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ASBMB today

May 2007

Mapping the Physical Interactome of *Saccharomyces cerevisiae*

American Society for Biochemistry and Molecular Biology

contents

MAY 2007

ON THE COVER:
A novel algorithm was applied to two large scale protein-protein interaction datasets in *S. cerevisiae*. Hierarchical clustering of the combined dataset shows the physical interactome for budding yeast. 28

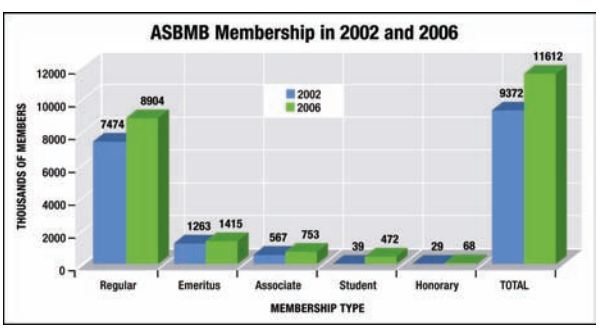
society news

science focus

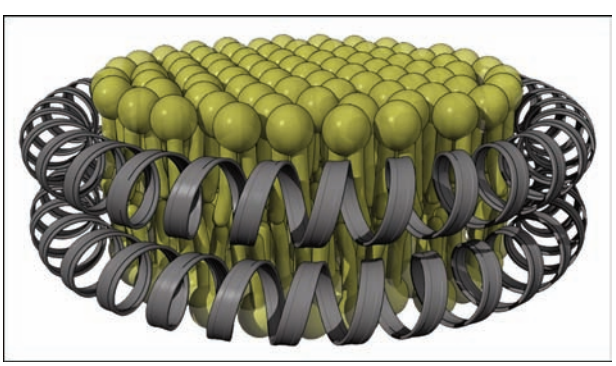
departments

resources

Gregory A. Petsko is elected president of ASBMB. 12



A look at some ASBMB membership data. 14



The role of high density lipoprotein in heart disease. 22

letters to the editor

Response to Dr. Zerhouni

To the Editor:

The drop in National Institutes of Health (NIH) funding rates was recently attributed primarily to increases in numbers of principal investigators by Dr. Zerhouni, director of the NIH (1). Dr. Zerhouni then articulated the NIH's plan to maintain current low funding rates (1). The implication is that either (i) the ramifications are deemed acceptable or (ii) the NIH is powerless to prevent the ramifications. But maintaining the status quo is predicted by many to hinder NIH's mission of making important medical discoveries. Furthermore, there is another important cause of the low funding rates that is addressable by the NIH.

Ramifications

Investigator-initiated R01 grants, often described as the most successful research mechanism devised, are now facing the following paylines:

NIH Institute	Budget rank	Payline FY2006	Payline FY2007 (2)
		%	%
NCI	1	11	11
NIAID	2	14	12
NHLBI	3	14	13

At about 8 applications per funded R01, the implications are dire. The main occupation of PIs will become grant writing, not research. Many highly worthwhile projects will not be funded, especially the risky ones that have potentially the biggest payoffs. Renewals without long gaps in funding will be unlikely. The funding lapses will cause widespread laying off of highly trained, productive, R01-funded scientists. Many of the best scientists will move to industry. Many of the best foreign scientists will return to their homelands. Physician-scientists will become physicians. The average age of first R01 award for new investigators, currently in the early 40s, may continue to rise. The best and brightest in training will face less opportunities and seek alternative careers. America's lead in biomedical breakthroughs, important for patient care and the economy, will be eroded.

Another Cause

The drop in R01 funding rates during 1998–2006 can be attributed to a slow increase in the number of R01s (1.2-fold) that did not keep pace with the rapid increase in the NIH budget (2.1-fold) (2). A contributing factor was a 48% increase in average R01 budget (2). Though principal investigators (PIs) increased over this period by 1.8-fold (1), this is not out of proportion to a 2.1-fold budget increase designed to take advantage of scientific opportunities. Thus, there are currently only 29,000 funded R01s for 34,000 PI applicants (1, 2), yet multiple R01s are required to maintain many labs at medical schools, hospitals, and institutes. Note that the number of applications per PI had little effect on funding rates, increasing from 1.27 to 1.35 (1), but this may become a big factor.

A Solution

Some of the NIH budget could be reallocated into R01s, taking advantage of the 2.1-fold increase in budget to double the number of R01s (in comparison with 1998). This could be aided by controlling growth of individual R01 budgets.

Anthony C. Forster
Assistant professor, Pharmacology Department
Vanderbilt University Medical Center
E-mail: a.forster@vanderbilt.edu

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1. E. A. Zerhouni (2006) NIH in the Post-Doubling Era: Realities and Strategies. *Science* **314**, 1088–1090
2. NIH Web sites and the Public Affairs Office, American Society for Biochemistry and Molecular Biology. FY2007 is 10/1/06–9/30/07

Tell Us What You Think

We appreciate receiving letters that are suitable for publication regarding issues of importance or comments on articles appearing in *ASBMB Today*. Letters should be sent to the editor at asbmbtoday@asbmb.org. Letters must be signed and must contain the writer's addresses and telephone number.

The editor reserves the right to edit all letters.

Educating Non-scientists

To the Editor:

In the March 2007 issue of *ASBMB Today*, I read with interest Heidi Hamm's comment that "most of our neighbors next door or across the street probably are not aware that they are living next to a scientist." This prompted me to write this letter to indicate an area where we can educate non-scientists as to what we do and why this is important to their well being. In addition, I will point out approaches we can initiate. This means being proactive.

In particular, we should offer to speak to various non-science organizations. My experience is that such organizations are always looking for interesting topics and speakers at their meetings. This is an opportunity to relate how your research contributes to medicine, biotechnology, and other areas more familiar to the general public. The talk should be an effort by a scientist to inform non-scientists what they do, why they do it, and what the benefits are. I believe it best—unless asked—not to address funding; otherwise, your talk might be regarded as a pitch by one with a vested interest.

So how do you begin to accomplish this educational goal? Clearly, the first step is to learn the names of program chairs of societies, service organizations, and other groups in your area looking for programs. Your institution's public relations office might be a good start. While in no way an inclusive list, a few other contact suggestions are Kiwanis, Rotary, women's clubs, PTAs, neighborhood associations, NAACP, chamber of commerce, high schools, church groups, and college and university alumni groups. Be willing to talk to small groups. If only one person writes to his or her respective member of congress, this is likely to have a profound impact, since it comes from someone without a vested interest. Not only that, many locals are influential members of their respective communities. I know from personal experience that this tends not to be an activity one relishes, because it is outside the realm of the kinds of talks we normally present.

In regard to developing a talk, here are a few suggestions: don't "talk down" or get too technical, do a lot of preparation, solicit help from colleagues and a good non-scientist friend, use slides, use humor, and point out that not all experiments are successful. I am sure you can add other tips. Another suggestion is that ASBMB prepare a brochure containing tips on developing a suitable talk. The brochure might even contain a brief outline and jokes.

I hope these brief comments are valuable and lead to new efforts to inform non-scientists of the importance of our efforts in the international, national, and local communities. As an aside, I volunteer at the National Academies' Marian Koshland Science Museum in Washington, D. C., and it is truly amazing how many people thank you and leave with a better appreciation not only of what scientists and engineers do but also why it is important.

Robert Newburgh
Professor emeritus & former dean,
Oregon State University
P.O. Box 1369, Rockville,
Maryland 20849-1369

Editor's note: While ASBMB does not have a brochure that specifically addresses how to develop a talk, we are currently producing a brochure called "Why Fund NIH Biomedical Research?" The brochure was available for ASBMB members before our annual meeting in Washington, D. C., at the end of April.

The editor reserves the right to edit all letters.

Tell Us What You Think about ASBMB Today

The new, redesigned ASBMB Today is on its fourth issue, and we want to know what you think of it. Please email your comments and suggestions to:

asbmbtoday@asbmb.org

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ASBMB Today

9650 Rockville Pike,
Bethesda, MD 20814-3996
Phone: 301-634-7145; Fax: 301-634-7369

Nicole Kresge *Editor*
nkresge@asbmb.org

Pat Pages *Science Writer*
ppages@asbmb.org

Nancy J. Rodnan *Director of Publications*
nrodnan@asbmb.org

Barbara Gordon *Executive Director*
bgordon@asbmb.org

For information on advertising contact FASEB AdNet at 800-433-2732 ext. 7157 or 301-634-7157, or E-mail mbowen@faseb.org.

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president's message

Where Is the Priority for Investigator-initiated Research at NIH?

HEIDI HAMM, PRESIDENT

I write regularly in this space about issues associated with the slow erosion of National Institutes of Health (NIH) funding of investigator-initiated NIH grants. ASBMB believes strongly that scientific directions set by investigators pursuing their science creatively and with passion often yields unexpected and unpredictable outcomes. This is the heart and soul of NIH research, and it should not be allowed to wither away. We have noticed a trend at NIH in recent years—the move toward funding larger "mega-projects"—that may be scientifically valid, but in an era of flat funding we worry that this will have a negative impact on the funding of investigator-initiated grants.

The proposed large scale, long-term study of genes, the environment, and disease got us thinking about this topic. A U.S. Department of Health and Human Services (HHS) advisory committee recently issued a report on such a study, and, although supporting its launch, the committee recommended that a number of policy issues be addressed first.

The report, called "*Policy Issues Associated with Undertaking a New Large U.S. Population Cohort Study of Genes, Environment, and Disease*," has been in the works since 2004. It focuses on a proposal to launch a large U.S. population study to ascertain where variations among individuals occur within the human genome and how particular DNA variants interact with environmental factors. Such studies are already under way in several countries around the world, and NIH has been investigating what questions need to be answered before mounting a similar study.

The report describes the preliminary questions that should be addressed to help policymakers decide whether the U.S. Government should undertake a new large population study (LPS) of genes, environment, and disease. The aim of such studies is to determine linkages between environmental factors and exposures and the risk for disease. Some scientists believe that a new large scale study involving 500,000 to 1 million participants is the next logical step for deepening our understanding of the relationship of genes and the environment in human disease.

The Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) report is based on 2 years of fact finding, public consultation, and deliberation. The report identifies five areas that require further analysis and consideration by the Secretary of HHS prior to making a decision on whether a new LPS could take place. It is interesting to note that the first issue to be identified is the

funding impact on other areas of medical research.

Obviously, the impact on the availability of individual, investigator-initiated, hypothesis-driven research grants is a major concern. According to FASEB Science Policy Analyst Laura Brockway, "Although there are no publicly available estimates of the project's cost, the figure could be as high as $3 billion or perhaps higher. Annual costs could be significant and have implications for other critical research and training programs. Some members of the scientific community have expressed concern about the impact of such a large allocation during flat funding periods and argue that a large project should be undertaken only if it is funded through sources that do not compromise investigator-initiated projects."

Yet again, consider another mega-project that is already under way—the Cancer Genome Atlas (CGA). This project aims to identify mutations in tumor cells from the 50 most common kinds of human cancer. It is now beginning a 3-year, $100 million pilot phase, which could amount to $1.5 billion over the course of the project. The project's rationale has been criticized by some knowledgeable people in the cancer field, as it will identify mostly trivial mutations in the primary tumor and not focus on mutations that cause metastasis, because the DNA that will be analyzed will be from biopsies from the primary tumor. The CGA was excoriated in the March 26 issue of *Newsweek* as a waste of money.

So what do we make of this? I believe that we need to keep a careful watch on the budget process and always be champions of investigator-initiated research, which has historically yielded dramatic discoveries and breakthroughs. There are many worthy large scale projects that are under way and many others that are being considered. Because such studies are tremendously expensive, we hope that the implications for investigator-initiated research are taken into consideration when funding decisions are made. The two projects that I mention above are estimated to cost close to $5 billion over the course of their funding periods. The idea that big projects can be funded out of magically available "new" money without having an impact on other funding assumes an infinite "pie." It is a much more likely scenario that in the face of flat NIH funding, such studies will continue to put strains on funding of individual researchers, and thus many breakthrough discoveries may never happen. We in the ASBMB leadership are committed to doing everything we can to keep funding for individual investigators from further erosion.

In this regard, when the NIH advertises symposia on particular topics of interest to you, please get involved with these meetings, as they are often strategy setting interactions with the extramural community. In addition, we continue to need your help, asking you to talk regularly with your elected representatives about the good work you do and the importance of your research and to advocate for more funding, so that we won't, in the future, be confronted with choosing between funding individual investigator-initiated research and mega-projects.

HHS Inspector General Looking at Extramural Conflicts

BY PETER FARNHAM

The U.S. Department of Health and Human Services (HHS) Office of Inspector General (OIG) has "recently begun a review of the way in which NIH oversees conflict of interest on the part of its grantees." In this sentence, near the end of a 4-page letter sent March 23 to Rep. Joe Barton (R-TX), HHS Inspector General Daniel R. Levinson showed that the conflict of interest issues that surfaced in the intramural program at National Institutes of Health (NIH) 2 years ago continue to have repercussions.

The letter went on to note that "Because the majority of NIH appropriated funds are distributed to NIH grantees who undertake extramural research and these extramural researchers are not covered by the Federal ethics rules that apply to NIH intramural researchers, OIG determined that this project was an important next step in examining NIH conflict of interest. This study will determine the extent to which the NIH oversees grantee institution's (*sic*) financial conflict-of-interest issues."

The statement immediately provoked a flurry of newspaper reports and comments from a number of representatives of the biomedical community. One of the principal comments was that any plan to regulate relationships between industry and academics runs the risk of going too far. The consensus of opinion seemed to be that relationships between industry and academia are in fact necessary and appropriate. "There have to be interactions between those doing the research and those doing the translation," noted David Korn, senior vice president for biomedical and health science research at the Association of American Medical Colleges, in an interview with *The Scientist.*

Levinson also said that his office was reviewing 103 NIH employees' cases involving conflict of interest to determine whether investigation is warranted. These cases include 81 NIH employees identified by the House Energy and Commerce Committee in 2003 as having relationships with biotechnology or pharmaceutical companies that were not reported by NIH. An additional 22 cases uncovered by NIH during the course of the investigation were called to their attention by the committee.

Of the initial 81 cases, 37 were cleared by NIH, and 44 were found to have committed violations. Only one was referred for criminal prosecution.

We Need Your Advice

It is likely that Congress will try, in the coming months, to develop conflict of interest legislation concerning the extramural community. ASBMB is monitoring this situation very closely and is hereby soliciting advice and comments regarding what our posture should be. Any comments you may have should be directed to Peter Farnham, ASBMB public affairs officer, at pfarnham@asbmb.org. If you have thoughts you'd like to share with the membership, a letter to the editor of this publication would also be appropriate.

Stem Cell Bill Passes Senate but Veto Looms

BY PETER FARNHAM

The Senate handily passed a bill on April 11 to allow Federal funding for embryonic stem cell research. However, the White House vetoed such legislation the last session of Congress (The President's first veto) and has said it will do so again if this bill reaches the President's desk. Even with a new Democratic majority, the vote total fell 4 votes short of the 67 needed to override.

The White House said the bill "would compel all American taxpayers to pay for research that relies on the intentional destruction of human embryos for the derivation of stem cells." The Administration does support an alternative bill to fund other methods of obtaining stem cells. Both this bill and the measure the White House opposes will go to the Senate floor under an agreement that each must receive at least 60 votes to be considered approved, and no amendments will be allowed.

The House passed its version of the stem cell bill in January as part of the new deocratic majority's "first 100 hours" legislative blitz. However, the House bill did not pass by the two-thirds majority needed to override a veto—in fact, the House vote was well short of the total needed. So even if the Senate bill had garnered enough votes to override a veto, the House vote assures that an override attempt would fail there, meaning the bill would not become law.

Meanwhile, Senate supporters vow to keep trying; they call for public pressure on opposing lawmakers as the only way to get a veto-proof majority this year.

Zerhouni Lauds Embryonic Stem Cells

In a statement that raised eyebrows among many observers, NIH Director Elias Zerhouni publicly supported a change in Federal policy regarding embryonic stem cells. He made the comments during testimony before the Senate Appropriations Committee's subcommittee on Labor/Health and Human Services, Education and Related Agencies on March 19.

Zerhouni noted that since 2004, the scientific community has agreed that the number of currently available stem cell lines is not sufficient, and the nation would be better served if additional lines were made available. He also discussed the role NIH would play in this area of research, including stimulating development, providing depth of research, and ensuring adequate oversight. He also expressed worries about the varying treatment that embryonic stem cell research receives from individual states. He characterized the value of much touted alternatives to embryonic stem cell research—such as those derived from adult cells or cord blood—as overstated and said it was important to pursue all approaches. He said the country must find a way to allow all approaches to research in this field to be supported. Although the remarks appear to contradict administration policy, there is no indication that Zerhouni has suffered any fallout from HHS or the White House.

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

Some Hope for NIH Funding This Year

BY PETER FARNHAM

Early signs in the 2008 budget and appropriations process indicate that there is at least a possibility of a decent increase for the National Institutes of Health this year after 4 years of cuts.

The action began in mid-march in the Senate Budget Committee, where a budget resolution that increased domestic discretionary spending by $18 billion over the President's request was approved. The overall increase was good news, because the increase will make it easier to find money to boost spending at NIH when the appropriations process begins.

The budget resolution does not set binding spending targets for individual agencies; however, the overall domestic discretionary figure is binding. Nevertheless, the budget resolution often specifies intent, so even though specific funding levels for agencies are not binding on appropriators, the fact that these may be mentioned is an important indication of congressional intent.

It was with this in mind that Sens. Tom Harkin (D-IA) and Arlen Specter (R-PA) offered an amendment during a Senate floor debate a few days later that called for increases in the 2008 NIH budget of more than $2 billion over the President's proposed level. The amendment increased funding for health-related programs by $2.2 billion and would allow for restoration of NIH funding to the fiscal 2005 inflation-adjusted level, along with increased funding for the Centers for Disease Control and Prevention as well as for health professions training programs.

During the floor debate, Sen. Specter spoke of two friends who had died of cancer, including a member of his staff and a federal judge. He also cited his own battle with Hodgkin's disease and noted that his amendment would only restore funding to the 2005 level. He also noted that the increase was "absolutely minimal" to avoid losing ground and said that during earlier testimony that biomedical research was starting to lose the "best and brightest of the talent."

Specter's plea was successful; on March 23, the Senate approved the amendment by voice vote as part of a package of amendments.

Although the House has not approved its version of the budget resolution yet, the fact that the Senate has boosted domestic discretionary spending overall makes it much more likely that the House will go along.

FASEB

FASEB Supports Scientific Communications Act

BY CARRIE D. WOLINETZ

The goal of the Scientific Communication Act of 2007 (H. R. 1453) is to provide training on how to communicate with non-scientists, specifically policymakers, to graduate students in science. The bill, which was introduced by Congresswoman Doris Matsui (D-CA) on March 14, would create a new, competitive grants program at the National Science Foundation (NSF) to fund institutional programs in communication skills development for scientists. H. R. 1453 provides very little detail on what such programs should entail, leaving that to the applicant institutions, but does require integration with existing NSF training programs, such as the Integrative Graduate Education and Research Traineeship (IGERT) program. Because it is authorizing legislation, the bill designates new money, at a level of $10 million per year, for the program as opposed to earmarking funds during the appropriations process.

The Scientific Communication Act of 2007 would create a new, competitive grants program at the National Science Foundation to fund institutional programs in communication skills development for scientists

According to a statement released by Matsui's office, her aim is to improve the capacity of scientists to convey technical information to members of Congress and the public. "Science and technology play an increasingly large role in policy debates, as demonstrated by recent national discussions on such topics as stem cell research, alternative energy sources, and nanotechnology. Scientists are a critical voice in these debates," stated Rep. Matsui. "Communications training provided through this legislation will better equip our scientists to articulate their expertise to help inform the American people and the decision making process."

FASEB has come out in strong support of the legislation, at the recommendation of our Training and Career Development Subcommittee, Science Policy Committee, and following endorsement by the Board of Directors. In a letter sent to Congresswoman Matsui, FASEB President Leo Furcht wrote, "Establishing a competitive, merit-based program at NSF to improve the communications ability of scientists is truly synergistic with the agency's investment in the talent, ideas, and tools that cross all boundaries of scientific inquiry." He added, "By providing scientists with the training necessary to communicate with diverse audiences, this legislation will help to ensure accuracy of and appreciation for science in discussion and formation of public policy."

The Scientific Communications Act is co-sponsored by the chair of the House Committee on Science and Technology, Rep. Bart Gordon (D-TN), and has been referred to the Subcommittee on Research and Science Education. The Subcommittee on Investigations and Oversight recently held a hearing on science communication, but it was primarily focused on the miscommunication of scientific information, particularly in relation to the science of climate change and global warming. Rep. Matsui is actively seeking co-sponsors for the bill, which will most likely be folded into the upcoming reauthorization of the NSF or one of the multiple competitiveness bills that have been introduced. It also remains to be seen whether appropriators will be willing to channel additional funds to NSF for such a program.

Meanwhile, FASEB is continuing its own efforts to enhance the ability of scientists to communicate with policymakers. Slides on the benefits of biomedical research and the importance of funding at the National Institutes of Health, customized to nearly two-thirds of the United States, are freely downloadable on our Web site. In addition, resources related to evolution education, embryonic stem cells, federal research funding, and other critical science policy issues are available for use by scientists for their own advocacy activities. Please visit opa.faseb.org for more information.

Carrie D. Wolinetz is with the FASEB Office of Public Affairs.

asbmb member spotlight

Varki Selected for Glycobiology Award

Ajit Varki, M.D., distinguished professor of Medicine and Cellular and Molecular Medicine, and founder and co-director of the Glycobiology Research and Training Center at the University of California, San Diego, School of Medicine, has been selected as the winner of the International Glycoconjugate Organization (IGO) award for 2007. The award, which is given every 2 years to "glycoscientists who have clearly advanced the field of glycoscience and show promise of continuing advancements," will be presented at the 19th International Symposium on Glycoconjugates scheduled in Cairns, Australia, July 15–20.

Varki has been a pioneer in the field of glycobiology. His research interests focus on a family of sugars called sialic acids and their roles in biology, evolution, and disease. He has studied how sialic acid biology differs between humans and great apes, which can help in understanding aspects of human health and disease. Varki is the chief editor of *The Essentials of Glycobiology*, a major textbook in glycobiology.

This IGO award is the highest international honor in glycobiology. Varki is also the 2005 winner of the Society for Glycobiology's Karl Meyer Award, the other major honor in this field.

Forsburg Elected AWIS Fellow

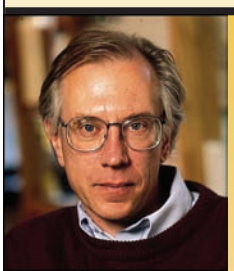
Susan L. Forsburg, Ph.D., a Professor of Molecular and Computational Biology at the University of Southern California, Los Angeles, has been named a 2007 Fellow of the Association for Women in Science (AWIS).

Forsburg and nine others were honored on February 18 in San Francisco at the annual meeting of the American Association for the Advancement of Science. They join an influential group of more than 100 association fellows dedicated to achieving equity and full participation of women in science.

Forsburg has received numerous awards, including the American Society for Cell Biology's junior faculty career award, a Stohlman Scholar Award from the Leukemia and Lymphoma Society, and a Research Scholar Award from the American Cancer Society.

Forsburg is an active member of the Women in Cell Biology Committee and serves as their liaison to AWIS. She created the Women in Biology Internet page, a popular site that provides career advice and chilly climate issues (www.womenbio.net).

Launched in 1996 as part of the 25th anniversary celebration of AWIS, the Fellows Program recognizes and honors women and men who have shown exemplary commitment to creating opportunities and breaking down barriers for women in science, technology, engineering, and mathematics. Since the program's inception, 119 women and men have been honored.



Cech to Receive Othmer Medal

Thomas R. Cech, president of the Howard Hughes Medical Institute, will receive the 2007 Othmer Gold Medal from the Chemical Heritage Foundation on May 17. The medal honors individuals who have made significant contributions to chemistry and science through innovation, entrepreneurship, research, education, public understanding, legislation, and philanthropy.

Cech is a distinguished professor in the Department of Chemistry and Biochemistry at the University of Colorado at Boulder. Science education has been at the top of Cech's priorities throughout his career. After winning the Nobel Prize, he continued to teach undergraduate general chemistry in addition to directing the research of graduate students. Cech has served on a number of outside review panels for organizations such as the Packard Foundation, the Burroughs Wellcome Fund, the Salk Institute, and the Whitehead Institute at the Massachusetts Institute of Technology.

The Chemical Heritage Foundation, established by the American Chemical Society and the American Institute of Chemical Engineers, serves the community of the chemical and molecular sciences, as well as the wider public, by carrying out outreach programs and maintaining a world-class collection of materials that document the history and heritage of the chemical and molecular sciences.

Previous recipients of the Othmer Gold Medal, which was established in 1997, include Arnold O. Beckman, Carl Djerassi, Ralph Landau, Robert S. Langer, Gordon E. Moore, and James D. Watson.

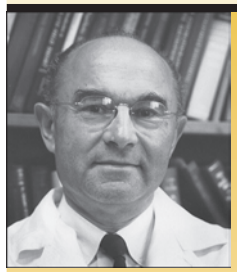
Ehlers Is John J. Abel Awardee

Michael D. Ehlers, M.D., Ph.D., associate professor of Neurobiology and Wakeman Scholar in the Department of Neurobiology at Duke University, Durham, North Carolina, and Howard Hughes Medical Institute investigator, received the 2007 John J. Abel Award from the American Society for Pharmacology and Experimental Therapeutics. Sponsored by Eli Lilly & Co, the award is given to a single young investigator for original, outstanding research contributions in the field of pharmacology.

Ehlers received his Bachelor of Science degree in chemistry at the California Institute of Technology before pursuing graduate and medical studies in neuroscience at the Johns Hopkins University. His research focuses on brain plasticity and protein trafficking andturnover in dendrites. Ehlers has shown that neurons regulate electrical activity in different ways. Recently, he has shown how internal cell structures called recycling endosomes trigger a prolonged burst in neuronal electrical activity by causing a surge in α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors.

Outside of his laboratory, Ehlers enjoys playing the French horn in a local symphony orchestra, is considered a concert level pianist, and enjoys kayaking.

Ehlers received the John J. Abel Award on April 28 at the Annual Meeting of the American Society for Pharmacology and Experimental Therapeutics/Experimental Biology 2007 Meeting in Washington, D. C.



IN MEMORIAM

David B. Sprinson 1910–2007

David B. Sprinson, Professor Emeritus of Biochemistry at Columbia University's College of Physicians and Surgeons, New York, died on February 28 at the age of 96.

Sprinson made major contributions in the understanding of pathways and mechanisms involved in intermediary metabolism. He was a key partner in a team of researchers who placed Columbia University in the vanguard of biochemistry in the late 1940s and early 1950s.

A major research effort in Sprinson's laboratory was the biosynthesis of the amino acids phenylalanine, tyrosine, and tryptophan. Sprinson and others also helped design drugs that block key enzymes in metabolic pathways associated with various diseases.

Born April 5, 1910, in Ukraine, Sprinson fled the country with his family in 1919 and arrived in New York City in 1921 with little formal education. He earned a B.S. degree from City College of New York, an M.S. degree from New York University, and a Ph.D. in 1946 from Columbia University.

Sprinson served on Columbia University's faculty from 1951 until his retirement in 1978. After retiring, he actively pursued research at St. Luke's Roosevelt Hospital Center, New York, on the biosynthesis of sterols in yeast.

In 1990, Sprinson was elected to the U.S. National Academy of Sciences, and in 1991 he was awarded the degree of Doctor of Science *honoris causa* by Columbia University. He also served as a member of the *Journal of Biological Chemistry*'s Editorial Board.

IN MEMORIAM

Herbert E. Carter 1910–2007

Herbert E. Carter passed away on March 10, 2007, at the age of 96. He was a towering figure in science and was President of ASBMB from 1956 to 1957.

Carter received his A.B. from DePauw University (1930) and his M.S. (1931) and Ph.D. (1934) in organic chemistry from the University of Illinois. He became an assistant professor at the University of Illinois-Urbana in 1934 and rose through the ranks to professor by 1945. He was head of the Department of Chemistry and Chemical Engineering (1954–1967) and also served as Vice Chancell or for Academic Affairs. In 1971, he moved to the University of Arizona as the coordinator of interdisciplinary programs, where he remained until his death.

One of Carter's most significant research projects was the proof of the structure of threonine as it occurs in proteins. He also made many other important contributions to science, particularly in antibiotic chemistry and the biochemistry of complex lipids. In the latter area, he determined the structure of sphingosine and cerebrosides and identified novel lipids in plants including phytosphingosine, phytoglycolipids, and galactosylglycerides.

Carter was a member, and then chairman, of the National Science Board, and in recognition of his chairmanship, a mountain ridge in Antarctica, "Carter Ridge," was named after him. He also served as a member of the *Journal of Biological Chemistry*'s Editorial Board.

Please submit news about yourself and other ASBMB members to asbmbtoday@asbmb.org.

ASBMB 2007

The results of the 2007 ASBMB elections are in. The Society's new president will be Gregory A. Petsko. Mark Lemmon will be the new secretary, and Joan Steitz and James Wells will become members of the ASBMB Council. Joining the Publications Committee are Kathleen M. Beckingham and Betty Eipper, and joining the Nominating Committee are Christopher Walsh and Robert Lefkowitz. All will begin serving their terms on July 1, 2007.

PRESIDENT

Gregory A. Petsko is currently the Gyula and Katica Tauber Markey Professor of Biochemistry and Chemistry at Brandeis University. He received his A.B. from Princeton University and his D. Phil. in Molecular Biophysics from Oxford University. Petsko's current research focuses on a range of biochemical questions encompassing the structural basis of enzyme catalysis, the dynamic properties of proteins, the control of virulence gene transcription, and the biology of the quiescent state of eukaryotic cells. He has been an ASBMB member since 1987.

SECRETARY

Mark A. Lemmon is a professor in the Departments of Biochemistry & Biophysics at the University of Pennsylvania School of Medicine. He received his B.A. from Oxford University and his M. Phil. from Yale University. Lemmon's research focuses on the biochemical and biophysical basis for growth factor receptor signaling and the biochemistry and structural biology of membrane targeting by phospholipid-binding domains.

COUNCIL MEMBER

Joan A. Steitz is the Sterling Professor of Molecular Biophysics and Biochemistry at Yale University School of Medicine as well as a Howard Hughes Medical Institute investigator. Steitz received her B.S. from Antioch College and her Ph.D. from Harvard University. Steitz's laboratory looks at the multiple roles played by small nuclear ribonucleoproteins (snRNPs) in gene expression in vertebrate cells. She has been a member of ASBMB since 1974.

COUNCIL MEMBER

James A. Wells is the Harry and Diana Hind Professor in the Departments of Pharmaceutical Chemistry and Cellular & Molecular Pharmacology at the University of California at San Francisco. Wells holds a B.A. in Biochemistry from the University of California at Berkeley and a Ph.D. in Biochemistry from Washington State University. Wells was the founding member of the Protein Engineering Department at Genentech, Inc. and is also founder of Sunesis Pharmaceuticals. His current research focuses on the discovery and design of small molecules that trigger or modulate cellular processes in inflammation and cancer.

Election Results

PUBLICATIONS COMMITTEE

Kathleen M. Beckingham is a professor of Biochemistry and Cell Biology at Rice University. She received her B.A., M.A., and Ph.D. from the University of Cambridge. Beckingham's research involves biochemical, molecular, and genetic studies of calcium signaling and gravitaxis in Drosophila. She has been an ASBMB member since 1982.

PUBLICATIONS COMMITTEE

Betty A. Eipper is a professor in the Neuroscience and Molecular, Microbial & Structural Biology Department at the University of Connecticut Health Center. She received her B.A. from Brown University and her Ph.D. from Harvard University. Her research focuses on peptide amidation, secreted cuproenzymes, and secretory granule biogenesis and trafficking. Eipper has been an ASBMB member since 1979.

NOMINATING COMMITTEE

Christopher T. Walsh is the Hamilton Kuhn Professor in the Department of Biological Chemistry and Molecular Pharmacology at Harvard Medical School. He received his B.A. from Harvard College and his Ph.D. from Rockefeller University. The current focus of his research is on the biosynthesis and mechanism of action of antibiotics and bacterial siderophores. Walsh has been an ASBMB member since 1977.

NOMINATING COMMITTEE

Robert J. Lefkowitz is the James B. Duke Professor of Medicine and Biochemistry at Duke University Medical Center and a Howard Hughes Medical Institute Investigator. He received his B.A. from Columbia University and his M.D. from Columbia University College of Physicians and Surgeons. His research program is concerned with the molecular properties and regulatory mechanisms that control the function of plasma membrane receptors for hormones and drugs under normal and pathological circumstances.

We thank the following outgoing Council and committee members for their service to the Society:

Peggy Farhnam
SECRETARY, NOMINATING COMMITTEE

Judith Bond
PAST PRESIDENT, NOMINATING COMMITTEE

Joan Conaway
COUNCIL MEMBER

Robert Copeland
COUNCIL MEMBER

William Sly
COUNCIL MEMBER

C. Robert Matthews
NOMINATING COMMITTEE

Shelagh Ferguson-Miller
PUBLICATIONS COMMITTEE CHAIR

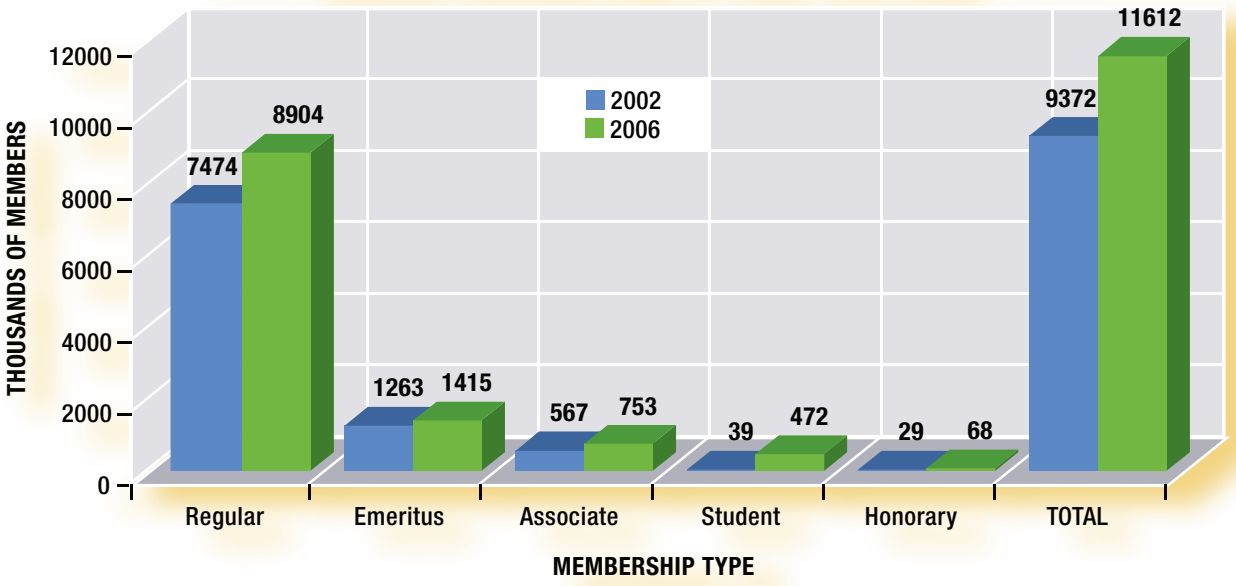
Paul E. Bock
PUBLICATIONS COMMITTEE

David A. Bernlohr
PUBLICATIONS COMMITTEE

ASBMB Member Snapshot:

FIGURE ONE:

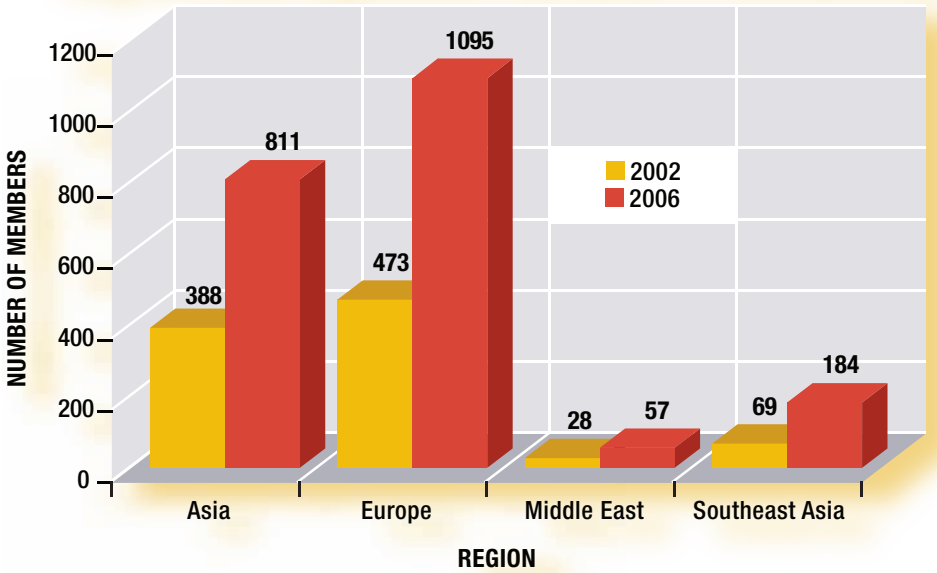
ASBMB Membership in 2002 and 2006



ASBMB membership increased 10-fold from 1956 to 2006, bringing the total number of members to 11,613

FIGURE TWO:

Regions with Significant Increases in Membership



A Look at Membership Numbers

Since its inception in 1906 ASBMB has experienced a steady increase in its membership. The Society began with 81 charter members, a number that expanded by an order of magnitude to 1,117 members by 1956. Over the next 50 years, membership again increased 10-fold bringing the total number of members to 11,613 in 2006. This article looks at some of our membership data from the past 5 years.

The society offers five types of membership: Regular, Emeritus, Associate, Student, and Honorary. Regular membership is available to any individual who holds a doctoral degree and who has published at least one paper in a refereed journal devoted to biochemistry and molecular biology. Associate memberships are offered to graduate students and postdoctoral fellows whose applications are endorsed by a mentor or faculty member. Student membership is open to any student working toward completion of a bachelor's degree, and emeritus membership is available to any ASBMB Regular Member who has retired from active employment. Honorary members are people who are not otherwise eligible for membership but who have rendered distinguished service to biochemistry or molecular biology. Fig. 1 shows a breakdown of membership for 2002 and 2006. Overall membership increased from 9,372 to 11,612 over that 5-year period. The most significant increase was seen in student membership, which went from 39 in 2002 to 472 in 2006.

The past 5 years have also seen a noteworthy increase in membership in several geographic regions. The United States, which represents our largest source of members, saw its ASBMB membership increase from 8,074 in 2002 to 9,008 in 2006. Membership in countries outside of the United States has also increased significantly. In 2002, 14% of the Society's members were from countries other than the United States. In 2006, foreign membership increased to 22%. Fig. 2 shows that Asia, Europe, the Middle East, and Southeast Asia experienced significant member growth between 2002 and 2006. Table 1 gives a breakdown of the countries in those regions that contributed to membership increases.

ASBMB recently established a new membership committee to analyze membership and make recommendations regarding recruitment, retention, and benefits. The Committee is composed of scientists at various stages of their careers, including full professors, junior faculty, and postdoctoral fellows. There are representatives from industry and several foreign members. If you have any suggestions for the membership committee on how the ASBMB can make your membership more valuable, please send your suggestions to asbmb@asbmb.org.

TABLE ONE:

Countries with significant increases in ASBMB membership

Country	Members in 2002	Members in 2006
Austrailia	33	98
Austria	9	26
Belgium	15	38
Finland	6	17
France	58	122
Germany	96	211
Italy	45	118
Japan	252	569
New Zealand	5	12
Norway	8	17
Portugal	4	13
Russia	2	10
Singapore	4	24
Spain	26	95
Sweden	25	89
Switzerland	28	72
Taiwan	42	118
United Kingdom	67	142

Photoshop: Friend or Fraud?

The following editorial by Journal of Biological Chemistry Deputy Editor Robert D. Simoni was recently posted on JBC Online. We feel the topic will be of interest to all ASBMB members.

In the past several years, there has been increasing concern with inappropriate manipulation of digital images presented in scientific papers (1). Although software for digital images has been an enormous technical advance, the boundary between appropriate and inappropriate manipulation has become "pixilated."

Even though image manipulation is often desirable for clarity and/or brevity of presentation, manipulation for deceptive purposes either to unfairly enhance or eliminate or otherwise obscure data is misconduct.

Clearly, there are as many ways to alter data as there are those who might want to misrepresent their work, and detecting all fraud is not possible

Within the past year, we have, both during and after the review process, detected cases of fraud: re-use of figures from one paper to another for new purposes, re-use of control images within a single paper without explicitly noting the repetition, removal of "contaminating" bands from gel patterns, etc. After investigation of such cases, papers have been rejected or withdrawn and institutional officers notified of misconduct.

There are more subtle *alterations* that are more difficult to detect but are also inappropriate, such as selective adjustment of backgrounds on gels, cropping of micrographs for field selection, and altering resolution. Clearly, there are as many ways to alter data as there are those who might want to misrepresent their work, and detecting all fraud is not possible.

In light of the increasing detection of fraud, however, we have adopted a policy taken from *The Journal of Cell Biology* (see www.jcb.org/misc/ifora.shtml#image_acquisition): "No specific feature within an image may be enhanced, obscured, moved, removed, or introduced. The groupings of images from different parts of the same gel, or from different gels, fields or exposures must be made explicit by the arrangement of the figure (*e.g.* using dividing lines) and in the text of the figure legend. Adjustments of brightness, contrast, or color balance are acceptable if and as long as they do not obscure or eliminate any information present in the original. Nonlinear adjustments (*e.g.* changes to gamma settings) must be disclosed in the figure legend."

In light of this policy and in an effort to meet our responsibilities to insure the scientific integrity of the work we publish, we have established the following procedures.

1. Reviewers will be reminded to carefully scrutinize images for any manipulation not explicitly reported in the paper and report them to us for investigation.
2. When suspect images are discovered, authors will be required to provide the original data. Failure to comply will result in rejection or withdrawal of the paper in question.
3. After due process involving the JBC editors, editorial staff, and the ASBMB Publications Committee, papers found to contain inappropriately manipulated images will be rejected or withdrawn and the matter referred to institutional officers.

The integrity of science relies on a very high standard of conduct upon which the public trust and the progress of science depend.

REFERENCE

1. Rossner, M., and Yamada, K. *J. Cell Biol.* **166,** 11–15, 2004

RASHMI NEMADE: *Moving Science from the Lab to the Home*

Rashmi Nemade

Rashmi Nemade received her B. A. in Biology from Boston University and her Ph.D. from the Program in Molecular Developmental Biology at the University of Cincinnati and Children's Hospital Medical Center in Cincinnati, Ohio. She was a postdoctoral fellow in the Laboratory of Genetics and Physiology at the National Institutes of Health before becoming a regulatory compliance specialist at Technical Resources International, Inc., in Bethesda, Maryland. Currently, Rashmi has her own biomedical writing company, BioMedText, Inc., and lives in Columbus, Ohio.

After spending several years working at the lab bench, I am now a freelance biomedical writer. I took my science, packaged what I most loved about it, and brought it home. Now, I work part-time, enjoying rigorous and intellectually challenging projects, enormous flexibility, and most importantly a fulfilling family life.

I didn't always know that I would become a writer. In fact, my writing for the school newspaper or an article here and there was a hobby. It was something fun and different from what I was doing in my coursework or at the bench. In graduate school, through the process of writing my qualifying exam and thesis, it became clear to me that I was very good at working independently on self-determined deadlines, and I enjoyed writing more than I had ever imagined. By the time I was ready for my postdoctoral training, I knew that I wanted writing to be a significant part of my future, but I wasn't quite sure of my options. Moreover, I wasn't ready to let go of the traditional academic path. After all, the reason I went to graduate school was to do research and teach.

Fortunately, for my postdoctoral work I found a well established, well known lab with an open minded and supportive mentor who encouraged me to pursue various writing options. As I became more entrenched in my postdoctoral work, I began to realize that I was disenchanted by the academic lifestyle, *i.e.* lots of hard work and personal sacrifice for risky gains. I looked around my lab and found that even the brightest, hardest working, dedicated, and well published scientists were, after at least a year or two of interviewing, landing academic positions at institutions that were not their first choices. My colleagues that got academic positions had to work seven days a week trying to prove to their new department members that they were worthy of the appointment. In the long run, I didn't want to work that hard for that long and make so many personal sacrifices, *i.e.* time with family for a last choice institution and a low salary.

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

For many of us who leave the bench, it is never an easy decision. I found it challenging and enjoyable for a long time, but the novelty was wearing off as I repeated the same techniques I had learned early in my career, and my days were filled with the mundane tasks of mouse colony organization and breeding schemes, extensive hours at the microscope, and tedious and time consuming experiments that many times did not work. Essentially, I had grown too impatient to do research, and this did not bode well for my future as an academic.

With my mentor's support, I began writing for the *NIH Catalyst*, an in-house publication, which

allowed me to build a writing portfolio of samples and joined the National Association of Science Writers (NASW).

Shortly thereafter, I made the leap, left the bench, and started working for a company that did, among other things, regulatory affairs. It was interesting to see what kinds of work someone with my background could do away from the bench, and I learned a lot there. However, I always wondered if I had what it took to launch a freelance career. So when my son was born and we had an opportunity to move to a family friendly city in the Midwest, we jumped at the prospect. Because of the affordable cost of living, we could live without my steady paycheck, and I could try my luck at freelancing.

With hard work, help from mentors at the NASW, and family support, I was able to get my freelance writing business going. I started out writing fact sheets for pharmaceutical companies, health encyclopedia entries, and health and science articles for Web sites, which was good busy work, but my real break came in the form of grants. Grant writing is intellectually stimulating, challenging, and rewarding. I can use my scientific background, learn what's new in a particular field, and apply my logical experimental design skills. It's a perfect match. In fact, I love writing grants! These days, I write grants mostly for professors with large labs and small biotech companies looking to obtain money for research. My clients typically give me an outline with some ideas of specific aims, some basic information, and preliminary data. I do the background research and writing, flush out the aims with the principal investigators, and do most of the experimental design. I haven't had to do any of the administrative tasks of the grants such as compiling biographies, budgets, or electronic submissions. I just do the science portion. It took a while, but it has all come together now, I took what I most loved about science—the intellectual rigor—and brought it home.

I can use my scientific background, learn what's new in a particular field, and apply my logical experimental design skills. It's a perfect match

The best feature about my current work situation is that I am experiencing all the firsts with my children! They go to daycare and have lots of social interaction for part of the week while I get my work done, and the other part of the week we go to the Science Museum, zoo, Spring Butterfly Releases at the local conservatory, etc. I get to be there when they experience their first ice cream truck popsicle treat, the first time they sit on a swing, or the first time they find a bug in the backyard—just precious, precious life memories. I couldn't have planned this any better—it's a dream come true!

I guess the moral of the story is that if you find that you can and want to take your career in a different direction, you simply have to find a way to do it. Eventually, all your hard work will make the pieces fall together so that you can have what you want out of life.

Teaching Undergraduates to Write Scientific Papers

BY LUBOMIR TOMASKA

Success in science depends in a large part on the scientist's writing skills. It is both the number of papers published in high profile journals and their citation output that count for one's career. Teaching students how to write scientific papers is one of the main roles of Ph.D. supervisors during graduate school and the postdoctoral period. However, undergraduate courses on this subject may also be very helpful in preparing prospective scientists for their future in an increasingly competitive world. In my experience, undergraduate students often lack even a basic understanding of the process of publishing scientific articles. For example, I was recently asked by a student if the editorial boards of scientific journals consist of retired scientists lacking funds for their research. Many students perceive the idea that authors should pay journals for publishing their research as pure nonsense, and the possibility that a manuscript might be rejected even without sending it to reviewers is seen by students as the worst kind of arrogance.

Many schemes exist for training undergraduates in writing a scientific paper. Probably the most ambitious program of research training for undergraduates—and thus indirectly for the training of their writing skills—is sponsored by the Howard Hughes Medical Institute (HHMI) in the form of HHMI Professors (www.hhmi.org). The program showed its potential by producing a number of high quality publications co-authored by students. Another initiative started in 2001 when the Office of Science of the U. S. Department of Energy started to release the *Journal of Undergraduate Research*, which publishes papers with undergraduate students as principal co-authors (www.scied.science.doe.gov/scied/JUR.html). Although these and other similar projects, including those guided by ASBMB, are highly instrumental in training students to write scientific reports, they lack "a control sample" that shows students how the same results would be described by an established and successful scientist. This is the basic concept for my recently described seminar course (1) that represents an alternative means for teaching undergraduate students to write a manuscript for a scientific journal.

The ultimate goal of the course is to guide the students through all stages of publishing a scientific paper. It starts with a simple question: If I have interesting results, how do I publish them in a scientific journal? First of all, how is a journal in which to publish the results chosen? Is the impact factor (IF) the "magic" indicator? One can address this question by using the following experiment. Students are provided with a list of titles and abstracts from articles recently published in a wide variety of journals with IFs ranging from 0.5 to 20. Students are then asked to assign the titles and abstracts to the journals, assuming that the most important articles are published in journals with the highest IFs. The students often discover that articles published in the high profile journals are not those expected. An important conclusion might be that it is worth choosing journals with lower IFs. This exercise also shows that it is sometimes difficult to understand why some papers are deemed important and are published in prestigious scientific journals. The goal of this exercise is to motivate students to read the scientific literature as critically and open mindedly as possible.

Next, I ask students to browse the scientific literature in genetics and molecular biology from the past one to two years and choose an experimental paper that they think presents the most interesting discovery. The students briefly describe the main points of the paper and explain why they believe it is the best article of a given year. After all the presentations and a brief follow-up discussion, the students decide which presentation was most convincing and select not only the best paper, but also a topic for the course. Letting undergraduate students choose a topic may increase the possibility of selecting an unsuitable area of research, but I've had the opposite experience. During the past years, selected topics included the role of prions in neuronal communication, involvement of microRNA in development and carcinogenesis, and DNA changes associated with the evolution of the human brain. The teacher's role is to provide background information about the research area either as a brief presentation based on both textbooks and recent review articles or by selecting a series of recent experimental articles on the topic and asking the students to prepare journal club presentations summarizing the data.

Now comes the critical part of the course. The teacher selects an article called a "secret paper" that will be the subject for the remainder of the course. The teacher then provides the students with all the necessary information presented in the paper without revealing its identity. It is important to choose a secret paper that (i) is on the topic selected by students, (ii) represents an important contribution to the field, (iii) is based on sound experimental results, and (iv) is based on experimental methods understandable by undergraduate students. The data presented in the paper are reviewed by the class so that each student understands every experiment and the main take-home messages of the work. At the same time, students are informed about the basic rules of writing various parts of a manuscript.

After students understand the experiments in the secret paper and have an idea of the purpose of each part of a scientific manuscript, they are asked to write a scientific paper on the subject. To ensure that all papers are in the same format, the teacher gives students the "instructions to authors" from the chosen journal. Students submit an unsigned (anonymous) copy of their manuscript to another student who will act as an anonymous reviewer. Before "sending the papers for review" the teacher describes the details of the review process, especially the structure of the reviewer's report. As an example, the teacher might show real referee comments from one of their own papers. The student referees then read and evaluate the strengths and weaknesses of the manuscript and indicate what changes should be made before it can be accepted by the journal. A great advantage is that referees are also authors of a manuscript on the same subject, so they can compare their way of writing with that of their classmates.

The seminar course has advantages for teachers as well. Since a new course topic is chosen every year, the teacher needs to prepare new material for every new course. This requires them to follow literature from a wide range of fields and can be beneficial for their own research. Also, the course is not limited to genetics and molecular biology and can be easily adopted by other disciplines. The teacher can also compare rules for writing a scientific paper with those for writing a thesis. All of these advantages underline the fact that this course could be mutually beneficial for students and teachers.

REFERENCE

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Unlocking the Causes of Heart Disease

BY PAT PAGES

Scientists at the University of Washington in Seattle have provided the first compelling evidence that high density lipoprotein (HDL) contains key components of the innate immune system. The unexpected discovery, described in the March issue of the *Journal of Clinical Investigation*, showed that it may be possible to improve heart attack treatments by better understanding some new properties of HDL.

HDL is popularly known as a "good" cholesterol molecule because it removes cholesterol from arteries—as opposed to its sister molecule, low density lipoprotein (LDL), known as the "bad" cholesterol molecule. People with low levels of HDL often develop premature heart disease, but many people with atherosclerosis—a heart disorder in which blood flow in the arteries is blocked—have normal or even high levels of HDL. It is not clear why, but the HDL of those individuals may have changed over time so that it no longer protects the heart.

To better understand HDL's role in atherosclerosis, Jay Heinecke, professor of Medicine at the University of Washington, and his team decided to use shotgun proteomics—a mass spectrometric technique in which proteins are broken down into peptides and then sequenced—to take a closer look at the proteins that make up HDL. The scientists found 48 proteins, 13 of which were not previously known to be part of HDL. Most of the proteins identified so far are involved in lipid transport, but Heinecke's team showed that HDL also contains unsuspected proteins that are part of the immune system.

"HDL's role in heart disease has always been a bit mysterious," Heinecke says. "These additional proteins provide important clues about how HDL either protects against or promotes atherosclerosis."

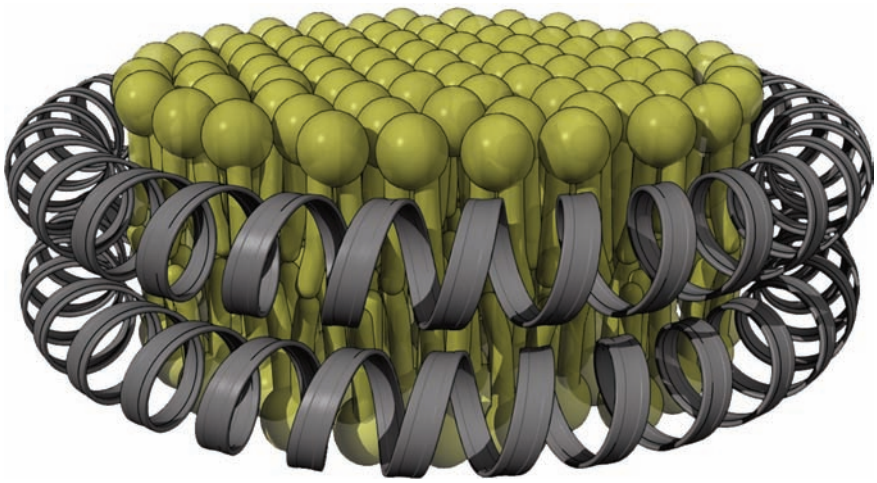
Heinecke and his colleagues suggest that these proteins can act in two

Jay W. Heinecke

Jay W. Heinecke is professor and Karasinski Chair in Metabolic Research of the Department of Medicine at the University of Washington, Seattle. He received a B.S. in chemistry from Antioch College, Yellow Springs, Ohio, and a medical degree from Washington University, St. Louis, Missouri.

Heinecke's laboratory was the first to propose that myeloperoxidase, a heme protein secreted by activated phagocytes, plays a role in oxidative tissue damage. His research group has a long history of using mass spectrometry and other sophisticated chemical approaches to understand the biochemical pathways of protein oxidation in atherosclerosis and other inflammatory disorders.

Heinecke is a member of the Association of American Physicians and serves on the editorial boards of the *Journal of Clinical Investigation* and the *Journal of Lipid Research*.



Proposed structure of one form of HDL that protects the artery wall from atherosclerotic vascular disease. In this model, two molecules of an apolipoprotein called apoA-I form a "belt" surrounding a bilayer of lipid molecules. ***Figure courtesy of Michael Oda (Children's Hospital Oakland Research Institute).***

opposite ways. When cholesterol hasn't built up too much in the arteries, the proteins help remove cholesterol and repair injury, but as cholesterol increases, the proteins may start to damage the artery as well, thus contributing to vascular disease.

One group of six proteins that were identified by the scientists, called serpins, are known to regulate potentially dangerous proteases—enzymes that degrade proteins—and foster blood coagulation. Although these proteins are normally beneficial and probably help clearing up arteries, altered versions of them may also destroy artery wall proteins, such as collagen and elastin, when cholesterol levels increase, Heinecke says.

Another family of newly identified proteins is involved in the complement system. Created by the liver and by immune cells such macrophages, complement components C3, C4, and C9 attack bacteria or viruses by forming holes in their cell membrane and then making them burst from the inside. The newly discovered HDL proteins may do the same with arteries and heart tissue when humans suffer from acute tissue injury during a heart attack.

The scientists also found a third category of proteins, called acute-phase proteins, which are released in the blood in large amounts following injury and play an important role in the innate immune system and inflammation. They discovered more acute-phase proteins in HDL than proteins involved in cholesterol transport.

"These proteins are giving us a completely new way to look at HDL," Heinecke says. "Until now, we thought that HDL was mostly involved in clearing up arteries from cholesterol. Now, we need to rethink what we knew and understand HDL's role as an integral part of the immune system."

Heinecke and his team plan to understand not only how HDL's proteins work within the arteries, but also where they come from. Some of the newly discovered proteins could come from HDL or be produced by macrophages located in the arteries or other inflamed tissues and then integrate into HDL. The latter possibility would support the idea that HDL's composition changes while the disease progresses, changing HDL's function along the way.

In the new study, Heinecke and his team found that HDL molecules in atherosclerotic patients contain more of certain proteins than healthy individuals. Some of the additional proteins are associated with cholesterol transport while others are involved in the immune system. By looking at how the amount of HDL's proteins increases over time, it may be possible to understand their role in the progression of atherosclerosis and to use them to tailor better drugs against the disease.

These proteins are giving us a completely new way to look at HDL

"We suspect that looking at HDL's blood level alone is not a good diagnostic test for atherosclerosis," Heinecke says. "Our hope is that, by knowing the molecular composition of HDL, we may be able to improve the diagnosis and treatment of this disease."

Potential Role for Key Protein in Migraines

BY PAT PAGES

Migraines may be caused by too much of a certain protein that is present only in some individuals, making them more susceptible to these painful headaches. The new finding, published in the March 7 issue of *The Journal of Neuroscience*, raises new hopes that by better understanding the protein, called Receptor Activity-Modifying Protein 1 (RAMP1), it may be possible to design more effective treatments against migraines.

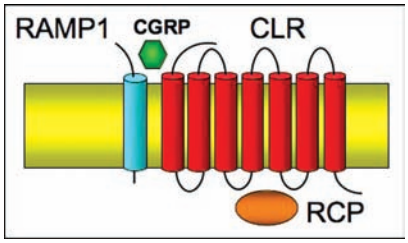
"Our team showed that mice that express human RAMP1 have more neurogenic inflammation—an inflammation linked to migraines—than normal mice, suggesting a key role for this protein in producing migraines," says Andrew Russo, professor of Molecular Physiology and Biophysics at the University of Iowa, Iowa City, and head of the team of scientists that conducted the study. "We hope to show that RAMP1 is associated with migraines in humans, which could bring us a step closer to understanding migraines."

Although no one really knows what causes migraines, studies have shown that they occur when brain chemicals are out of balance and when the trigeminal nerve—a major nerve linking the brain to the head and face—is abnormally excited by brain chemicals.

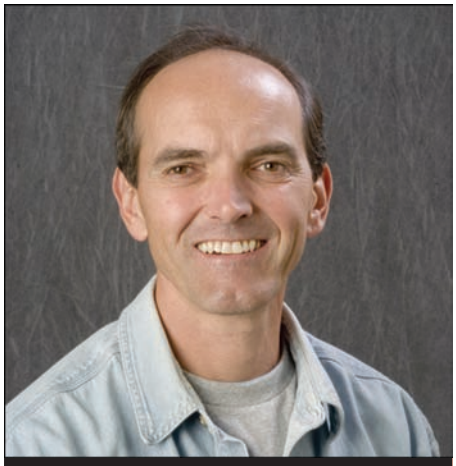
The new study showed that RAMP1 is working with a neuropeptide called calcitonin gene-related peptide (CGRP), which is well known for inducing inflammation. The scientists studied the effect of RAMP1 in transgenic mice that express human RAMP1 in their nervous system (in addition to the mouse version of the protein). They injected CGRP into the whisker pads of both the transgenic and normal mice. The transgenic mice had twice the amount of inflammation as did normal mice, confirming that elevated levels of RAMP1 helped CGRP increase inflammation.

Russo's team also looked at what was happening at the cellular level. So far, scientists had shown that CGRP contributes to inflammation by binding to a G protein-coupled receptor, which then activates other proteins inside the cell. In this study, Russo and his colleagues showed that RAMP1, which is part of the CGRP receptor (see figure), also activates intracellular proteins that increase CGRP gene expression. RAMP1 was shown to also stimulate the release of the neuropeptide substance P. Both CGRP and substance P contribute to neurogenic inflammation.

"Although scientists knew that RAMP1 was part of the CGRP receptor, they hadn't shown that RAMP1



Simplified representation of the proteins making up the receptor for CGRP: RAMP1, calcitonin-like receptor (CLR), and receptor component protein (RCP).



Andrew F. Russo

Andrew F. Russo is a professor of Molecular Physiology and Biophysics and director of the Biosciences Program at the University of Iowa, Iowa City. His team is using genetic tools to understand how plasticity is controlled within the nervous system. His major research efforts focus on understanding how the neuropeptide calcitonin gene-related peptide works and studying its role in migraines and the cardiovascular system.

He received his Ph.D. in Biochemistry from the University of California, Berkeley, in 1984 with Daniel E. Koshland, Jr., a renowned expert in both enzyme kinetics and sensory signaling mechanisms. He did his postdoctoral training at the University of California, San Diego, with Michael G. Rosenfeld, a leading molecular neurobiologist.

Russo has received several awards, including a Collegiate teaching award, and has served on a number of National Institutes of Health panels and professional society committees.

has such an active role in triggering inflammation," Russo says.

Russo and his colleagues also suggest that a newly identified brain area may be important for treating migraines. Scientists had previously established that CGRP can attach to brainstem neurons, blood vessels, or mast cells located in the meninges—membranes surrounding the brain. Russo and his team showed that cultured neurons from the trigeminal ganglion—a group of neurons connected to the meninges—displayed CGRP receptors that caused inflammation and were inhibited by a new antimigraine drug called BIBN4096S. These results indicated that CGRP receptors on the trigeminal ganglion are a fourth potential migraine area that could be further investigated.

Russo says that his study raises the possibility that people who have migraines may have subtle genetic differences in the RAMP1 gene that result in increased levels of the RAMP1 protein. His team is looking for genetic variations in the RAMP1 gene between people with and without migraines, which would show whether some people are genetically predisposed to migraines.

"People who get migraines have different versions of certain genes than people who are not affected, and we think that one of those genes could be RAMP1," Russo says. "Our studies provide a reason to look for variations in the DNA that encodes RAMP1 in humans."

Russo and his colleagues also would like to determine whether the inflammation they observed in mice actually makes them suffer from migraines. He will test whether the mice have symptoms of human migraines, which include sensitivity to light and sound and nausea. Ensuring that mice have migraines like humans do will encourage more studies using mice in addition to making comparative studies in humans, Russo says.

Russo's research results may have applications in other types of pain, including arthritis. Russo predicts that his group's findings about RAMP1 will have implications for pain research beyond migraines.

People who have migraines may have subtle genetic differences in the RAMP1 gene that result in increased levels of the RAMP1 protein

Vitamin B12 Mystery Solved

BY PAT PAGES

MIT and Harvard researchers have discovered the final piece of the synthesis pathway of vitamin B12, a molecule made mostly by bacteria and found primarily in meat, eggs, and dairy products. The new finding solves a 50-year mystery, which started when scientists set out to understand how the molecule is made naturally but never succeeded in finishing the task—until now.

"This study completes a piece of our understanding of a process that is a part of our scientific heritage and has resulted in four Nobel Prizes," says Graham Walker, professor of Biology at the Massachusetts Institute of Technology (MIT) and senior author of a paper on the work that appeared in the March 22 issue of *Nature*.

Vitamin B12 is essential for human health because it helps form red blood cells and maintain the myelin sheath that insulates nerve fibers. Its deficiency can lead to various forms of anemia, nerve degeneration, cognitive impairment, and even paralysis.

Although the vitamin is now available either from food or food supplements, scientists have, since the mid-1950s, tried to understand how vitamin B12 is synthesized in nature. So far, all the chemicals needed to make vitamin B12 and nearly all the chemical reactions that assemble the chemicals are known. The only missing reactions are those that produce the last piece of the puzzle, called 5,6-dimethylbenzimidazole (DMB).

In the new study, Walker and his colleagues described how DMB is produced, a process which, unexpectedly, requires only one enzyme and involves fragmenting a form of vitamin B2 called flavin mononucleotide (FMN) (Fig. 1). The enzyme, called BluB, is produced by a soil microbe.

For the past 35 years, scientists knew that DMB could be produced from FMN, but they could not find the enzymes needed to make it happen. Surprisingly, the discovery of BluB as the missing enzyme resulted from work on a completely different topic. Walker's team was trying to understand how soil microbes live in symbiotic relationships with plant roots.

While studying a symbiotic nitrogen-fixing bacterium called *Sinorhizobium meliloti* in the mid-1980s, the

Graham C. Walker

Graham C. Walker is an American Cancer Society Research Professor in MIT's Biology Department. He and his team study the biochemistry and physiology of how organisms respond to DNA damage and the molecular mechanisms underlying the symbiosis between nitrogen-fixing soil bacteria called rhizobia and their plant hosts.

Walker received his Honors B.Sc. from Carleton University, Ottawa, Canada, and his Ph.D. from the University of Illinois at Urbana-Champaign. He did his postdoctoral work at the University of California, Berkeley.

Walker has served as the editor-in-chief of the *Journal of Bacteriology* and is a co-author of the textbook *DNA Repair and Mutagenesis*. He is a Fellow of the American Academy of Arts and Sciences, a Fellow of the American Academy of Microbiology, and has recently received the Environmental Mutagen Society Award.

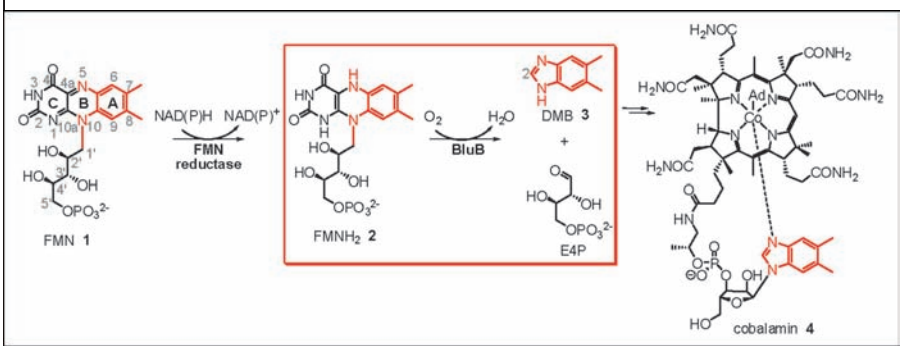


Fig. 1. Overall chemical reactions involved in DMB biosynthesis and vitamin B12 formation. The atoms converted to DMB are shown in *red*; the reaction catalyzed by BluB is in the *red box*.

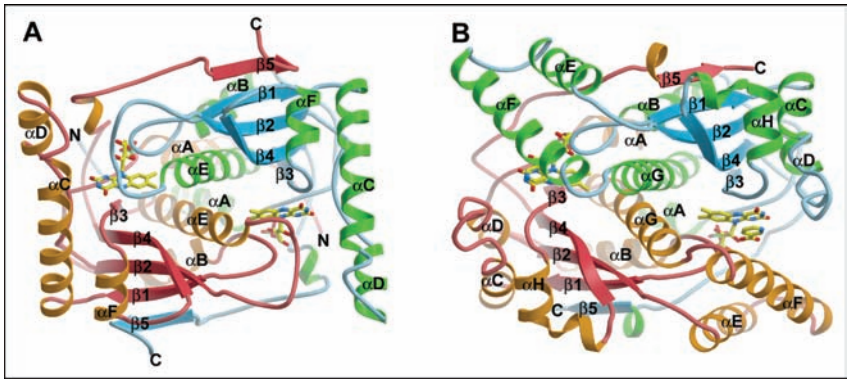


Fig. 2. *A*, *ribbon diagram* of BluB with FMN coenzyme (*stick representation*) in the binding pocket. *B*, *Escherichia coli* nitroreductase with FMN and nicotinic acid (*stick representation*) in the binding pocket.

researchers pioneered a technique that later allowed them to isolate a mutant form of the bacterium that failed to establish symbiosis with alfalfa unless vitamin B12 or DMB were supplied. While trying to tease out the details of how vitamin B12 and DMB were involved in this failed symbiosis, the scientists concluded that BluB must be involved in the conversion of FMN into DMB.

The discovery created an "Aha" moment that made the scientists wonder whether that one enzyme could perform all of the complicated chemistry needed to produce DMB or if more enzymes were needed. One early clue to BluB's function was that the gene that makes the protein is located near other genes involved in vitamin B12 synthesis in a different bacterium. So the researchers began searching for other genes that, like the BluB gene, might play a role in DMB synthesis. But they couldn't find any. This led them to discover that BluB was the only protein required to convert FMN to DMB.

BluB's small active site gave away the molecular details of what actually happens

They then decided to crystallize BluB to understand its role in the chemical reaction. Based on BluB's amino acid sequence, the researchers initially thought that it would be similar to nitroreductase, an enzyme that uses FMN as a coenzyme. As scientists had previously shown, FMN is used as a substrate—instead of a coenzyme—to make DMB, but nobody knew how this was possible.

BluB's crystallographic structure revealed that the site where FMN sits in the enzyme is surprisingly small (Fig. 2). After looking at the structure more closely, the scientists were able to understand how BluB's small site was helping it use FMN as a substrate.

"Normally, FMN assists in a reaction by temporarily holding electrons and then giving them away; coenzymes are not consumed in chemical reactions," Walker says. "In the case of BluB, its small active site gave away the molecular details of what actually happens."

Now that Walker and his colleagues have identified the enzyme that converts FMN to DMB—which is later added to a vitamin B12 precursor to form vitamin B12—they need to determine the precise mechanism by which BluB catalyzes the reaction. In their paper, the scientists propose two possibilities, but more research will be needed to confirm either one or to find an alternative mechanism.

Another question that Walker's team will address is why soil bacteria synthesize vitamin B12 at all. Walker speculates that synthesizing the vitamin may help the bacteria withstand challenges—such as oxidative stress—from the host plant so they can live in symbiosis within plant cells.

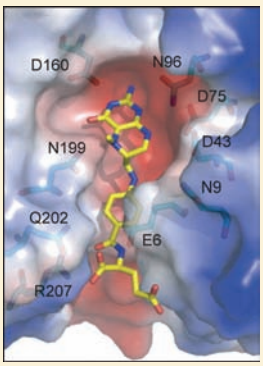
biobits asbmb journal science

J. Biol. Chem. 2007 282: 6609–6618

Structural and Kinetic Evidence for an Extended Hydrogen-bonding Network in Catalysis of Methyl Group Transfer

Tzanko I. Doukov, Hisashi Hemmi, Catherine L. Drennan, and Stephen W. Ragsdale

The methyltetrahydrofolate corrinoid-iron-sulfur protein methyltransferase catalyzes transfer of the methyl group of methyltetrahydrofolate to cob(I)amide. This transfer requires electrophilic activation of methyltetrahydrofolate's methyl group, which includes proton transfer to the N5 group of the pterin ring. In this *JBC* paper, the authors use a combination of kinetic and structural evidence to show that in this methyltransferase, an extended H-bonding network is involved in proton transfer to N5. This includes an asparagine, a conserved aspartate, and a water molecule. The asparagine residue swings from a distant position to within H-bonding distance of the N5 atom upon methyltetrahydrofolate binding. The evidence in this paper suggests that even a poor hydrogen-bonding residue such as asparagine can contribute to a cumulative hydrogen-bonding network such that the overall effect on the transition state is greater than suggested by the individual components alone.



The active site of methyltransferase with bound CH_3H_4folate.

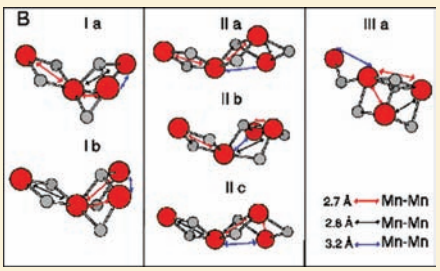
jbc

J. Biol. Chem. 2007 282: 7198–7208

Structure and Orientation of the Mn_4Ca Cluster in Plant Photosystem II Membranes Studied by Polarized Range-extended X-ray Absorption Spectroscopy

Yulia Pushkar, Junko Yano, Pieter Glatzel, Johannes Messinger, Azul Lewis, Kenneth Sauer, Uwe Bergmann, and Vittal Yachandra

The oxygen-evolving complex of photosystem II uses energy derived from light to oxidize water and create oxygen. Recent crystal structures of the complex reveal that the site of water oxidation contains a tetranuclear manganese cluster and a calcium atom. Unfortunately, it is now clear that the x-ray fluxes used for the diffraction experiments produce severe damage to the cluster with accompanying modifications of ligand-metal interactions. However, the EXAFS (extended x-ray absorption fine structure) technique, which uses lower energy x-rays and cryogenic conditions, has been used successfully to probe the manganese cluster without damage. In this paper, the authors use the EXAFS technique to generate new structural information on the undamaged metal cluster. By comparing their results to proposed manganese cluster models based on spectroscopic and diffraction data, the authors provide input for refining and selecting among these models.



Models for the manganese cluster in the oxygen-evolving complex of photosystem II.

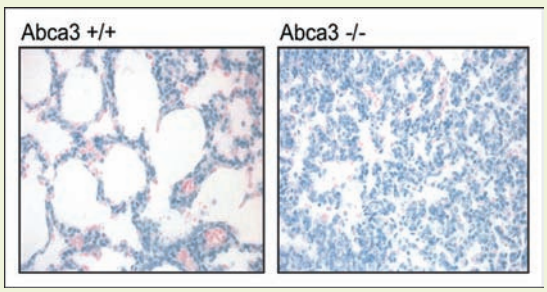
jbc

J. Lipid Res. 2007 48: 621–632

ABCA3 inactivation in mice causes respiratory failure, loss of pulmonary surfactant, and depletion of lung phosphatidylglycerol

Michael L. Fitzgerald, Ramnik Xavier, Kathleen J. Haley, Ruth Welti, Julie L. Goss, Cari E. Brown, Debbie Z. Zhuang, Susan A. Bell, Naifang Lu, Mary Mckee, Brian Seed, and Mason W. Freeman

ABC transporters are large membrane proteins that move molecules across bilayer membranes by hydrolyzing ATP. Mutations in the human ABCA3 transporter are associated with childhood respiratory disease. To explore the physiologic transport function of ABCA3, the authors of this *JLR* paper generated mice that lack the transporter. The mice had normal lung development but failed to inflate their lungs at birth and quickly died from respiratory failure. Analysis of the Abca3$^{-/-}$ lungs revealed an absence of surfactant in the alveolar space and a profound loss of mature lamellar bodies, the intracellular storage organelle for surfactant. The mice also showed a dramatic reduction in their phosphatidylglycerol levels as well as selective reductions in phosphatidylcholine species containing short acyl chains. These results show that ABCA3 is needed for lamellar body formation and pulmonary surfactant secretion.



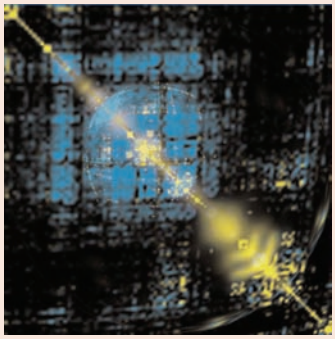
Abca3$^{-/-}$ pups have collapsed airspaces in their lungs.

Mol. Cell. Proteomics 2007 6: 439–450

Toward a Comprehensive Atlas of the Physical Interactome of *Saccharomyces cerevisiae*

Sean R. Collins, Patrick Kemmeren, Xue-Chu Zhao, Jack F. Greenblatt, Forrest Spencer, Frank C. P. Holstege, Jonathan S. Weissman, and Nevan J. Krogan

Because most cellular functions are mediated by groups of physically associated proteins or complexes that work in a coherent fashion, it is of great interest to systematically map protein-protein interactions. Two recent affinity purification/mass spectrometry studies in *Saccharomyces cerevisiae* have vastly increased the available protein interaction data. The practical utility of such high throughput interaction sets, however, is substantially decreased by the presence of false positives. In this *MCP* paper, the authors created a novel probabilistic metric that takes advantage of the high density of these data, including both the presence and absence of individual associations, to provide a measure of the relative confidence of each potential protein-protein interaction. This analysis largely overcomes the noise inherent in high throughput immunoprecipitation experiments.



Hierarchical clustering of the combined dataset gives a view of the interactome for yeast.

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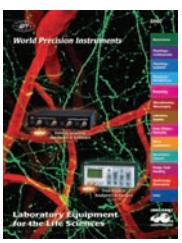

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Tel.: 301-634-7277

94th Annual Meeting of the American Association of Immunologists
MAY 18–22, 2007
MIAMI BEACH, FL
www.immunology2007.org/

National Lipid Association Annual Scientific Sessions
MAY 31–JUNE 3, 2007
SCOTTSDALE, AZ
www.lipid.org/chapters/swla

Epistasis: Predicting Phenotypes and Evolutionary Trajectories
MAY 31–JUNE 3, 2007
IOWA STATE UNIVERSITY, AMES, IA
www.bb.iastate.edu/%7Egfst/PSIframeset.html
Tel.: 515-294-7978

JUNE 2007

55th ASMS Conference on Mass Spectrometry
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INDIANAPOLIS, IN
www.asms.org
Tel.: 505-989-4517

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Organizers: Conly L. Rieder
E-mail: rieder@wadsworth.org
Robert E. Palazzo
E-mail: palazr@rpi.edu

76th Annual European Atherosclerosis Society Congress
JUNE 10–13, 2007
HELSINKI, FINLAND
www.kenes.com/eas2007
Tel.: 41-22-908-0488
Fax: 41-22-732-2850

American Diabetes Association's 67th Annual Scientific Sessions
JUNE 22–26, 2007
CHICAGO, IL
www.wynjade.com/ada07/

20th American Peptide Symposium
JUNE 23–27, 2007
MONTREAL, QUEBEC, CANADA
E-mail: 20thAPS@UMontreal.ca

JULY 2007

XXIII International Conference on Yeast and Molecular Biology
JULY 1–6, 2007
MELBOURNE, AUSTRALIA
www.yeast2007.org/program.php
E-mail: Yeast2007@meetingplanners.com.au
Tel.: 61-3-9417-0888

32nd FEBS Congress: Molecular Machines and Their Dynamics in Fundamental Cellular Functions
JULY 7–12, 2007
VIENNA, AUSTRIA
Registration is open until March 31
www.FEBS2007.org

Life Sciences 2007: A Joint Meeting of the Biochemical Society, the British Pharmacological Society, and the Physiological Society
JULY 8–12, 2007
THE SECC, GLASGOW, UK
www.lifesciences2007.org/

EUROCOMBI 4
JULY 15–18, 2007
FLORENCE, ITALY
www.polosci.unifi.it/eurocombi4
E-mail: marta.cocchi@unifi.it

21st Annual Symposium of the Protein Society
Proteins: From Birth to Death
JULY 21–25, 2007
BOSTON, MA
www.proteinsociety.org

Gordon Research Conference–Molecular and Cellular Biology of Lipids
JULY 22–27, 2007
WATERVILLE VALLEY, NH
www.grc.org

4th British Society for Proteome Research/European Bioinformatics Institute Proteomics Meeting
Integrative Proteomics: Maximizing the Value of Proteomics
JULY 25–27, 2007
CAMBRIDGE, UK
www.bspr.org/
E-mail: meetings@bspr.org

Senescence, Aging, and Cancer Symposium
JULY 26–29, 2007
IOWA STATE UNIVERSITY, AMES, IA
www.bb.iastate.edu/%7Egfst/homepg.html
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Kern Aspen Lipid Conference–Diabetes, Obesity and Atherosclerosis
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www.uchsc.edu/kernconference/
E-mail: julie.morris@uchsc.edu

8th International Symposium on Mass Spectrometry in the Health & Life Sciences
AUGUST 19–23, 2007
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www.donatello.ucsf.edu/symposium/
E-mail: sfms@itsa.ucsf.edu
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234th American Chemical Society National Meeting
AUGUST 19–23, 2007
BOSTON, MA
chemistry.org/meetings/boston2007

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13th Nordic Mass Spectrometry Conference
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SAVONLINNA, FINLAND
www.nsms.no/moter.html

SEPTEMBER 2007

48th International Conference on the Bioscience of Lipids
SEPTEMBER 4–8, 2007
TURKU, FINLAND
www.icbl2007.abo.fi

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www.bmss.org.uk/meetings.htm
E-mail: bmssadmin@btinternet.com
Tel.: 44-(0)-1480-880-669

5th Euro Fed Lipid Congress
SEPTEMBER 16–19, 2007
GOTEBORG, SWEDEN
www.eurofedlipid.org/meetings/goeteborg/index.htm

10th International Conference of the Eicosanoid Research Foundation: Bioactive Lipids in Cancer, Inflammation and Related Diseases
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bioactivelipidsconf.wayne.edu/

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www.lorenzinifoundation.org/download/dalm2007.pdf

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