group will apparently recommend that the Step 1 Exam, as currently constituted, be eliminated, and instead be given as part of the current Step 2 Exam, at the end of the *third* year of medical school.

Although this doesn't appear to be a major change, it does have a number of implications for the teaching of basic science to medical students—few of them beneficial, in ASBMB's view. The Society has expressed a number of concerns about the plan in a letter sent on December 10, 2007 to Donald E. Melnick, President of the National Board of Medical Examiners.

ASBMB's main objection is that, as our letter states, "…the proposed change will diminish the role and importance of the scientific basis of contemporary medicine in the minds of medical school students and the clinical faculty at a time when it is crucial to increase evidence-based practice of medicine." The proposal to combine an exam on basic science with an exam on clinical science will undoubtedly diminish the importance of basic science in the minds of some students—after all, they might think, "if basic science is so important, why isn't it tested separately?"

The proposal to combine an exam on basic science with an exam on clinical science will undoubtedly diminish the importance of basic science in the minds of some students

As our letter notes, "Physicians also need to know more than the general public and pharmaceutical sales personnel to make considered decisions and recommendations. In addition, graduates need to understand the outcome and implications of clinical trials. Understanding the basis of biomedicine and continuing to learn and adapt to new information is fundamental to 'possessing the knowledge and skills for safe and effective patient care'—the first priority of the medical licensing authorities."

Finally, we note that "…a medical student graduating today can expect a career of practicing medicine in the range of forty years. When one considers the astounding amount of new biomedical knowledge that has been developed over the past forty years, one can only imagine how much new basic knowledge will be uncovered in the next forty. To diminish the importance of biomedical science in the mind of a new physician will have the long-term impact of making the physician less effective, and worse, this will inevitably impact on the health and well being of the citizen-taxpayer, whom the physician ultimately serves."

Another problem pointed out by the Association of M.D./Ph.D. Program Directors is that those training to become physician/scientists through the Medical Scientist Training Program (MSTP) will not take the test until six years after starting medical school, since in the MSTP program, a three-year Ph.D. curriculum is usually followed after the second year of medical school.

Ph.D. work usually focuses on a very specific and narrow area, and so it is highly unlikely that M.D./Ph.D. students would do well on a basic science exam under such circumstances, unless by chance a major portion of the exam focused on their specialties. These physician-scientists will be the vanguard of conducting medical research in the future, and thus ought to be evaluated in their knowledge of basic science sooner than six years after starting medical school.

We are happy to point out that there still is time to react to this proposal. The group making recommendations to the full NBME will make its recommendations by the end of 2007, but the NBVME itself will spend all of 2008 considering the proposal and coming up with a final plan. The earliest medical school class that will be affected by this proposed change (if it is implemented) would be the class entering medical school in 2009, and they would not take the new exam until their third year.

Nevertheless, the further along a proposal moves during a decision-making process, the harder it becomes to make changes in it. So, if you teach basic science at a medical school or teaching hospital and are concerned about this proposal, you might want to write to the NBME about it. The NBME address and a copy of our letter can be found on the ASBMB website under the "What's New" column. If you still need help, you can contact Peter Farnham, our public affairs officer, at pfarnham@asbmb.org

The point of all this, of course, is that seemingly small changes in timing and content can have profound and unforeseen changes in the long run, especially in areas such as public policy and education. I hope this little essay helps to drive this home.

As always, we value feedback from our members on ASBMB positions on public policy issues. If you would like to write to me, please do so in care of the Society offices in Bethesda. Or, if you would like to share your views more widely, you can write a letter to the editor of *ASBMB Today*.

FASEB Launches Presidential Campaign Initiative: ScienceCures

BY CARRIE D. WOLINETZ

In anticipation of the 2008 presidential election, FASEB has launched a voter education initiative, aimed at raising the profile of federal funding for biomedical research among the candidates and the general public. According to FASEB President Robert Palazzo, "The presidential election represents an opportunity to bring the critical importance of medical research to the national stage. We want to give scientists the tools they need to raise awareness about the role of the National Institutes of Health (NIH) in developing the treatments and cures that positively affect our quality of life." The new initiative is called ScienceCures and may be viewed at http://www.sciencecures.org.

The recent standoff between Congress and the President over appropriations for science agencies, including NIH and the National Science Foundation, has emphasized the integral role of the Administration in securing science funding. Moreover, given that health care remains a central issue in the ongoing presidential race, FASEB is working to ensure that NIH and biomedical research are part of that discussion. Over the course of the next year, ScienceCures will give scientists the opportunity to express their support for medical research in the context of the election while educating voters about the connection between today's science and tomorrow's medical advances.

As one of the first steps in this exciting new project, FASEB has launched several videos on YouTube (http://youtube.com/sciencecures) featuring biologist and FASEB society member, Sally Moody, of the George Washington University Medical Center, asking the presidential candidates to support biomedical research. "Medical research and improved health are top priorities for the American people," said Palazzo. "Our elected leaders should recognize that NIH and the hope it provides to millions of patients is both a national treasure and a national priority." In the first week alone, more than 600 visitors viewed the FASEB videos, which were submitted for consideration in presidential debates. FASEB encourages all of its societies' members to view and comment on the videos or to submit video content of their own.

Science Cures allows scientists to become engaged in calling on our leaders to reinvigorate national investment in scientific research through a variety of tools and resources. Through the website, researchers and members of the public can contact the candidates, write letters to their local media outlets, sign a pledge to vote for candidates who support federal funding of research, and even register to vote. The site includes a number of resources emphasizing the benefits of biomedical research, including a number of interactive features designed to provide key facts about medical research, at both the national and local level. There will also be the opportunity for scientists to sign up for FASEB's e-Action list, which will allow them to stay abreast of the most recent developments in the presidential initiative, legislative news relevant to biomedical researchers, and to receive action alerts on breaking legislative issues.

In addition to mobilizing the scientific community through the ScienceCures website, FASEB is working to highlight the importance of medical research among all presidential candidates. This includes providing all candidates and their campaigns with information about the role NIH and biomedical research play in improving the health of the nation, engaging moderators and sponsors of presidential debates, and alerting the media to critical national issues related to medical research. "From the aging population to emerging diseases to drug-resistant 'superbugs,' there has never been a more important time to prioritize biomedical research," stated Palazzo in a recent press release. "FASEB hopes that anyone running for President of the United States would make NIH a key part of their healthcare platform."

ASBMB to NCRR—No More CTSAs for Now

BY PETER FARNHAM

In a November 29, 2007, letter to Barbara Alving, Director of the National Center for Research Resources (NCRR) of the National Institutes of Health (NIH), ASBMB President Heidi Hamm asked NCRR to refrain from funding any additional Clinical and Translational Science Awards (CTSAs) until the existing ones are evaluated and the NIH budget begins to grow again.

The letter was sent just prior to an NCRR strategic planning retreat held in Bethesda in early December. ASBMB heard back from Alving within 48 hours of sending the letter; a meeting between her and ASBMB representatives is scheduled for mid-December to discuss ASBMB's concerns. The letter is posted on the ASBMB website under the *What's New* column.

ASBMB mentions four reasons why the CTSA program should be put on hold. First, NCRR cannot fully fund the 24 CTSAs currently awarded, even though commitments were made when the awards were granted. The program is slated to grow to a total of 60 CTSAs over the next several years. The NIH budget has lost almost 13% of its purchasing power since 2003. As the letter notes, "It is a common complaint among the current CTSA Consortium Directors that, while the CTSAs are required to promote outreach programs and pediatric research, for example, the funds to produce these new outcomes, as opposed to the old General Clinical Research Centers programs, are simply not being provided when the funding decisions are being made."

In addition, the CTSAs soak up funding at NCRR needed for many other programs such as Shared Instrumentation, High-End Instrumentation, and Biomedical Technology Research Resource grants, which provide essential infrastructure and technology development to support American bioscience research, as well as funds for individual, investigator-initiated grants (which only make up 8% of NCRR's budget to begin with). ASBMB expresses great concern about "troubling reports that grant applications receiving top priority scores are not being funded because the CTSA program is absorbing so much of NCRR's budget."

The NIH budget has lost almost 13% of its purchasing power since 2003.

Finally, ASBMB notes that the CTSA program is not yet a proven success and calls for a detailed assessment of the 24 currently funded CTSAs, as well as the next 12 to be reviewed since these applications have already been submitted, before proceeding with the planned expansion.

This letter follows up on an initial set of comments ASBMB submitted on August 23, 2007, in response to an NCRR request for responses to six questions related to NCRR's strategic planning. These comments are available for review on the ASBMB website under the "public policy statements" page.

Comments from Retreat

ASBMB Today has learned that the NCRR planning retreat, held December 3-4, 2007, featured several prominent participants who recommended that the CTSA program be slowed down. A keynote speaker on the 1st day of the retreat noted that "there was nothing magic" about 60 CTSAs, the ultimate number planned, and that external peer review was needed of the ones extant.

In addition, the Biomedical Technology Research Resources Program was given "high marks" and also touted as absolutely necessary to the success of the CTSAs. Also praised were the Shared Instrumentation and High-End Instrumentation grant programs.

Attendance at the retreat was estimated to be well over 100, including representatives from many of NIH's other institutes and centers. Discussions in the breakout sessions were characterized as "frank." According to one participant, "what can be done that is politically palatable remains to be seen," but there seems to be considerable support for slowing down the awards process until an assessment of current CTSAs is made and until the funding climate improves.

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

House Fails to Override Presidential Veto

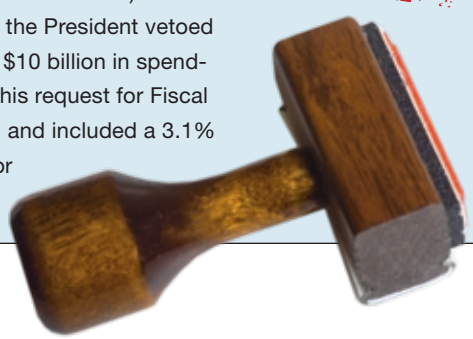
The House of Representatives attempted to override the President's veto of the Labor, Health and Human Services, and Education (L/HHS) funding bill, which funds the NIH, but failed to do so. Although the vote appeared close, the override attempt failed by only two votes, the numbers probably do not reflect the President's total support. 142 Republicans voted to sustain the veto, but 151 Republicans signed a pledge earlier this year to support the President if necessary to sustain such a veto. It is thus likely that, once the Republican leadership knew they had the votes needed to sustain the President's veto, as many as nine Republicans were given a pass by the leadership to vote to override due to political considerations in their districts.

No attempt was made to override in the Senate since the attempt failed in the House (a veto must be over-ridden by a two-thirds majority in both houses).

The bill the President vetoed had about $10 billion in spending above his request for Fiscal Year 2008, and included a 3.1% increase for NIH, raising the budget for that agency to $30 billion and coming close to meeting biomedical inflation for the first time since the doubling of the agency's budget ended in 2003.

The House leadership is considering a variety of ways to deal with the impasse on L/HHS funding, including sending a bill to the President with reduced spending but still above what he had proposed. However, it is unclear that this strategy will work. Another option is a long term continuing resolution, with a few select agencies "cherry-picked" for increases while most remain funded at current levels.

Many of you wrote to your congressman and senators urging them to vote to override the President's veto. While we did not prevail in the effort, your willingness to take the time to do this was much appreciated. We hope you will be willing to go to bat for biomedical research again in the coming year.



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

asbmb member spotlight

Please submit news about yourself to asbmbtoday@asbmb.org

Bannerman Receives Presidential Early Career Award

Douglas D. Bannerman, a scientist with the Agricultural Research Service of the U.S. Department of Agriculture, was one of 58 early career scientists who was awarded the Presidential Early Career Award for Scientists and Engineers. Established in 1996, this presidential award is the highest honor bestowed by the U.S. Government on scientists and engineers at the beginning of their independent careers. The awardees were recognized by President George W. Bush at a ceremony at the White House on November 1, 2007.

Bannerman's research focuses on developing novel therapeutics and approaches for the prevention and treatment of mastitis, one of the most prevalent diseases in dairy cattle. His research utilizes a systems-based approach to investigate host innate immune responses to intramammary and systemic bacterial infections at the genomic, cellular, and whole animal levels. In particular, he is focused on identifying host innate immune responses that result in successful eradication of intramammary infections and developing immuno-modulators that can facilitate host clearance of chronic infections. Bannerman's research program transcends the field of veterinary medicine and also focuses on investigating the pathogenesis of vascular complications associated with sepsis in humans.

Bond Honored by International Proteolysis Society

Judith S. Bond, Professor and Chair of Biochemistry and Molecular Biology at Penn State University College of Medicine, was named Honorary Life Member of the International Proteolysis Society (IPS) at its meeting in Patra, Greece, October 18-23, 2007. Bond is one of eight Honorary Life Members and the only member who is a woman. In presenting the award, Robert Pike, chair of the IPS council, cited Bond's scientific achievements, documented in more than 150 technical publications; her contributions to the organization of international proteolysis meetings and newsletters; her record in training graduate students and postdoctoral scholars; and her leadership as President of the American Society for Biochemistry and Molecular Biology, as an associate editor of the *Journal of Biological Chemistry*, and in public policy.

Bond has been a strong advocate for federal funding of fundamental research, especially for innovative projects conceived of by individual investigators. She reported to the 500 attendees at the IPS conference some of the results of research from her laboratory on the role of the proteolytic enzymes she discovered, called meprins, in inflammatory bowel disease and urinary tract infections.

Harrison Named Director of Oncological Sciences Center

Marietta Harrison, Professor of Medicinal Chemistry and Molecular Pharmacology at Purdue University's College of Pharmacy, Nursing, and Health Sciences, will become director of Purdue University's Discovery Park Oncological Sciences Center. Harrison has served as interim director of the center since its launch in July 2005, and will lead the Oncological Sciences Center as it integrates the broad areas of research in life sciences, liberal arts, engineering, and chemical sciences to focus on wider aspects of the cancer problem. Harrison will also remain as associate director of the Purdue Cancer Center, a post she has held since 1999.

Harrison, who received her doctorate in biochemistry from the University of Wyoming and did postdoctoral training at the Fred Hutchinson Cancer Research Center in Seattle, joined the faculty of Purdue's College of Pharmacy in 1989. Her research focuses on mechanisms underlying the activation of the immune system. She has authored more than 60 peer-reviewed articles.

The Oncological Sciences Center was formed to build on existing research areas and is expanding Purdue's thrust into nanotechnology, drug delivery, and cancer care and prevention. Harrison said she will continue working closely with the Purdue Cancer Center, expanding research in experimental therapeutics for new cancer drugs and diagnostic tools and in structural biology for examining cancer cell proteins to help drugs target them more effectively. She also will seek new opportunities, forge new partnerships, and cultivate new relationships to advance cancer research beyond the laboratory.

Wong Named Cotton Medalist

Chi-Huey Wong, Professor of Chemistry at Scripps Research Institute in La Jolla, California, and President of Academia Sinica in Taipei, Taiwan, is the recipient of the F. A. Cotton Medal, sponsored by the American Chemical Society and Texas A&M University Department of Chemistry. Wong was selected to receive the award for his many contributions to new chemical and enzymatic strategies and methods for the synthesis of biologically active compounds.

The medal consists of a gold medal and a bronze replica and is named for the late F. Albert Cotton of Texas A&M University. Wong will formally receive the medal at a ceremony in the spring of 2008 at Texas A&M University.

Wong's research encompasses a wide variety of projects directed toward the development of new chemical and enzymatic strategies, methods for the synthesis of biologically active compounds, and designed molecules as mechanistic probes and inhibitors of carbohydrate-mediated biological recognitions, sequence-specific RNA recognitions, and enzymatic reactions.

Retrospective: Sophia S. Simmonds & Joseph S. Fruton

Sofia S. Simmonds and Joseph S. Fruton, both Emeritus ASBMB members, passed away after short illnesses on July 27 and 29, 2007, respectively. Simmonds, who was 90, and Fruton, who was 95, were both professors emeriti at Yale University.

Simmonds and Fruton married in 1936 and pursed independent research careers in biochemistry. However, they also published a textbook together in 1953. *General Biochemistry* was the first rigorous and comprehensive textbook in the field and was translated into a number of languages including Japanese.

Simmonds grew up in New York City and graduated from Barnard College. She then enrolled in graduate school at Cornell University where she worked with Nobel Prize winner Vincent du Vigneaud. After receiving her Ph.D. in 1942, she moved to Yale University where she eventually became a professor of biochemistry and then a professor of molecular biophysics and biochemistry. Simmonds served as director of undergraduate studies at Yale for many years and also served as associate dean of Yale College.

Simmonds' research focused primarily on the metabolism of amino acids and peptides in *Escherichia coli*. In recognition of her contributions to science, she was awarded the Garvan Medal by the American Chemical Society in 1969. This award recognizes the research accomplishments of outstanding women chemists.

Fruton was born in Czestochowa, Poland, but he and his family immigrated to the United States when he was 11 years old, eventually settling in Brooklyn, NY. He received his B.A. in 1931 and his Ph.D. in biological chemistry in 1934 from Columbia University. Fruton then spent the next 10 years working with Max Bergmann at Rockefeller Institute for Medical Research (now Rockefeller University). During that time, he became interested in the chemistry of peptides and the mechanism of proteases and discovered that these enzymes have demanding chemical specifities for their substrates.

In 1945 Fruton went to Yale University to become an associate professor of Physiological Chemistry and later professor of Biochemistry (1950). He served as chair of the Department of Biochemistry from 1951 to 1967, and as director of the Division of Science from 1959 to 1962. He was also the Eugene Higgins Professor of Biochemistry from 1957 to 1982.

Fruton's primary research concerned the use of synthetic peptides to determine the specificity and mechanisms of the catalytic action of protein-cleaving enzymes such as pepsin.

Fruton was also the author of several historical books including *Molecules and Life: Historical Essays on the Interplay of Chemistry and Biology* (1972), *A Bio-Bibliography for the History of the Biochemical Sciences Since* 1800 (1982, 1985, 1994), *Contrasts in Scientific Style: Research Groups in the Chemical and Biochemical Sciences* (1990), and *Proteins, Enzymes, Genes: The Interplay of Chemistry and Biology* (1999). He eventually established himself as a leading historian of science and was appointed professor of the history of medicine at Yale in 1980.

Fruton was awarded various honors throughout his lifetime including the Eli Lilly Award in Biochemistry from the American Chemical Society (1944), the Pfizer Award from the History of Science Society (1973), the John Frederick Lewis Award from the American Philosophical Society (1990), and the Dexter Award in the history of chemistry from the American Chemical Society (1993).

In 2005 Fruton and Simmonds endowed the "Joseph S. and Sofia S. Fruton Teaching and Research Fund" for the History of Science at Yale University.

ASBMB would like to recognize the following members who passed away in 2007

John M. Buchanan
Ronald A. Butow
Paul Byvoet
Kenneth R. Cutroneo
Robert B. Dickson
Setsuro Ebashi
Robert E. Feeney
Edwin H. Flynn
Joseph S. Fruton
David K. Fukushima
Martin Gibbs
Jack Gorski
Elizabeth L. Gross
Frank R N Gurd
Harold C. Helgeson
Roger W. Jeanloz
Ian N. Jongewaard
Arthur Kornberg
Rosalind H. Kornfeld
Daniel E. Koshland, Jr.
David Kritchevsky
Yong-Hwan Lee
Aaron B. Lerner
Leo Levenbook
Stanley L. Miller
Victor A. Najjar
Charles A. Nelson
Lewis I. Pizer
Forrest W. Quackenbush
Joseph J. Rackis
Abraham Rosenberg
Harry Rudney
Leland L. Smith
Antero G. So
Jaro Sodek
David B. Sprinson
Marian T. Stankovich
Paul K. Stumpf
David M. Tennent
Wayne W. Umbreit
Chih H. Wang
Eugene C. Weinbach
Seymour Zigman

National Institutes of Health Holds Mentoring Workshop

BY ANGELA HVITVED

The National Institutes of Health (NIH) Working Group on Women in Biomedical Careers and the Office of Research on Women's Health hosted a 2-day National Leadership Workshop on Mentoring Women in Biomedical Careers on the NIH campus in November, 2007. The theme of the workshop was "Mentoring Is Everybody's Business" and focused on addressing the mentoring needs of women in biomedical research careers. The conference was structured around multiple workshop sessions in which participants explored specific topics in detail and developed a list of recommendations. Some of the workshop topics included "Can Mentoring Be Taught: Training of Mentors and Mentees," "Mentoring in Clinical Departments," and "Mentoring Minority Women in Biomedical Research." In addition to the breakout sessions, panel discussions focused on successful models of mentoring programs and continued development of leadership in mentoring. The program concluded with reports from the breakout sessions and review of the multiple recommendations developed in these sessions. The recommendations spanned a wide range of concerns and mechanisms of implementation, from highly individualized and institution-based policies to proposals that would cover all of the major funding agencies. Videocasts of the panels and presentations can be found at http://orwh.od.nih.gov/index.html.

The NIH Working Group on Women in Biomedical Careers was created by NIH Director Elias Zerhouni in response to the recently released National Academies report, "Beyond Bias and Barriers, Fulfilling the Potential of Women in Academic Science and Engineering," that highlighted concerns about retaining women in academic research positions. The Working Group is co-chaired by Elias Zerhouni and Vivian Pinn, the Director of the Office of Research on Women's Health, and is charged with responding to the challenges issued by the report from the National Academies of Science and developing strategies to maximize the potential of women in both the NIH intramural and extramural research communities. Building on the work of the November meeting, another workshop will be held March 4-5, 2008, titled "Women in Biomedical Research: Best Practices for Sustaining Career Success." More information about these programs and others can be found at http://womeninscience.nih.gov/.

ASBMB Named Affiliate Partner of Biology Scholars Program

The American Society for Biochemistry and Molecular Biology (ASBMB) was recently named an affiliate partner of the Biology Scholars Program, a multiyear leadership program for college biology faculty that aims to bring about reforms in undergraduate education.

The Program is based on three independent, but intertwined, virtual residency programs, in which faculty employ rigorous evaluations of their own teaching with the goal of publishing results demonstrating improved student learning in the laboratory or classroom and leading colleagues in national efforts to sustain undergraduate biology education reform. The Research Residency focuses on developing biologists' knowledge and skills in evidence-based research in learning. The Writing Residency moves biology faculty who are conducting scholarly work in student learning and advances their performances to publish in biology and/or science education journals and on-line collections. The Leadership Residency advances biology faculty to develop as leaders in building communities, transforming professional societies and institutions, and sustaining reform efforts.

Adele J. Wolfson from Wellesley College and ASBMB Public Affairs Officer Peter Farnham will represent ASBMB on this national initiative for the next 3 years. Wolfson will act as a Writing Residency Advisor and serve on the Biology Scholars Program Writing Residency Advisory Committee. Farnham will act as a staff liaison for the program.

More information on the Biology Scholars Program can be found on their Web site: http://www.biologyscholars.org.

New Commentary Section in *JLR*

Starting in January, the *Journal of Lipid Research* (*JLR*) will be featuring a new Commentary section at the front of each issue of the journal. The commentaries, written by experts in the field, will highlight articles published in that issue or in recent issues of the journal and will discuss the relevance and importance of the findings of the article as well as known and potential ramifications. The highlighted articles will be those that the *JLR* Associate Editors and Editorial Board Members feel are especially significant.

In an editorial in the January issue of *JLR*, Edward A. Dennis, *JLR* Editor-in-Chief, and Joseph L. Witztum, *JLR* Deputy Editor-in-Chief, write, "We know that not every *JLR* reader is able to read every article in every issue of the journal, and we hope this Commentary will highlight articles that have special significance for the lipid community and that have far-reaching implications for a wide cross-section of our readers."

The first commentary is by Associate Editor Roger Davis of San Diego State University. In his commentary, Davis discusses the article "Differential Regulation of Bile Acid Homeostasis by the Farnesoid X Receptor in Liver and Intestine" by Insook Kim, Sung-Hoon Ahn, Takeshi Inagaki, Mihwa Choi, Shinji Ito, Grace L. Guo, Steven A. Kliewer, and Frank J. Gonzalez (published in the December 2007 issue of *JLR*).

ASBMB

Australian Society for Biochemistry and Molecular

BOOMERANG AWARD

The Australian Society for Biochemistry and Molecular Biology offers the Boomerang Award to an outstanding expatriate Australian biochemist or molecular biologist. The awardee will return to Australia to present their work in a symposium at ASBMB's annual ComBio scientific meeting and give seminars at universities or research institutes. The awardee will gain exposure in Australia and interact with local researchers. The award includes free registration at ComBio, a significant contribution to the cost of a return airfare and accommodation for ComBio, and towards domestic travel expenses to visit at least one other Australian city. Applicants must have been a member of a recognised Australian scientific society for at least 2 years (not necessarily ASBMB) and be no more than 7 years since the award of their PhD.

Applications close 28 February 2008
For more information visit our website
or contact Marie Bogoyevitch
marieb@unimelb.edu.au

http://www.asbmb.org.au/awards.html

2008 ASBMB Annual Meeting

DNA & RNA Biology

Genome Dynamics: Replication, Recombination and Damage Response

- DNA Replication Mechanisms
- DNA Damage Response and the Cell Cycle
- Double-Stranded Breaks and DNA Recombination
- DNA Repair Mechanisms

Dynamic Chromatin and Gene Expression

- Chromatin Regulation of DNA Repair, Recombination, and Genome Stability
- Chromatin Structure in Gene Activation
- Chromatin Changes in Development
- Non-Coding RNAs in Gene Regulation and Chromosome Structure

RNA-Mediated Gene Expression

- Regulation of Nuclear RNA Metabolism
- Ribonucleoproteins
- RNA Transport and Localization
- RNA Turnover

Small RNAs and Dynamic RNA Elements

- Riboregulation
- Dynamic RNA Structures
- The Emerging Non-Coding RNA World
- Roles for Small Non-Coding RNAs

Molecular Structure & Dynamics

Protein Synthesis and Turnover

- Protein Turnover and Quality Control
- Protein Turnover in Cell Regulation
- Mechanisms of Protein Synthesis
- Protein-Assisted Folding and Misfolding

Form and Function of Molecular Machines

- Helicases
- Replication
- Gene Expression
- Filament Dynamics

Biomolecular Catalysis, Folding and Design

- Protein Interactions in Catalysis
- Enzymes as Drug Targets
- Energetics and Design
- Macromolecular Folding and Fluctuations

Cell Systems & Metabolism

Metabolism

- Metabolism and Diabetes
- Metabolism and Cancer
- Metabolism and Neurodegeneration
- Metabolic Networks

Systems Biology

- Global Systems Biology: Parts
- Global Systems Biology: Relationships
- Global Systems Biology: Dynamics
- Local Systems Biology: Subsystems and Simulation

Cell and Organelle Dynamics

- Cell Division
- Intracellular Dynamics
- Cell Migration
- Pathogen Exploitation of Host Machinery

Signaling

Lipid Signaling and Metabolism

- Tissue-Specific Regulation of Lipid Metabolism
- Lipids and Control of Gene Expression
- Stress and Lipid Metabolism
- Lipids and Inflammation

Signal Transduction

- Signaling in Disease and Therapy
- Growth Regulation
- Post-Translational Modifications
- G Proteins and Protein Kinases

ASBMB/ASPET

- Integration of Second Messenger Signaling
- The G-Whizards of GPCR/G-Protein Signaling
- G12/13 Signaling of Cell Surface Receptors: Molecular Insights and Disease Context
- Nicotinic Receptors and Ligand Gated Ion Channels

Chemical Biology

Chemical Biology

- New Strategies for Imaging Protein Localization and Dynamics
- Chemical Perspectives in Neurobiology
- Small Molecule Control of Protein Folding and Assembly
- Chemical Probes and Their Use in Identifying New Therapeutic Targets

Drug Discovery

- Drug Discovery in Academic Settings: Is There a Role for Academic Scientists in Early Drug Discovery
- Targets for Drug Discovery: Has Target-Based Screening Failed for Antibacterials?
- Targets for Drug Discovery: Nuclear Hormone Receptors
- Developing and Commercializing University Biomedical Inventions

Special Sessions

The Histochemical Society, HCS

- The *Journal of Histochemistry and Cytochemistry* Plenary Lecture: Genome-wide mapping of gene expression in the adult mouse brain
- Live Imaging of Developmental Processes
- Laser Capture Microdissection for Molecular Analysis
- Phenoms in the Phenome: Experts in Cellular Imaging from Single Molecules to Mice
- Principles and Application of Immunocytochemistry, (HCS Short Course)**

**Register at: www.histochemicalsociety.org

Minority Affairs—Mental Health

- Health Disparities in Alzheimer's Disease: Advances in Understanding Disease Pathogenesis
- CNS Diseases—Depression and Anxiety
- Discovery and Applications
- Drug Abuse

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- Assessment Issues Workshop
- Classroom of the Future III
- Incorporating Research into Formal Laboratory Courses Workshop
- Starting and Sustaining Undergraduate Research Workshop
- Writing Your First Grant Application Workshop

Public Affairs

- Advocacy Training for ASBMB Members

San Diego

San Diego, CA
April 5-9, 2008

www.asbmb.org/meetings

Abstract Submission Deadline: November 7, 2007

Speak Up for Science

New Survey Reveals Scientists Have Role to Play in Fostering Science Education

BY NICK ZAGORSKI

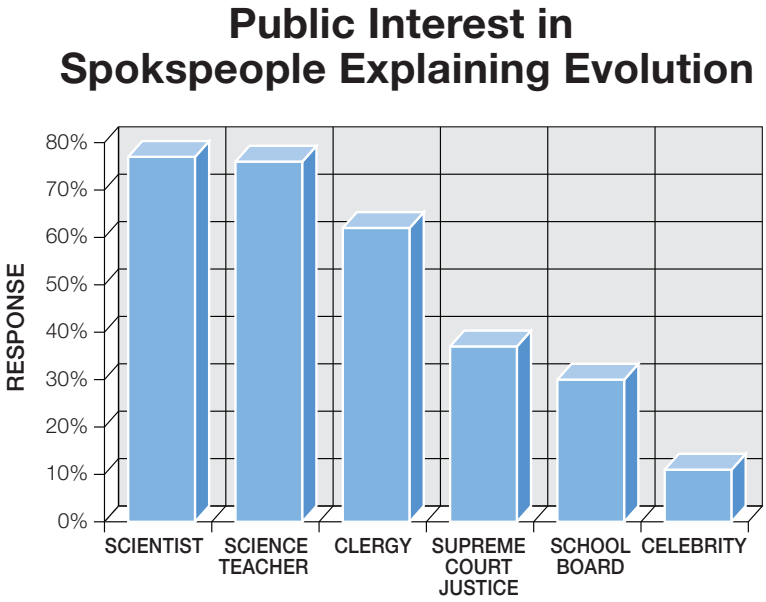
In 2006, Nobel winner Peter Agre made an unusual stop on his yearly lecture circuit, appearing on the "Colbert Report" to debate the conflict between science and religion. He admits that some of his colleagues jokingly chastised him for this unorthodox forum, but he counters that he achieved a goal that would be unattainable in even the largest university lecture hall: carrying his message about the importance of using sound science in education and policy to millions of people.

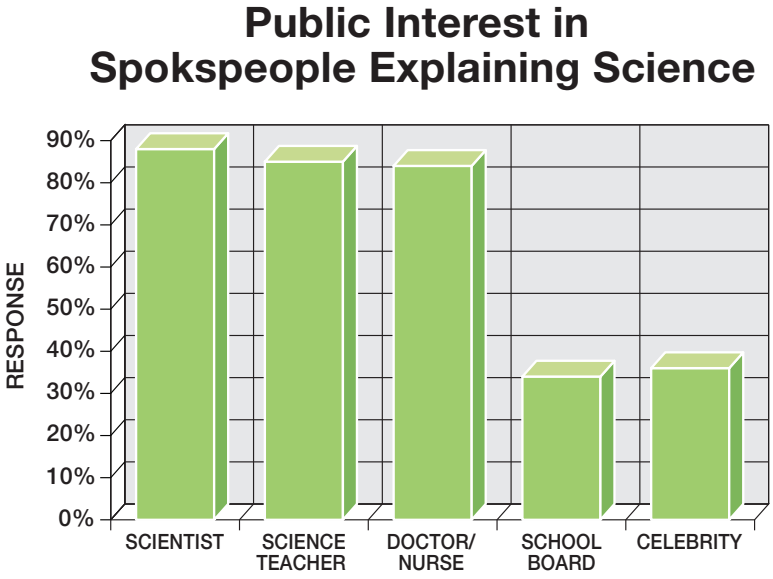
A recent survey on the attitudes toward evolution, conducted by the Coalition of Scientific Societies as part of a larger effort to bolster the role of science in educating our youth and the general public, suggests that more Agres need to emerge from the scientific community. The survey results confirm much that had already been known: Americans are fairly well split on their evolutionary beliefs (~30% accept natural evolution, divinely guided evolution, or creationism) and the degree of evolution acceptance correlates with scientific literacy. However, the data also suggest that the divide can be narrowed, if scientists are willing to shoulder the responsibility and alter their approach.

The survey found that scientists, physicians, and teachers are viewed quite favorably by the public (69, 76, and 79% had positive views, respectively), and a much larger majority of respondents (85%) would prefer to hear about evolution or other science topics from a scientist or teacher as opposed to a member of a school board or a celebrity. Certainly, the pro-science publicity efforts of individuals like Al Gore are laudable and valuable, but the imprimatur that a researcher or medical doctor can give on evolution, climate change, or other scientific issues would be even more valuable.

How scientists can best educate the public on such matters, or at least attempt to, poses a thornier problem, as pre-existing beliefs for subjects like evolution can be strongly embedded. Most interestingly, the concepts behind evolutionary science (and all science for that matter), such as drawing conclusions from evidence, critical thinking, and rigorous experimentation, were all rated by survey participants as important skills that can be gained from science classes. The key may therefore be to repackage how evolution is taught; if scientists can bridge evolution to other subjects that hold more interest, greater relevance, and less innate opposition to people, then it may gain more public support.

Health and medicine would be one clear choice; 63% of respondents ranked curing diseases as the most important contribution science has made to society, and a similar number believed that understanding how evolution can improve medical science would be a convincing reason to teach it in school. For example, the headlines made by the recent rise of hospital methicillin-resistant *Staphylococcus aureus* (MRSA) infections or lingering concerns over an





avian flu outbreak could be used as a platform by scientists to introduce people to evolutionary thinking. Other areas of public interest where evolution has contributed and where scientists can make inroads include agriculture and forensics.

Of course, not every researcher has to follow Agre's lead and try to book an appearance opposite Stephen Colbert or an interview with National Public Radio. There are plenty of opportunities for willing scientists to take advantage of the public's respect and to communicate sound science. These could include writing letters to local newspapers, speaking with various community groups, initiating a café scientifique in the area, or partnering with non-science educators to design courses that may introduce science into other fields (the history of evolution, for example).

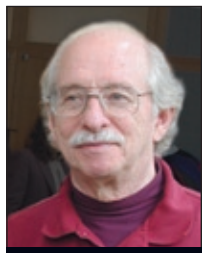
"There are plenty of opportunities for willing scientists to take advantage of the public's respect and to communicate sound science."

Regardless of the method, to truly communicate the value of science, scientists must emphasize the outcomes that matter to people, and they must do so clearly and understandably. Technical expositions on scientific topics will not capture the attention of the public or policymakers. Scientists have to explain their work in ways that are comprehensible and meaningful to non-scientists, or else their value as spokespeople for science is gone.

In summary, the coalition stresses the need for scientists to become involved in promoting science education. They note: "If our nation is to continue to develop the talent necessary to advance scientific and medical research, we must ensure that high standards in science education are maintained and that efforts to introduce non-science into science classes do not succeed. Failure to reach out effectively to a public that is supportive of science and open to information from the scientific community is not just a missed opportunity; it is a disservice to the scientific enterprise."

More information on the survey can be found at: http://opa.faseb.org/pages/PolicyIssues/sciencecoalition.htm.

The 2008 Herbert A. Sober Lectureship: S. Walter Englander


Englander

The 2008 Herbert A. Sober Lectureship will be given by S. Walter Englander of the University of Pennsylvania School of Medicine. This lectureship, which is awarded every 2 years, recognizes outstanding biochemical and molecular biological research with particular emphasis on development of methods and techniques to aid in research. Englander is an expert in hydrogen exchange and has been a central figure in the development and application of hydrogen exchange-base methods that revolutionized insight into the biochemistry and biophysics of proteins. He will present his lecture in San Diego on Tuesday, April 8, at 2:15 p.m.

The method of hydrogen exchange is based on examining the rate at which hydrogen atoms in the peptide bond exchange with the water solvent. By measuring hydrogen exchange rates, one can access conformational changes in proteins and nucleic acids and kinetic folding intermediates in reactions. In the late 1950s, Kaj Linderstrøm-Lang initiated the use of hydrogen exchange using deuterium to probe the structure, dynamics, and energetics of proteins. However, this procedure was difficult to use, and the experimental data lacked accuracy.

In the early 1960s, Englander devised a simple rapid method of investigating hydrogen exchange using hydrogen-tritium exchange and Sephadex separation to determine the properties of macromolecules. Eventually, Englander applied high pressure liquid chromatography technology to increase the resolution of these studies.

Using these methods, Englander was able to explain the dynamic structural processes that produce hydrogen exchange behavior and formulated the concept that proteins "breathe" at a time when it was believed that proteins were rigid molecules. Hydrogen exchange was quickly adopted by others and led to early measurements of the breathing rate of double-stranded DNA. Englander also studied hydrogen exchange in DNA and attempted to investigate the dynamics of even more complicated structures, including the ribosome.

In the early 1980s, Englander used trace deuterons and NMR to spectroscopically identify the chemical origin of each exchangeable hydrogen, eliminating much of the guesswork that was involved in hydrogen exchange. He has also promoted and developed the addition of mass spectrometric methods to hydrogen exchange for use with molecules too large for NMR.

Over the last 15 years, Englander has focused on the protein folding problem. He showed how to detect and characterize folding intermediates that exist for less than 1 s in kinetic folding, and how to access the infinitesimally populated protein forms that populate the high free energy landscape at equilibrium under native conditions. These results revealed not only the structure of the partially formed intermediates that account for protein folding pathways but also their pathway relationships, their thermodynamically relevant free energies, and their kinetic formation and decay rates.

According to George Rose, Krieger-Eisenhower Professor at The Johns Hopkins University, "Scientists are of many types. Among the very best are those rare individuals who devise an important approach as an end in itself, like virtuoso instrumentalists perfecting their art. Rarer still are those who respond to a higher music, developing innovative new methods to pursue fundamental problems. Walter Englander is among the very few who fall squarely into this latter category."

Englander earned his B.S. from the University of Maryland in 1951 and then attended the University of Pittsburgh where he earned his M.S. in 1953 and his Ph.D. in 1958, both in Biophysics. After he graduated, Englander became a postdoctoral fellow with Christian Anfinsen at the National Institutes of Health. In 1960, he became an Instructor in Biochemistry at Dartmouth Medical School where he remained until 1967 when he joined the faculty of the University of Pennsylvania as an Associate Professor of Biochemistry. In 1974 he was promoted to Professor of Biochemistry & Biophysics, and he served as Associate Chairman in the Department of Biochemistry & Biophysics from 1979 to 1982. Englander is currently the Jacob Gershon-Cohen Professor of Medical Science at the University of Pennsylvania.

The 2008 Howard K. Schachman Public Service Award: **Micheal N. Castle**

BY PETER FARNHAM


Castle

The ASBMB Public Affairs Advisory Committee has chosen the Honorable Michael N. Castle (R-DE) as the recipient of the 2008 Howard K. Schachman Public Service Award. ASBMB established the Award in 2001. It recognizes dedication to public service in support of biomedical science, as exemplified by the award's namesake, Howard K. Schachman, who served as chairman of ASBMB's Public Affairs Advisory Committee for more than 10 years (1989-2000) and made numerous contributions to biomedical research policy in both governmental and nongovernmental capacities.

The Society wanted to recognize Castle's exemplary efforts in recent years to support biomedical research through increased funding for the National Institutes of Health (NIH), as well as his ongoing efforts in support of a more rational federal policy regarding human embryonic stem cell research. Castle is a member of the Republican Main Street Partnership, which, according to his office, he co-founded in 1998 to promote "thoughtful leadership in the Republican Party, to serve as a voice for centrist Republicans, and to partner with individuals, organizations, and institutions that share centrist values."

Castle has made numerous efforts in recent congresses to pass a bill that would ease restrictions on the use of embryonic stem cells in biomedical research. He co-sponsored the Stem Cell Research Enhancement Act in 2005 and during the 109th Congress shepherded it to passage in the House. The bill also passed in the Senate and then went to the President for his signature. In July 2006, President Bush vetoed the bill, the first veto of his presidency, and although a majority of the House voted to override, it did not gain the required two-thirds majority support needed to allow the bill to become law.

His efforts to enhance funding at the National Institutes of Health are also exemplary. Castle led a group of moderate Republicans in insisting that the 2007 Budget Resolution include an additional $7.1 billion to fund necessary domestic programs, including the NIH. In a meeting with the senior republican leadership in the spring of 2006, he took the courageous stand that he and his group of centrist Republicans would not support a budget resolution that did not include such an increase. This resulted in a budget impasse that lasted several months in 2006, but ultimately, Castle prevailed; the Republican leadership agreed to the change and promised to find the additional $7 billion.

ASBMB recognized Castle's efforts in a letter from then-President Judith Bond, which noted that "your efforts are greatly appreciated, and we will be sure our members are aware of your good work to help make it possible for them to continue their research on alleviating diseases that affect all of us like cancer, heart disease, diabetes, and other life-threatening disorders. Thank you for your good work, courage, and dedication."

PAAC member Robert Palazzo, also current FASEB president, noted that "Over the past 3 to 5 years Castle has championed both stem cell legislation and NIH funding in the House; Castle is key legislator working on behalf of basic biomedical research."

Castle has had a long history in Delaware politics, including two terms as governor of the state (he remains Delaware's most popular politician). He is currently serving a record eighth term as Delaware's lone Member in the House of Representatives. Since coming to Congress in 1993, he has worked to bring a common sense bipartisan approach to legislating. According to his website, "He has been building bridges and forming coalitions to find pragmatic, bipartisan solutions to some of the most pressing problems facing the country and believes strongly in returning the Congressional agenda to issues that really matter to the American people."

The Schachman Award is given annually, and candidates are considered by the Society's Public Affairs Advisory Committee. The award consists of a permanent keepsake, an honorarium of $5,000, an opportunity to deliver a talk or lecture at the Society's annual meeting or other suitable venue, and travel expenses to the meeting. The ASBMB staff is working with Castle's office to find a suitable venue for the presentation of the Schachman Award.

ASBMB Today offers its congratulations to Rep. Castle on his selection as the 2008 recipient of the Howard K. Schachman Public Service Award.

From Pipelines to Pathways: Partnerships for Excellence and Equity in Research Science

BY PAT MARSTELLER

Unfortunately, when it comes to minorities in science, the leaky pipeline model still applies. Although there is a significant national consensus on what changes are required to achieve a diverse scientific workforce, changing filters and sieves into pumps that attract and assist under-represented students to attend college, enter and succeed in STEM majors, successfully complete doctoral programs, and join the faculty and scientific workforce is still a work in progress.

Here I describe a few of the programs led by the Emory College Center for Science Education (ECCSE) that attempt to replace the leaks and sieves in the pipeline with pumps to increase diversity in STEM disciplines. The heart of the ECCSE mission is to improve science education at all levels. I call it a "K through gray initiative." We are particularly interested in attracting and retaining under-represented students, women and minorities, for careers in science.

Socialization and Acculturation: Building the Community of Scholars

In the early 1990s, we instituted an intensive residential summer bridge program for under-represented students who were admitted to Emory University. Substantial costs allowed us to reach only a few of the students interested in science. In 1994, based on evaluation data and the desire to reach all interested minority students, we created a new approach, consisting of a week-long summer institute, followed by weekly meetings during the first year of college. Since then, over 650 Black, Hispanic, and first generation college students have participated in the Hughes Undergraduates Excelling in Science (HUES) program. The program follows these students throughout their Emory career in order to promote their performance in science and mathematics courses and their pursuit of science-related careers. HUES is designed to help students develop a "personal action plan" for success in science-related and other course work at Emory, to expose them to a wide range of science careers, and to familiarize them with the preparatory steps leading to these careers. Our data indicate that participants are retained in science majors, choose to take more science courses, and perform better academically than their counterparts who have not participated in this program.

Supplemental Instruction for Gateway Introductory Courses

Science and math can serve as major obstacles, particularly to women and under-represented minority students, despite decades of curricular reform. What started as a small tutorial program supported by a Howard Hughes Medical Institute (HHMI) grant in cooperation with the Office of Multicultural Programs and Services in 1989 has become a multifaceted series of programs supported by Emory. Over the past several years, the departments of science and math at Emory have piloted a number of different approaches based on supplemental instruction and peer-led team learning models to provide academic support for undergraduate students. Emory now supports an associate dean and a staff of seven to provide academic support for all students. Part of the program focuses on supplemental instruction and peer mentoring for all science classes, led by a Ph.D. scientist who is the director of learning programs. For details see www.college.emory.edu/current/support/learning[lowen]programs/index.html. An evaluation demonstrated that students who participated in seven or more sessions showed a full letter grade improvement in test scores.

Mentoring, Mentoring, Mentoring

If you can only find funds and support for one kind of program, mentoring is the key. Peer to peer mentoring coupled to academic classes, peer mentoring as a form of social support, and mentoring of students by faculty and staff are crucial elements for adaptation and acculturation to college. However, mentoring is an art and a learned skill. Mentors, whether they are undergraduate peers, graduate students, or faculty, need preparation for

this difficult role. Establishing clear expectations and finding the right balance between the teacher, advisor, role model, and friend is difficult. We offer mentoring seminars for graduate students and postdoctoral fellows based on Jo Handelsman's *Entering Mentoring* and shorter workshops for faculty. We also prepare our undergraduate peer mentors for their role in reaching other peers and high school students.

Early mentoring and early research are essential for attracting students to doctoral careers in sciences. Since 1990, 170 individual faculty and over 1000 students have participated in the Emery Summer Undergraduate Research Experience. Of the 225 graduates for whom we have solid data, 216 chose graduate or professional school. We are also beginning a first year research program in collaboration with faculty from Emory University, Morehouse College, Spelman College, and Oxford University. First year students participate in a research careers seminar course that introduces relevant techniques, the primary literature, the kinds of research projects available, and short laboratory rotations. The students also write a proposal for a summer research project and are mentored by faculty, graduate students and postdoctoral fellows, and advanced undergraduates.

Working with K to 12 Students, Educators, and Systems: Think Globally, Act Locally

The largest leaks in the STEM pipeline occur well before college admissions. Reaching students and their families and changing the way science is taught are essential to stemming this flow. Emory University began a science and mathematics summer enrichment program for high school students in 1988. Our goals for these students center on increasing the number of students taking appropriate course work for admission to college, and improving the students' knowledge of requirements for science careers. The Emory University Preparatory Research Education Program provides Atlanta students with college level instruction in math, science, critical thinking, literature, and Scholastic Aptitude Test (SAT) preparation. Students reside on campus during the summer months, attend classes in college classrooms, and are often instructed by college professors.

At many colleges and universities, admissions officers give workshops on the college applications process as part of their effort to increase access. We decided to collaborate with admissions, school counselors, and teachers to deliver a more focused CollegeEd program using materials created by the College Board to educate middle and high school students and their families. Students who participate in the program complete units and lessons on college applications, financial aid, scholarships, funding opportunities to pay for their education, and techniques for becoming a more competitive applicant. We also host an Annual Minority Health and Science Professions Career Conference and a College Access Weekend for these families. We are also currently implementing CollegeEd as an after school program at Turner and King Middle Schools and at Carver and South Atlanta high schools.

Focusing on helping teachers in overwhelmingly minority schools is a more cost-effective way for universities and faculty to plug the leaks in the pipeline. The Center for Science Education supported over 300 metro area teachers in research fellowship and curriculum development positions and professional development workshops. In 2003 we began a new initiative, Problems & Research to Integrate Science and Mathematics, sponsored by the National Science Foundation. The program matches graduate students with working middle and high school teachers to promote science and mathematics education and to develop skills that will help the graduate students become better scientists. Using problem-based learning and investigative case-based learning, the program hopes to use real world applications as a way to teach the basics of science to students.

Lessons Learned

Many elements of our grand vision are working; some beyond our fondest hopes. If we had to give just a few words of advice to newcomers, they would be: Find allies, be flexible; try, try again; and write more grants. You can also form successful programs and institutions. Work with minority-serving colleges in your area. For some examples of successful programs, visit the website set up by a collaborative group of HHMI-sponsored institutions (www.williams.edu/biology/divsciences/) or the Building Engineering and Science Talent website (www.bestworkforce.org/). Collect more data and use it to learn from your successes and failures and be willing to adapt and try again when confronted with barriers. School systems and colleges are slow to change and hard to change: think of trying to move a huge battleship with your bare hands.

For more information on Emery's programs and our emerging web communities, please visit www.cse.emory.edu/

Sometimes There Is No Career Path

BY MURIEL CUNNINGHAM

I was always interested in biology. As a child of two artists, I'm not really sure how this happened. My father's attitude toward science was one of "I don't care how it works as long as it works." My high school had an abysmal science program, so I was excited to go away to a liberal arts college that was not only strong in science but encouraged us to be multifaceted, problem-solving individuals. At the time, I didn't know where a degree in biology would eventually take me. Many of my classmates wanted to go to medical school or get a Ph.D., but I knew that wasn't for me. I wanted to work in science and make a contribution, but the exact job description was elusive. Getting to where I ultimately wanted to be ended up being a bit circuitous.

Darest thou now O soul,
Walk out with me toward the unknown region,
Where neither ground is for the feet nor any path to follow?
Walt Whitman (1819–1892)

As a college senior I received a scholarship to attend graduate school in a science writing program at a large west coast university. Unfortunately, the money for my grant disappeared at the 11th hour because of state budget cuts. With my plan disrupted, I worked as a lab technician in cell and molecular biology for several years, and I obtained my M.Ed., hoping to get a job in a scientific field where I could support myself. On the advice of a friend who had been a postdoc in a neighboring lab, I applied for and landed a position in molecular biology hepatitis research at a large pharmaceutical company. After a couple of years of working in the lab, I made a lateral move within the company and worked in clinical research as a monitor in clinical trials. My career really took off at this point, as my project management skills came to be highly valued. As I moved higher within the drug development organization, however, I became more and more removed from the science. I found that my responsibilities were becoming entirely focused on managing budgets. This is not what I wanted or intended, but I was unsure of the next step.

I decided the best approach would be to consult with a career counselor. I took a battery of tests that resulted in a report we jokingly refer to as "The Book of Muriel." It was weird yet fascinating reading and explained a lot of what I had been feeling. If you've never gone through a self-assessment, I highly recommend it as it is very enlightening! The final recommendations were as follows: 1) my personality type would be successful in managing my own business, and 2) I should focus on my two core strengths, medical writing and project management. I started to plan my exit strategy from my current job, selecting a departure date that wouldn't be detrimental to my projects. I then obtained my certification in pharmaceutical medical writing from the American Medical Writers' Association (AMWA) and took the Project Management Institute's (PMI) Project Management Professional examination.

Cunningham

Muriel Cunningham received her B.A. in Biology from Carleton College in Northfield, Minnesota, and her M.Ed. in Science Education from Vanderbilt University in Nashville, Tennessee. After 6 years in academic research and 14 years in the pharmaceutical industry, she started her own company (Winter Count Productions LLC) that provides medical writing and project management for pharmaceutical and medical publishing organizations. She lives in Kenosha, Wisconsin, with her husband Matt, a greyhound, a cat, and a quarter horse.

I left my job in January 2006, had my first medical writing job within 2 weeks, and the work and projects haven't stopped since. I am very fortunate to have more work than I can handle, so I currently limit my jobs to a handful of wonderful clients who give me a steady supply of projects. Life is good.

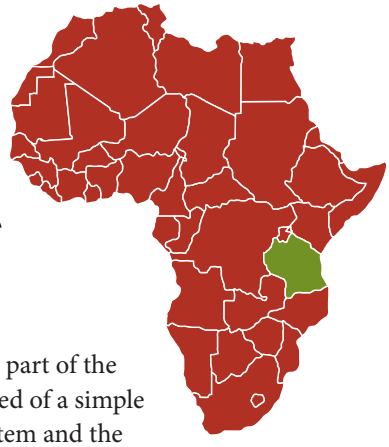
I'll share with you a little more about my two chosen fields as I think both

of them are enjoyable and marketable. As I'm sure many of you know, there are various types of medical writing. With my experience in clinical research, I primarily focus on clinical trial documents, clinical trial data reports, manuscripts reporting clinical trial results, scientific meeting coverage, and documents related to regulatory filings. Other medical writers generate grants, Continuing Medical Education materials for clinicians, patient information materials, or write about medicine for the general public. Medical writing is a growing field, and I found AMWA (www.amwa.org) to be an incredibly valuable resource. They provide training, a way to network with other writers, and hold a very informative annual convention. Before I left my job I consulted with several freelance medical writers who were very candid, helpful, and (most of all) encouraging.

Project management is a term that is often used, but many do not realize there is a formal project management approach that has been adopted worldwide to complete projects on time and within budget. This is another growing discipline, as more institutions struggle to handle additional work with greater efficiency. I have always enjoyed the challenge of taking complicated endeavors and turning them into a workable plan. My project management training built on the multitasking I did in college and in the lab and allowed me to apply it to much larger, long term ventures. PMI (www.pmi.org) is a global organization that seeks to grow project management as a profession, issues credentials for professionals in project management, and trains project managers in the best practices.

Working for myself brings me a great deal of variety and benefits such as having my dog in the office, setting my own hours, and getting the opportunity to work with former colleagues who have moved on to other companies. Throughout this entire experience I've learned that it's impossible to predict or plan every career step. On the surface that may appear negative, but I don't see it that way. If I had tried to plan everything and things fell through, it is quite possible that I may have overlooked opportunities that ended up shaping me to a large degree. In my book, the winding career road is the best route. Will I do this for the rest of my life? I don't know, but I'm curious to see what happens next!

Creating Outreach Activities to Match Students' Interest: HIV/AIDS Education in Tanzania*



BY JANE CASELTON, JESSICA KRAYNIK, HANNAH UNDERDAHL, AND NEENA GROVER

Students at Colorado College have consistently expressed interest in science outreach activities that link their course material with opportunities to use their knowledge to make a difference in the world. This idealism can be utilized in creating science courses that creatively link course material with working in our local communities. These course-linked outreach activities are also referred to as Service Learning. Here we present a case where students' interest in AIDS in Africa was the main impetus to create a HIV/AIDS education course.

Many poverty-stricken cities in Tanzania are overtaken by hunger and serious diseases such as human immunodeficiency virus (HIV) and AIDS. Although missionaries visit these cities and leave money and resources behind, once these resources are exhausted the missionaries are forgotten and new and old problems arise. What these people really need is effective AIDS education. I (Jane Casselton) heard this plea and expressed it to Hannah Underdahl and Jessica Kraynik, two fellow biology majors at Colorado College.

In our chemistry and biology classes we had learned some of the science behind AIDS and the HIV virus, and we were familiar with the seriousness of AIDS and the horrors it has caused in Africa. We had also heard that Professor Neena Grover was interested in HIV/AIDS education, and we talked to her about providing a class in that subject. Our conversations with Professor Grover led her to teach "Fundamentals in AIDS Education," a course focused on the biochemistry of the HIV virus and how it affects the human body. We also met weekly to discuss readings on topics such as the immune system, the viral replication cycle, HIV drug actions, and the transmission of the disease. Our goal was to gain a sufficient understanding of the virus so that we could answer the basic questions that were likely to arise as we discussed HIV infection cycle with the Tanzanians.

We also designed a curriculum for an education workshop in Tanzania as a part of the course. The curriculum consisted of a simple explanation of the immune system and the replication cycle of the HIV virus, and also included important information on transmission, prevention, signs and symptoms, and the social issues that arise around the HIV virus. To ensure that our workshop attendees developed some understanding of the virus, we incorporated visuals, included models and drawings, created lists, and made up games and plays that related to each of these areas. We printed a curriculum outline in bound handbooks that would be distributed to each workshop attendee, and we included a "question and answer" section in the back of the book for a post-seminar reference. Our curriculum was designed for the most influential and mature adults in the Tanzanian city of Iringa, *i.e.* the church elders.

Using written lists and pictures to teach the class about treatment.

When we arrived in Tanzania, we offered two 3-day workshop courses during our stay. The 1st day consisted of the signing of a group contract that included trust and confidentiality issues. Students needed to know that they could trust each other and that the sensitive issues that were going to be discussed would be kept confidential. A safe environment was created in the first few hours by sharing stories of our experiences with HIV/AIDS and listening to the experiences of the courageous students in the group. We emphasized that we aimed for a discussion-based environment where the attendees would feel comfortable.

The students from the first seminar in Iringa.

On the 2nd day of our seminar, we shared the basic knowledge of the HIV virus and AIDS with the students in a lecture-based class. The attendees soaked up this information and actively participated in the lecture and asked numerous questions. Most of the questions surrounded the use of condoms in Africa, a subject that is taboo to discuss because of the dominance of religion in the social realm. After much discussion on this subject, the class collectively developed multiple ideas to confront the tough situation. By the end of the 2nd day, the attendees understood the basics of the HIV life cycle from its biology to its transmission to prevention. Morale of the class had risen substantially during the course of the day, and many of the students were confident in what they had learned.

The 3rd day was devoted to teaching the attendees how to teach others in their community about HIV. We supplied them with various tools and observed the process as they paired up and taught each other the material that they had learned the day before. We concluded with a graduation ceremony and an ending discussion in which they told us that teaching other community members would be easy because they understood the material.

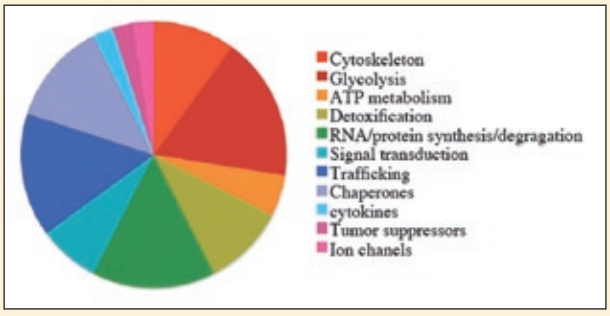
The overall goal of our teaching endeavor was not only to educate the students in our workshop but to implement an education process that would have a momentum of its own. Our hope is that the information that we shared will reach an exponential number of Tanzanians by a "ripple effect." We are in the process of sending surveys to the workshop students to determine how much information they retained from the workshop and how they have used the information since that time. A survey that we gave to our students on the 3rd day of our seminars told us that every student in our workshop planned to spread their new knowledge in one way or another.

If the seminar succeeds, then knowledge about HIV will continue to spread and will reach those who need it the most. The high involvement in and excitement about our program has sparked devotion in the three of us as well. A few years from now, we plan to return to Tanzania to teach not only groups of church elders, but also youth and women to encourage discussion and awareness among these groups as well. HIV and AIDS are an enormous part of the lives of many Tanzanians; teaching one class will not wipe out the disease, but if those in the classes leave their apathy behind and concentrate on eradicating AIDS, there will be hope instead of despair in Tanzania.

**This article has been reprinted from the March 2007 Issue of* Enzymatic*, the newsletter of the Undergraduate Affiliates Network. Back issues of the newsletter can be found at: www.faseb.org/asbmb/epd/Enzymatic.html.*

Salmonella: Killing Macrophages via Glycolysis Enzymes

Caspase-1 is an aspartate-specific cysteine protease that is essential during inflammation because of its role in the activation of cytokine signaling pathways. To better understand the function of this enzyme, the authors of this paper embarked on a systematic identification of its cellular substrates. Using the diagonal gel proteomic approach, they identified 41 proteins that are directly cleaved by caspase-1, including several proteins involved in the glycolysis pathway. The researchers showed that *Salmonella* infection, which is associated with pyroptosis, a specialized form of cell death mediated by caspase-1, causes a pronounced degradation of these glycolysis enzymes and lowers the glycolytic rate of wild-type macrophages but not that of caspase-1-deficient cells. Since glycolysis is essential for macrophage survival and activation, the cleavage of the glycolysis enzymes likely represents an essential step in toxic cell death associated with *Salmonella* infection.



41 proteins are directly cleaved by caspase-1

The Caspase-1 Digestome Identifies the Glycolysis Pathway as a Target during Infection and Septic Shock

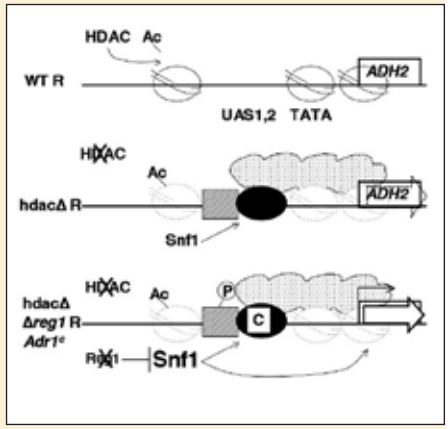
Wei Shao, Garabet Yeretssian, Karine Doiron, Sabah N. Hussain, and Maya Saleh

J. Biol. Chem. 2007 **282**, 36321-36329

jbc

Transcription Regulation in Layers

Studies in yeast have shown that the DNA-binding transcriptional activators Adr1 and Cat8 bind to the alcohol dehydrogenase II *(ADH2)* promoter and activate *ADH2* transcription when cells are placed in low glucose, in a process that requires the AMP-dependent kinase Snf1. In this study the authors exploit the previous observation that under glucose repression conditions, Adr1 and Cat8 bind constitutively (in a Snf1-dependent manner) to the *ADH2* promoter in yeast lacking the histone deacetylase (HDAC) genes, *HDA1* and *RPD3*. They obtain evidence that Adr1 and Cat8 recruit RNA polymerase II and its requisite transcriptional machinery to the *ADH2* promoter under glucose repression conditions in yeast lacking HDACs but that transcription does not occur. Based on their data, the authors argue that derepression of *ADH2* transcription involves activation of a poised RNA polymerase II initiation complex by Snf1, thus demonstrating that biological regulation is achieved not at any one step but through the superimposition of several layers of regulation.



Snf1 acts at a step after RNA pol II binding

A Poised Initiation Complex Is Activated by Snf1

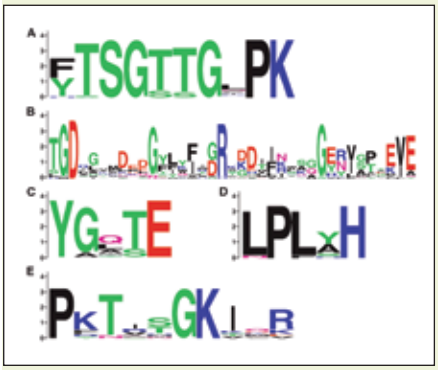
Christine Tachibana, Rhiannon Biddick, G. Lynn Law, and Elton T. Young

J. Biol. Chem. 2007 **282**, 37308-37315

jbc

Counting Human ACSs

Fatty acids serve many essential functions in living organisms. For example, they are the building blocks of lipids, and they can also be degraded for energy production, converted to alcohols or aldehydes, remodeled, or covalently bound to proteins. All of these metabolic processes have a common initial step, the "activation" of the fatty acid by forming a thioester with CoA. This reaction is catalyzed by the acyl-coenzyme A synthetases (ACSs). Because hundreds of naturally occurring fatty acid species exist, it is not surprising that higher organisms contain multiple enzymes with ACS activity. Using two conserved amino acid sequence motifs to probe human DNA data bases, the authors of this paper were able to identify 26 ACS family genes/proteins. Some of the enzymes have been previously characterized biochemically, whereas others have not yet been investigated. Examination of amino acid sequences of all identified 26 ACSs revealed conserved residues predicted by structural or biochemical studies to be important for catalysis and/or substrate binding. The existence of ACSs suggests that each plays a unique role, directing the acyl-CoA product to a specific metabolic fate.



Consensus sequences of human ACS motifs

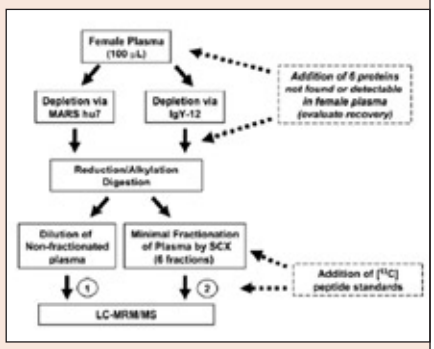
Evidence for 26 Distinct Acyl-Coenzyme A Synthetase Genes in the Human Genome

Paul A. Watkins, Dony Maiguel, Zhenzhen Jia, and Jonathan Pevsner

J. Lipid Res. 2007 **48**, 2736-2750

Detecting Low Abundance Biomarkers

Biomarkers are useful for diagnosing disease risk, determining the presence of disease in an individual, and tailoring treatments for the disease in an individual. Once a biomarker is discovered, its presence and levels in serum or plasma must be validated. However, many biomarkers are present in low numbers and are thus hard to quantify. In this paper, the authors present a new method for assaying low abundance proteins in plasma. Using multiple reaction monitoring coupled with stable isotope dilution mass spectrometry, the authors describe the development of quantitative, multiplexed assays for six proteins in plasma that achieve limits of quantitation in the 1-10 ng/ml range. These levels of assay performance represent up to a 1000-fold improvement compared with direct analysis of proteins in plasma by mass spectrometry, and were achieved by simple, robust sample processing involving abundant protein depletion and minimal fractionation by strong cation exchange chromatography at the peptide level prior to liquid chromatography multiple reaction monitoring mass spectrometry.



Experimental flow diagram for limit of quantitation studies

Quantitative, Multiplexed Assays for Low Abundance Proteins in Plasma by Targeted Mass Spectrometry and Stable Isotope Dilution

Hasmik Keshishian, Terri Addona, Michael Burgess, Eric Kuhn, and Steven A. Carr

Mol. Cell. Proteomics 2007 **6**, 2212-2229

Elizabeth Neufeld: From Plants to Patients

BY RASHMI NEMADE

Neufeld

Sometimes life turns us in unexpected ways. For Elizabeth Neufeld that meant starting out as a plant biologist and ending up applying that knowledge to developing groundbreaking treatments for human genetic disorders. Today, she focuses all of her research time on lysosomal disorders.

Elizabeth Neufeld got her start in biology in high school with an inspiring teacher. When she entered Queens College in New York City in 1944, she took all the biology classes she could find. After graduating, she worked briefly as a research assistant to Elizabeth Russell at the Jackson Memorial Laboratory in Bar Harbor, Maine. Subsequently, she moved to Baltimore because her husband was at Fort Meade during the Korean War. There she became a research assistant to Nathan Kaplan and Sidney Colowick at the McCollum-Pratt Institute at The Johns Hopkins University. "This is where I absolutely fell in love with science," recalls Neufeld. Along with Kaplan and Colowick, Neufeld studied chemistry of the pyridine nucleotide coenzymes and their associated enzymes and was a co-author in a series of classic papers in *The Journal of Biological Chemistry*.

At a time when very few women entered the scientific field, Neufeld went to graduate school at the University of California, Berkeley, in 1952. Until 1956, she studied under William Zev Hassid and received her Ph.D. in comparative biochemistry. For her postdoctoral training with Dan Mazia, she remained at Berkeley studying cell division in sea urchins, and then she returned to Hassid's laboratory to study the biosynthesis of plant cell wall polymers. Studying these polymers would have a profound impact on her career. "Learning about plant cell wall biosynthesis was relevant to how I thought about genetic diseases," Neufeld says. "Polymeric sugars in animals are similar to the sugars of plant cell walls."

In 1963, Neufeld was recruited as an independent investigator to what was then known as the National Institute of Arthritis and Metabolic Diseases (NIAMD), a part of the National Institutes of Health. Today, this institute is known as the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). In 1973, Neufeld was named Chief of NIH's Section of Human Biochemical Genetics, and later became Chief of the Genetics and Biochemistry Branch of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK). She served as deputy director in NIADDK's Division of Intramural Research from 1981 to 1983.

"I began my work with genetic diseases that had defects in the metabolism of mucopolysaccharides (MPS) in the 1970s. These diseases have a broad range of symptoms from seemingly normal to severe," says Neufeld. She began her work with Hurler syndrome, which is also known as mucopolysaccharidosis type I (MPS I) or Hurler disease. It is an autosomal recessive genetic disorder that results in the deficiency of α-L-iduronidase, an enzyme that breaks down MPS in lysosomes. Without this enzyme, the buildup of heparan sulfate and dermatan sulfate occurs in the body (the heart, liver, brain, etc.). Symptoms such as skeletal deformities, visual and hearing impairment, and delayed mental development appear during childhood, and early death can result because of organ damage.

The initial work on MPS disorders was done on human fibroblasts in culture. During the time that Neufeld was studying Hurler syndrome, she was also studying Hunter syndrome, which was similar in profile to MPS accumulation but has X-linked recessive mode

of inheritance. "A research fellow at the time, Joseph Fratantoni, was having a bad day in the culture hood and mixed Hurler and Hunter fibroblasts by mistake," recalls Neufeld. "To our surprise, this mixing actually cured the cells! It seemed as if something being secreted from one of the sets of cells was correcting the other, a corrective factor. We just had to figure out what it was." The Neufeld group worked hard to discover what was happening. They reasoned that the unknown factor was likely an enzyme missing in lysosomes and that one cell was taking up the corrective factor secreted by the other. "It was eventually discovered that the lysosomal enzyme missing from Hurler cells was α-L-iduronidase, which had to be tagged with a signal in order to be delivered to the cell," Neufeld says. The signal was eventually found to be mannose 6-phosphate (Man-6-P) by William S. Sly of Washington University in St. Louis. Neufeld and co-workers realized that exogenous delivery of the enzyme could be a potential treatment for patients with Hurler and Hunter syndromes.

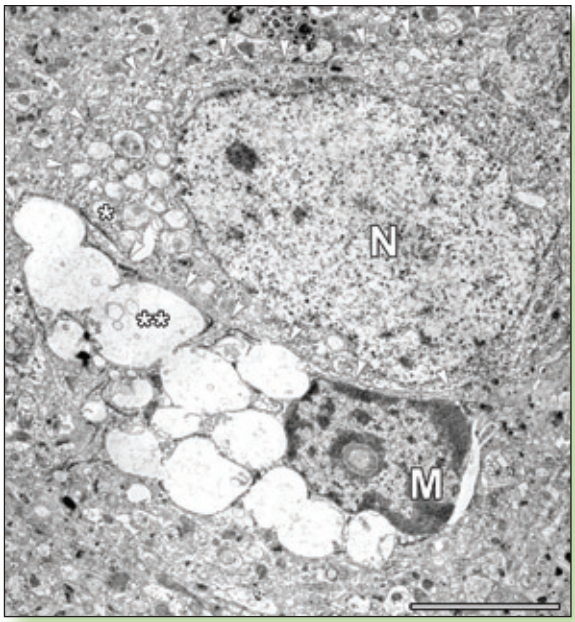
"Luckily, around the same time, a veterinarian colleague, Robert Shull, discovered a natural canine model of Hurler syndrome, and he developed the colony at the University of Tennessee. Along with a fellow in the Neufeld laboratory, Emil Kakkis, enough recombinant human α-L-iduronidase with the Man-6-P tag was made to treat these dogs, and the dogs improved! Their pathology, biochemistry, and whole clinical picture improved," exclaimed Neufeld. A subsequent long term study showed similar results. At this point, the work ceased to be basic research. BioMarin, a new biotech company in Novato, California, became interested in the work and further developed it with Kakkis, who is now Senior Vice President of the company. It was a long and arduous process, but after all the research and clinical trials were finished, the therapeutic enzyme was approved by the U.S. Food and Drug Administration for treatment in 2003. Today, BioMarin continues the work that was started by Neufeld by addressing other MPS disorders.

> **"It seemed as if something being secreted from one of the sets of cells was correcting the other."**

In the meantime, Elizabeth Neufeld moved forward with other basic science projects in her laboratory. In 1984, she moved her research back to California to the Department of Biological Chemistry at UCLA where, among other topics, she has the continued work that she started in the 1970s on Sanfilippo syndrome B, also known as MPS IIIB. This is a rare autosomal recessive disease caused by deficiency of α-*N*-acetylglucosaminidase (NAGLU), one of the enzymes required for the lysosomal degradation of heparan sulfate. "Nobody was working on this, and it's devastating. The defects are primarily neurological in that everything seems normal until nursery school, at which point affected children regress developmentally. This leads to behavioral problems and hyperactivity, and eventually, these patients die in adolescence," Neufeld says.

To study the syndrome further, a mouse model was produced by targeted disruption of the gene encoding NAGLU. The *Naglu*$^{-/-}$ mice were healthy and fertile while young and could survive for 8-12 months. They were totally deficient in NAGLU and had massive accumulation of heparan sulfate in liver and kidney, as well as secondary changes in activity of several other lysosomal enzymes in liver and brain, showing that these mice were a good model for study of the pathophysiology and development of therapy for Sanfilippo syndrome type B.

"In an effort to find a treatment, we aimed to administer exogenous



Electron micrograph showing characteristic pathology in the brain of the Sanfilippo type B mouse model. A microglial cell (*M*), with huge lysosomes (seen as large, empty inclusions in the cytoplasm) is opposed to a neuron (*N*) that has smaller lysosomes.

FROM RYAZANTSEV, S., YU, W. H., ZHAO, H. Z., NEUFELD, E. F., AND OHMI, K. (2007) MOL. GEN. METAB. 90, 393-401.

NAGLU to these deficient mice," says Neufeld. Recombinant human α-*N*-acetylglucosaminidase (rhNAGLU) was administered to *Naglu*$^{-/-}$ mice. The rhNAGLU was taken up by liver and spleen but marginally, if at all, by thymus, lung, kidney, heart, and brain. In the liver and spleen, only macrophages were involved in enzyme uptake and correction in these two organs, yet the storage of glycosaminoglycan was reduced to almost normal levels. The results showed that the macrophage-targeted rhNAGLU can substantially reduce the body's burden of glycosaminoglycan storage in the mouse model of Sanfilippo syndrome III B.

Elizabeth Neufeld's work has spawned an entire area of therapeutics; however, "the biggest challenge to lysosomal enzyme treatments is that even though the enzymes make it into major organs of the body, they still cannot cross the blood-brain barrier. This barrier makes it very difficult for therapeutic enzymes to reach the brain and correct the neurologic and behavioral difficulties. So the focus in my lab now is to get enzymes across the blood-brain barrier," says Neufeld.

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Anton Bennett: Understanding How Protein Tyrosine Phosphatases Work

BY PAT PAGES

Since their discovery in 1979, protein tyrosine kinases (PTKs) have been the subject of intense research. Whole families of such enzymes have been identified, and their roles in many signaling pathways have been elucidated, leading, in December 2002, to the publication by *Science* of the first human "kinome," a phylogenetic tree depicting the relationships among all known kinases—which included both PTKs and serine/threonine kinases.

Not as much can be said of PTKs' counterparts, the protein tyrosine phosphatases (PTPs). These enzymes, which, instead of transferring phosphate groups to tyrosine residues on proteins—like PTKs do—remove them from proteins. PTKs were discovered in 1988, yet their role in signaling pathways is not fully understood, and how these enzymes are involved in human diseases still remains a burning question to scientists.

But things are changing thanks to scientists who are working exclusively on PTPs. One of these scientists is Anton Bennett, associate professor of Pharmacology at Yale University School of Medicine, New Haven, Connecticut, who has been studying these enzymes for the past 14 years and has provided unique insights into their roles in the cell.

"The reason we know less about PTPs than we do about PTKs is mostly because PTKs affect proteins in ways that are easier to detect," Bennett says. "Proteins that have been phosphorylated by kinases are easy to see because they have the additional phosphate group. But if proteins are dephosphorylated, they look like any other protein. So finding target substrates for PTPs—which is vital to understand how these enzymes work—has been pretty challenging, but we are starting to see the light at the end of the tunnel."

> "How these enzymes are involved in human diseases still remains a burning question to scientists."

For the past decade, Bennett and other scientists have used original ways to detect the proteins that are dephosphorylated by the PTPs and, as a result, understand how PTPs are involved in various biological processes. This research is showing that phosphatases are part of an increasing number of signaling pathways, which could provide new ways to treat diseases in which such pathways are altered.

Early Interests in Biology and the Study of Diseases

Bennett grew up in the Hertfordshire suburb of London. His interest in science at an early age came from reading science books and enjoying his science classes in school. In high school, he remembers feeling challenged by physics and chemistry, but he loved biology. He developed a keen interest for this field and decided he would probably pursue a career in biology or medicine.

Bennett

After high school, Bennett went to Liverpool John Moores University (LJMU), which offers four-year degree programs developed with leading industrial companies. During his junior year, he was one of five students selected to work for a pharmaceutical company for one year as part of the academic program. He worked for Imperial Chemical Industries (ICI), now AstraZeneca, the largest European pharmaceutical manufacturer, in Manchester, United Kingdom.

At ICI, Bennett studied compounds that become toxic when exposed to light. His advisor was

Oliver Flint, a scientist now working at Bristol-Myers-Squibb, Princeton, New Jersey, who pioneered a technique to create embryo biomass cultures for the study of birth defects. Bennett's research led to his first two scientific papers—along with a research report as part of his degree requirements.

"This training and research year at ICI helped define my future research interests," Bennett says. "I became increasingly interested in how drugs work at the cellular level, and I wanted to learn more about how a given drug affects signaling pathways inside a cell."

During his senior year at LJMU, Bennett continued to take classes in biochemistry, which motivated him to pursue a Ph.D. in toxicology and pathology. He also wanted to move to the United States because U.S. Ph.D. programs offered the possibility of taking additional courses, which he felt would broaden his understanding of drug mechanisms and human disease while pursuing research—unlike English Ph.D. programs.

Understanding How Drugs Work

One of the U.S. universities to which Bennett applied and was accepted was New York Medical College, Valhalla, located 30 miles north of New York City. During the first year, he took courses in pathology with the other medical students, doing medical autopsies and learning about diseases.

"Unlike most of these students, I was not taking these courses to become a physician," Bennett says. "I was more interested in how diseases occur at the cellular level. But we had to digest a large amount of information about the mechanisms of human disease, which, with hindsight, has proven to be very helpful."

After passing his qualifying exam and receiving his M.S. in experimental pathology, Bennett started his Ph.D. thesis with Gary Williams, a well established scientist who showed that certain drugs caused cancer in the liver.

During his thesis, Bennett examined why fibric acid derivatives, which are drugs used to lower the amount of fats in the blood, also caused liver cancer in rodents. He showed that the drug caused calcium to be released from intracellular calcium stores, which in turn induced cell proliferation in the liver. During his work, Bennett also explored in detail the signaling pathways that were affected by the drug.

"How drugs work at the molecular level is often very poorly understood," Bennett says. "In the case of fibric acid derivatives, I tried to better understand how they actually work and why they induced liver cells to proliferate and cause liver cancer in rodents. Such information would be useful in understanding the risk of potential harmful effects of these drugs in humans."

Early Work on SHP-2

After completing his Ph.D. in 1993, Bennett was hired as a postdoctoral research fellow by Benjamin Neel, now the director of the Ontario Cancer Institute, Toronto, Canada. Neel's group has provided many original insights into the biological functions of PTPs, but when Bennett joined Neel's team, the study of PTPs was still very much in its infancy—having only been discovered five years earlier. Bennett saw the study of PTPs as a new and exciting field in which to develop his scientific career.

In the early 1990s, PTPs were known to remove phosphate groups from various substrates, but the nature of most of these substrates was unknown. Also, how PTPs were involved in regulating intracellular signaling pathways was unclear. So Bennett and other members of Neel's laboratory tried to define the role of a PTP called Src homology 2 (SH2)-containing PTP (SHP-2) in cell signaling pathways.

Bennett discovered that SHP-2

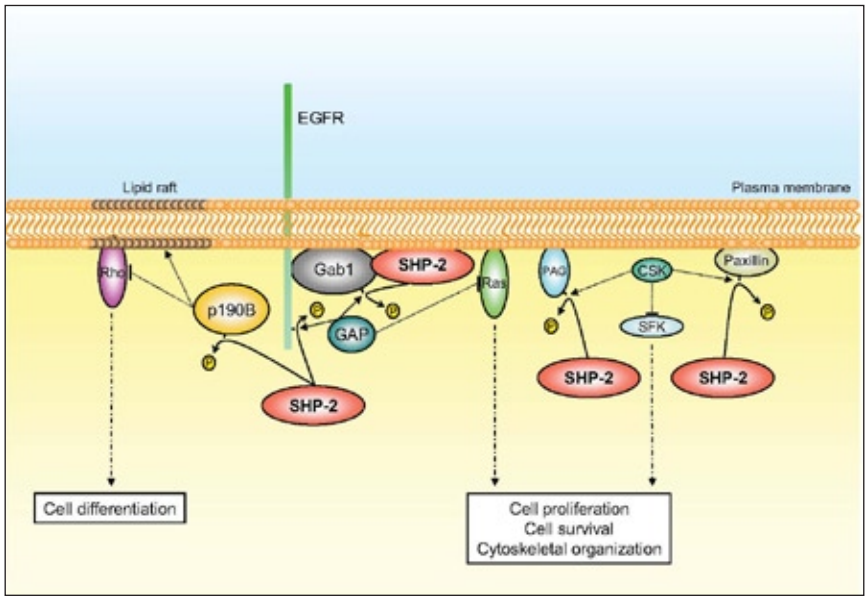

Fig. 1. Signaling pathways induced by the epidermal growth factor, showing the various roles of SHP-2. The pathway that leads to muscle cell differentiation (*left*) is described in the text.

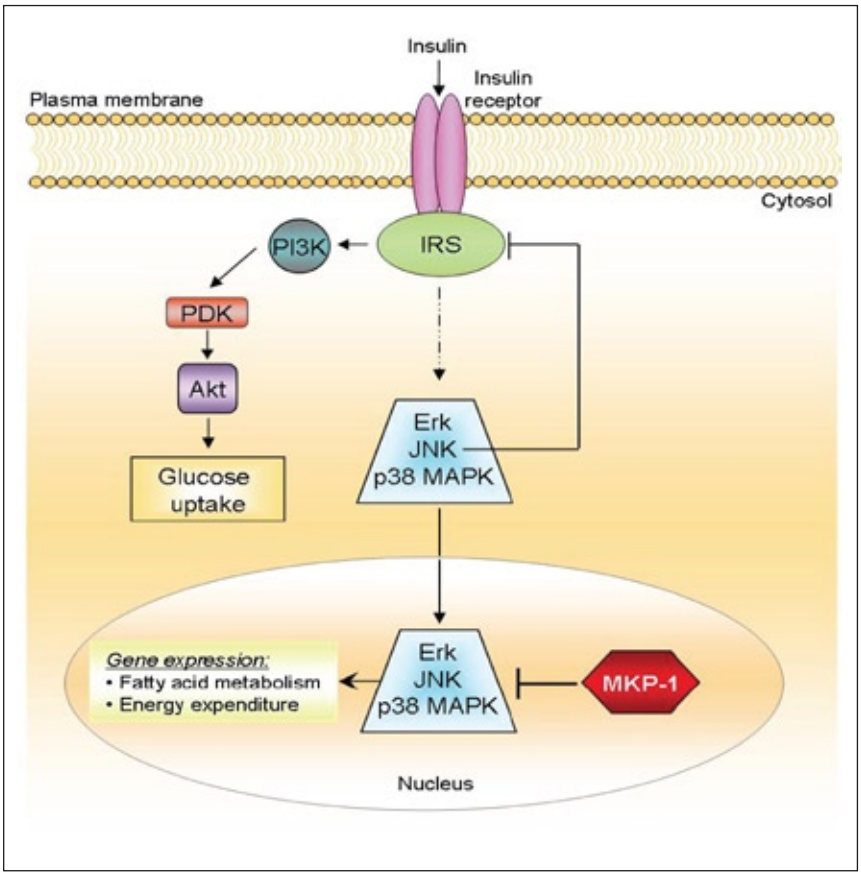

Fig. 2. Model depicting the nuclear inactivation of the MAPKs by MKP-1 in the control of gene expression events involved in fatty acid metabolism and energy expenditure.

ACKNOWLEDGEMENT: "REPRINTED FROM *CELL METABOLISM,* VOL. 4, WU, J. J., ROTH, J. R., ANDERSON, E., HONG, E., LEE, M., CHOI, C., NEUFER, D., KIM, J., SHULMAN, G. S., AND BENNETT, A. M. ENHANCED MAP KINASE ACTIVITY AND RESISTANCE TO DIET-INDUCED OBESITY IN MICE LACKING MAP KINASE PHOSPHATASE-1, PAGES 61–73, ©2006, WITH PERMISSION FROM ELSEVIER."

plays an essential role in helping cells progress through the cell cycle and ultimately divide in response to epidermal growth factor. This result was quite surprising since it had been predicted that PTPs would serve to reverse the actions of PTKs, but in this case, SHP-2 promoted PTK signaling.

The two years Bennett spent at Harvard Medical School were exceptionally formative, he says. "The learning experience and training at Neel's laboratory were absolutely phenomenal," Bennett says. "Neel was one of the most respected scientists I have ever met, and he taught me a great deal, not just about PTPs but also about how to think about scientific problems in general."

First Insights into MKP-1

In 1995, Bennett went to Cold Spring Harbor Laboratory (CSHL) in Long Island, New York, where he worked with Nicholas Tonks, a senior scientist who pioneered the study of PTPs and identified the first known PTP in 1988. When Bennett came to CSHL, Tonks had just identified the phosphatase that dephosphorylates MAP kinase.

Bennett worked on the biological role of this phosphatase, called MAPK phosphatase-1 (MKP-1), and found that it controlled muscle cell differentiation, or myogenesis. He showed that muscle cells proliferate under the influence of MAP kinases and then start differentiating under the action of MKP-1, suggesting that MKP-1 acts as an important switch in controlling MAP kinase signaling in myogenesis. These results were the first to define a role for PTPs in muscle growth and differentiation.

"My experience at CSHL in Tonks's group was extraordinarily positive," Bennett says. "Working under the auspices of a scientist who founded the PTP field was quite inspirational."

SHP-2 Reveals More Secrets

In 1998, Bennett was hired as an assistant professor at Yale University School of Medicine's Department of Pharmacology, and he set up his research team with the goal of further investigating the role of the two phosphatases on which he worked during his postdoctoral years: SHP-2 and MKP-1.

At the time, although new PTPs and the signaling pathways regulated by PTPs were being discovered, the target substrates of PTPs remained elusive. One of the main difficulties in identifying these substrates is that PTPs bind to them so quickly that it is very difficult to capture the fleeting moment when both the PTP and substrate are attached.

Scientists in Tonks's laboratory created a mutated version of the PTP called a substrate-trapping mutant phosphatase—in which an aspartate (D) from its active site is replaced with an alanine (A)—which has the advantage of binding to the substrate longer than the wild type PTP but does not dephosphorylate the substrate. One of Bennett's goals was to use this "substrate-trapping" technology to identify substrates for one of his favorite PTPs, SHP-2.

By using a substrate-trapping mutant of SHP-2, the team found that a protein called p190B RhoGAP is an SHP-2 substrate. Then they discov-

ered that dephosphorylation of p190B RhoGAP dissociates it from a muscle cell membrane, resulting in increased activity for RhoA, a protein known to be essential for muscle growth and differentiation (Fig. 1).

Recently, the researchers showed that, in mice, SHP-2 is involved in a pathway that activates a protein called nuclear factor of activated T cells (NFAT) to promote muscle growth. NFAT is involved in many developmental processes, including the development of heart valves.

Since mutations in SHP-2 cause a human developmental disease called Noonan syndrome that gives rise to congenital heart defects, the discovery linking SHP-2 to NFAT provided new insights into the potential cause of the disease. The researchers showed that mutations in SHP-2 found in patients with the disease disrupt the ability of SHP-2 to regulate NFAT action, suggesting a potential mechanism for the onset of the heart defects in Noonan syndrome patients.

Bennett and his team also discovered an entirely new SHP-2 substrate by using a combination of techniques that included substrate trapping mutant and mass spectroscopy techniques. The new substrate, called major vault protein, is the main component RNA-protein complexes called vaults of unknown function.

"This discovery was quite exciting," Bennett says. "Although much more research is needed to understand how MVP and SHP-2 work together, this work is a proof of principle that by combining existing techniques it is possible to find new substrates."

MKP-1 and Obesity

Last year, Bennett and colleagues found that MKP-1, the phosphatase that opposes MAP kinase activity, is involved in controlling the body's metabolism. The scientists showed that mice bred without MKP-1 resisted weight gain despite consuming high fat foods.

Although the mechanism by which MKP-1 regulates how energy is consumed is not yet clear, the results suggest that MKP-1 opposes the activity of the MAP kinases, which are known to promote the activation of transcription factors that regulate energy expenditure (Fig. 2).

"If, in normal mice, MKP-1 limits the MAP kinases' ability to turn on genes involved in burning energy, then in mice with inactivated MKP-1, the MAP kinases are unchecked, resulting in unusually high levels of energy consumption," Bennett says. "These results may give us new therapeutic ways to fight obesity by reducing the activity of MKP-1."

To further understand the role of MKP-1 in energy metabolism, Bennett and his team are now trying to understand how the phosphatase is involved in controlling the expression of genes that regulate metabolism.

The field of phosphatase research is rapidly developing, and scientists have shown much excitement about its future. Next year, Bennett will be co-organizing the 10th biennial summer research conference on protein phosphatases. He hopes that this conference, which is sponsored by the Federation of American Societies for Experimental Biology, will provide further insights into the roles of these enzymes in human health and disease.

"All these discoveries appear to show that PTPs are involved in many more pathways," Bennett says. "The knowledge gained so far and the techniques that have been developed to study them promise to reveal many more roles for PTPs, which could help us better understand how our cells work and how to correct cellular mechanisms that are not working properly in important diseases such as cancer, heart diseases, obesity, diabetes, and skeletal muscle diseases."

"The field of phosphatase research is rapidly developing, and scientists have shown much excitement about its future."

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The Sanibel Conference: Ion Mobility and Related Emerging Areas
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DAYTONA BEACH, FL
www.asms.org

Keystone Symposium—Diabetes Mellitus, Insulin Action and Resistance
JANUARY 22–27, 2008
BRECKENRIDGE, CO
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http://www.biophysics.org/meetings/2008/

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http://www.med.miami.edu/mnbws/

Keystone Symposium—Biomarker Discovery, Validation and Applications
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Drug Discovery for Neurodegeneration
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International Conference on Neural Signaling: *Opportunities for Novel Diagnostic Approaches and Therapies*
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medicine.ucsf.edu/conferences/asilomar2008/index.html
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Tel.: 415-476-9892

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VENTURA BEACH, CA
www.gre.org

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American Society for Neurochemistry 2008 Annual Meeting
MARCH 1–5, 2008
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asneurochem.org/

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MARCH 17–19, 2008
MANCHESTER, UK
www.genomestosystems.org/

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GENEVA, SWITZERLAND
www.esci.eu.com/default.asp?page=meetings&file=future

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www.keystonesymposia.org/Meetings/ViewMeetings.cfm?MeetingID=956

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E-mail: meetings@asbmb.org
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SAN FRANCISCO, CA
http://scientificsessions.diabetes.org

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www.endo-society.org/apps/Events/Event.cfm?EventID=1253

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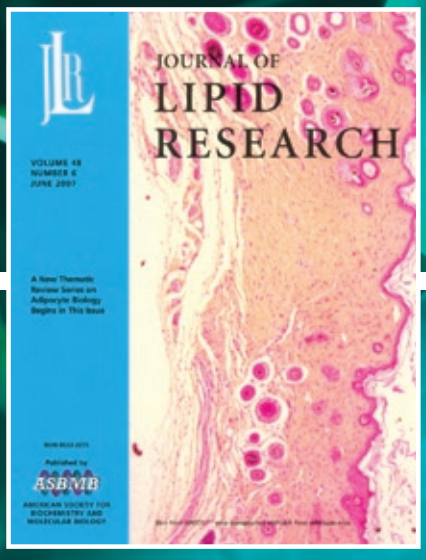

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