

JANUARY 2004

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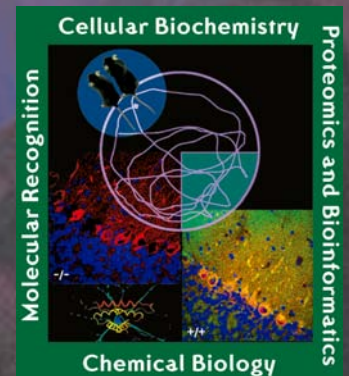
AMERICAN SOCIETY FOR BIOCHEMISTRY AND MOLECULAR BIOLOGY

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Lipids, Rafts and Traffic

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- Roger Y. Tsien (Howard Hughes Medical Institute La Jolla, CA, USA) – Opening Lecture
- Stephen O’Rahilly (Cambridge, UK)
- Tony Pawson (Toronto, Canada)
- Chris Dobson (Cambridge, UK)
– The EMBO Lecture
- Karen Vousden (Beatson Institute, Glasgow, UK)
- Graham Warren (Yale, New Haven, CT, USA)

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ASBMB Today

AMERICAN SOCIETY FOR BIOCHEMISTRY AND MOLECULAR BIOLOGY

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Christopher Reeve Receives Public Service Award

Christopher Reeve has received the 2003 Mary Woodard Lasker Award for Public Service in Support of Medical Research and the Health Sciences.


"Instead of bowing to a sudden, life-altering injury, he mustered his internal resources and exploited his connections to advance research that targets spinal cord repair," stated the Lasker Foundation. "Reeve has informed himself about the scientific as well as political aspects of his mission; this approach, along with his role as a public figure, have earned him unique status with researchers, lawmakers, and private citizens alike. Although he must endure the physical and emotional hardships of living in a body that is largely immobile, he is far from paralyzed."

In 1995, an equestrian accident paralyzed Reeve from the shoulders down. Unable to breathe without the help of a machine, Reeve confronted a new life. Within months of his injury, Reeve joined the Board of Directors of the American Paralysis Association (APA), and less than a year later became its chair.

In 1996, Reeve and his wife Dana established the Christopher Reeve Foundation; in its first year of operation, it raised \$750,000 for the APA as well as groups dedicated to quality of life issues. In 1999, this foundation merged with APA, the name was changed to the Christopher Reeve Paralysis foundation (CRPF), and Reeve continued to serve as chairman of the board. CRPF funds research that paves the way toward treatments and cures for paralysis caused by spinal cord



Christopher Reeve, victim of a catastrophic spinal column injury in 1995, will receive the 2003 Mary Woodard Lasker Foundation's Award for Public Service in Support of Medical Research and the Health Sciences, the Foundation announced in early December. Mr. Reeve was active in lobbying and testifying before Congress on behalf of the doubling of the NIH budget in five years. In part because of his efforts, the NIH budget grew from \$12 billion in 1998 to nearly \$25 billion in fiscal 2002. In 1996, Mr. Reeve and his wife Dana established the Christopher Reeve Foundation; now known as the Christopher Reeve Paralysis Foundation, which in 2003 awarded almost \$7.4 million in grants for neuroscience research and more than \$620,000 in Quality of Life awards.

injury and other central nervous system disorders; the organization also allocates a portion of its resources to grants that improve the quality of life for people with disabilities. In 2003, the foundation awarded almost \$7.4 million in grants for neuroscience research and more than \$620,000 in Quality of Life awards. 

Just What Are the Effects of Low-Dose Radiation?

Whether there is a safe dose of radiation is a question that scientists at the Medical College of Georgia are seeking to answer. There has long been experience with the effects of high-dose radiation; what is not known is the effect of long-term, low-dose radiation such as we are subject to every day. Key issues still unexplored are whether the low levels of radiation all around us—even inside us in unstable forms of common elements such as potassium and hydrogen—cause problems and exactly what genes and proteins in the body help repair and, more importantly, prevent damage.

Armed with a grant from the U.S. Department of Energy, the scientists are using the rapidly developing zebrafish embryo to study the effects of low doses of radiation—the kind many people encounter daily—during the earliest and

most delicate stage of life. Zebrafish were used because, as a vertebrate, they share many developmental and anatomical features with humans, yet the embryos develop completely outside the mother, are optically transparent, and are amenable to genetic and molecular manipulation. Plans for MCG's cancer research building include an expanded zebrafish facility to support the search for other genes, such as those that predispose people to colon cancer.

Ionizing radiation—which has shorter, more powerful wavelengths than visible or ultraviolet light—undoubtedly is strong enough to break apart chemical bonds in the body, including DNA, says ASBMB member William S. Dynan, Biochemist and Chief of the Program in Gene Regulation at the Medical College of Georgia Institute of Molecular Medicine and Genetics.

Dr. Dynan, principal investigator on the new \$750,000, three-year grant, has been studying how cells respond to radiation that can break one or both strands of the double-stranded DNA, leading to cell death, successful cell repair or misrepair that may result in cancer.

The researchers are exposing zebrafish embryos—which grow outside the mother and have developed, functioning organs within three days—to levels of radiation that mimic what humans routinely receive. A high-powered microscope enables them to look inside a live embryo and mark specific brain cells with a fluorescent dye to see if the numbers change after irradiation. They also plan to document double-strand breaks and repairs within single cells.

“We want to know what bad things happen to an early embryo both at the

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Announcing

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The American Society of Biochemistry and Molecular Biology is pleased to announce the support of two meetings for 2004 and two meetings for 2005.

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GRANLIBAKKEN, LAKE TAHOE

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Fe-S Proteins: Biogenesis, Structure and Function

May 19–22, 2005

Organizer: Elizabeth A. Craig, *University of Wisconsin, Madison*

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May 31–June 5, 2005

Organizers: Julian A. Peterson and Sandra E. Graham, *U.T. Southwestern Med. Ctr., Dallas, Texas*

www.asbmb.org/meetings

by Peter Farnham, CAE, ASBMB Public Affairs Officer

FASEB President Says Meeting

“It’s hard to see how the meetings could have gone any better.”

This was FASEB President Bob Wells’ assessment of a series of meetings he and four Nobel laureates held on November 20 with Vice President Dick Cheney and several other high-ranking administration officials. Dr. Wells was ASBMB President in the two years immediately preceding his term at FASEB’s helm.

Dr. Wells noted that “this was the first time that I can recall that a group of scientists had such a high level meeting.” He praised Patrick White, FASEB’s outgoing Director of Legislative Relations, for facilitating the meetings, and former House Minority Leader Bob Michel, who is now with Hogan & Hartson LLP, for his role in bringing them about.

“The meetings were very positive,” Dr. Wells reported. “We had no specific requests for funding or anything else. We simply wanted to talk about scientific research and how important this was in terms of economic growth and the tremendous opportunities that are avail-



FASEB President Robert Wells

able to us” as an outgrowth of the new knowledge developed from the recently-completed doubling of the NIH budget. “Vice President Cheney in particular was very encouraging,” Dr. Wells told *ASBMB Today*. “He told us that he himself was living proof of the value of research,” apparently referring to the various medical procedures he has undergone in recent years for his heart ailments. “We were told going in that we’d get 10 minutes with the Vice President. Instead, we were with him for almost 40 minutes.”

The group also met separately with Office of Management and Budget Director Joshua Bolten, and had a similar, encouraging experience—a promised 10-minute meeting that went closer to an hour. In addition, the group met over breakfast with Presidential Science Adviser John Marburger, and later with White House Deputy Chief of Staff for Domestic Policy Harriet Miers.

The FASEB President made the decision to seek these meetings because he was greatly concerned about the parsimonious administration request for NIH in FY 2004—only two percent—after five years of annual increases in the range of 15 percent. The amount the administration requests for research sets an important parameter for Congress’ future actions and is frequently key to future progress. “We

were all struck by the fact that both the Vice President, and OMB Director Bolten, told us unsolicited that our timing couldn’t be better to talk about this,” Dr. Wells said, “since the 2005 budget was still being formulated.”

He noted that the four Nobel laureates represented a cross-section of disciplines and perspectives in American scientific research. Yale University biochemist Sidney Altman, a naturalized U.S. citizen, represented the international nature of modern scientific research. Howard Hughes Medical Institute President Thomas Cech could speak authoritatively about the private foundation world. Alfred Gilman, head of the University of Texas Southwestern Medical Center’s Department of Pharmacology, represented academic medicine and has strong interests in pharmaceutical research and development. Atmospheric chemist Sherwood Rowland, University of California at Irvine, was from a field outside biomedicine. The latter point—the synergy between all fields of science—was stressed as an extremely important component of the nation’s total effort in research.

The 40-minute Cheney meeting touched on a wide variety of themes, including how important long-term, sustained federal research funding was to our country’s endeavors, from the continued viability of our universities and medical schools to economic growth. The group discussed the funding of young investigators and the danger of bright young people choosing other careers because of funding difficulties in research. The reported difficulties of foreign scholars and students in obtaining visas came up briefly as well.

with Cheney 'Very Encouraging'

The group also discussed the importance of the NIH doubling, and indicated that the fluctuations in NIH funding that seem to be in the cards—rapid growth, followed by several years of at best inflationary increases, would seriously hurt continued progress in the field. Dr. Wells said the Vice President assured the group that the administration believed that NIH was a very appropriate place to spend federal money, and that he would do all he could for the NIH.

It will be interesting to watch the administration's proposals for science

funding in the FY 2005 budget that will be released early next month. So far, the biomedical research community is expecting a proposed increase for NIH in the range of 2 percent. This is what the administration proposed for FY 2004, although Congress finally settled on an increase of 3.7 percent, about \$1 billion.

Thus, in spite of the Vice President's assurances, it remains to be seen whether the meetings will have any impact in the short-term, although there is little doubt that the meetings were highly useful in

the long-term. "Meetings like this never hurt," Dr. Wells said, stressing that they had not gone into the meetings with a series of specific requests, and so did not necessarily expect immediate payoff, such as a major increase for NIH next year. Rather, Dr. Wells said that it was important that the administration know that the scientific community was "paying attention."

"All of us came away from the meeting in an upbeat, positive frame of mind," Dr. Wells summed up. "There is no doubt that we were well received. ∞"

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NIH Meeting Focuses on Digital Biology

By John D. Thompson, Editor

Computing has become so integral to biomedical research that you just can't do without it.

That was the assessment made by Eric Jakobsson, Director of the Center for Bioinformatics and Computational Biology at the National Institute of General Medical Sciences, who spoke at an NIH symposium, Digital Biology: The Emerging Paradigm.

Dr. Jakobsson, who chairs NIH's Biomedical Information Science and Technology Initiative Consortium (BISTI) which organized the November meeting, lamented that the variety of computer networks and software currently in use do not intercommunicate well and therefore present an obstacle to the development of an efficient nationwide operating system.

The Center for Bioinformatics and Computational Biology Chair, who last June took that post which had been vacant for two years, told *The Scientist* at that time, "I'm envisioning this job as putting together a nationally distributed software engineering project. Now, a program for molecular dynamics and another that simulates a complex system such as a pathway in a cell aren't linked. We want to seamlessly connect them."

BISTI's first major project—an attempt to update networking and integration capabilities—will be to award \$3 to \$4 million per year for 5 years to three or four nonprofit "computational centers of excellence."

That view was seconded by the symposium's keynote speaker, Nathan Myhrvold, Cofounder and Managing

Director, Intellectual Ventures, who as Chief Technical Officer at Microsoft from 1986 to 2000 was responsible for founding Microsoft Research and technology groups that developed many of that company's leading products.

Dr. Myhrvold commented that Moore's Law, which states that the number of transistors on a microprocessor would double approximately every 18 months, was applicable to the multitude of increasingly cost-efficient, sequenced "omes," including the entire "biome." The GenBank itself, he noted, is doubling about every 18 months. In order to efficiently handle the sea of data issuing from a multitude of computational projects, he said better connected labs with better integrated data are essential.

Regarding the gap, perceived or otherwise, between computer people and scientists, Dr. Myhrvold said he is often asked, "Can computer people be real biologists?" His answer, "You tell me. When are you gonna treat them as real colleagues?"

Fred S. Roberts, Director of the Center for Discrete Mathematics and Theoretical Computer Science (DIMACS) at Rutgers University, who chaired a workshop on Information Processing in the Biological Organism (A Systems Biology Approach) prior to the BISTI symposium, described the challenge this way:

"If you know what an airplane does, you can figure out how to make one, but in biology there is a sea full of islands of data which need to be

linked. We need a map to see where the links should be. You can't just link every piece of data to every other piece. There are tons of data and data are being generated all the time. How do you find out how it will affect your research? Exponential genomics is rivaling computing and internet in importance. The more we know, the more we need to learn."

"Understanding how the parts work is also important, but it is not enough. We need to know how they work together. This is the systems approach. The list of parts is a necessary but not sufficient condition for understanding biological function. Understanding biological systems from this point of view can be greatly aided by the use of powerful mathematical and computer models."

Also at the symposium was NIH Director Elias Zerhouni, who presided over a panel on "A Vision for Biomedical Computing." He expressed a recognition of the need to make the investment in better tools to get better information. Referring to his Roadmap for NIH, he stressed the need to develop capabilities and invest in improving the quality of data, cross-train life scientists and mathematicians, develop interdisciplinary teams, and integrate physics and biological systems.

Dr. Zerhouni, who recently outlined specific computing initiatives in his NIH Roadmap, suggested that "brute force" computation is not the right approach for biomedical research and

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NHGRI Selects Sequencing Centers For Next Generation Large-Scale Sequencing Projects

The National Human Genome Research Institute (NHGRI) has selected centers to carry out a new generation of large-scale sequencing projects designed to maximize the promise of the Human Genome Project.

Over the next three years, the five centers in NHGRI's Large-Scale Sequencing Research Network will use high-throughput, robotic technologies to sequence a strategic set of animal genomes totaling as much as 54 billion base pairs, or the equivalent of 18 human genomes. For fiscal year 2004, NHGRI has earmarked \$163 million for the sequencing centers, which were selected through a competitive, peer-reviewed process. Funding levels for FY 2005 and 2006 are planned to be \$163 million and \$133 million respectively.

The NHGRI-supported, large-scale sequencing centers and their approximate FY 2004 funding levels are: Agencourt Bioscience Corp., Beverly, Massachusetts, \$10 million; Baylor College of Medicine, Houston, \$35 million; The Eli & Edythe L. Broad Institute, Massachusetts Institute of Technology (MIT), Cambridge, Mass., \$59 million; The Institute for Genomic Research, J. Craig Venter Science Foundation Joint Technology Center, Rockville, Md., \$10 million; and Washington University School of Medicine, Saint Louis, \$49 million.


These centers will make up the NHGRI Large-Scale Sequencing Research Network, encompassing representatives of academia, private industry and the non-profit sector. Their primary mission is to produce a pub-

licly available resource of high quality assembled genome sequences that researchers can use to address human biology and human health.

Currently, NHGRI-supported sequencing centers are close to completing working drafts of the genomes of additional organisms that improve the understanding of genomes that have already been sequenced and provide insights into the evolution of humans. The genome sequences of the chimpanzee, the chicken, the sea urchin, the honeybee and a set of four fungi are nearly in draft form. The sequence of the domestic dog, which is a major model for studying genetic diseases and developing pharmaceuticals, is also approaching deep draft coverage. Last summer, the centers started initial sequence production for creating a reference version of the genome of the rhesus macaque, which is widely used in studies of human immunodeficiency virus (HIV) infection.

Other organisms on NHGRI's high-priority list are: the cow; the South American gray, short-tailed opossum (a marsupial); the red flour beetle; the acorn worm; the flatworm *Schmidtea mediterranea*; 10 more species of fruit fly; four more species of fungi; and two ciliated microorganisms, *Oxytricha fallax* and *Tetrahymena thermophila*.


NHGRI recently instituted a new process for choosing target organisms for comparative sequencing. Rather than placing the entire responsibility for advocating the sequencing of various organisms upon individual researchers, NHGRI established three working groups of experts from across the research com-

munity. Each working group is expected to develop a plan for sequencing organisms that advances knowledge in one of three scientific areas: understanding the human genome, understanding the genomes of major biomedical model systems' and evolutionary biology of genomes. 

Low-Dose Radiation ...

Continued from page 3

DNA level and how that affects development," says Dr. David J. Kozlowski, developmental geneticist and Director of MCG's Transgenic Zebrafish Core Laboratory. "Say for example, a whole bunch of cells gets these double-strand breaks and they die. What happens to the embryo? Does it fix itself or is there irreparable damage? And, if we have a gene we think protects the embryo from radiation, if we reduce the function of that gene, does that make the embryo more sensitive to even lower doses of radiation?"

"There may be some way you can genetically alter the environment in the cell that makes the cell repair damage better," according to Dr. John T. Barrett, MCG radiation oncologist who is helping with experiment design. "From a therapeutic standpoint, there also may be a way in cancer cells that you can increase the damage or disable the repair mechanism for these double-strand breaks so that you get better cell kill." 

Common Genetic Damages in Non-Dividing Cells Lead to Creation of Mutant Proteins

‘Transcriptional Mutagenesis’ may contribute to neurodegenerative diseases, cancer, and aging

Two types of DNA damage that frequently befall most cells on an everyday basis can lead to the creation of damaged proteins that may contribute to neurodegeneration, aging and cancer, according to research by scientists at Emory University School of Medicine, published in the October 24 issue of the journal *Molecular Cell*.

The investigators used *E. coli* cells as a model system to study specific kinds of genetic damages that occur in all non-dividing cells undergoing transcription—the everyday activity in which cells produce the proteins necessary to carry out bodily processes. The vast majority of scientists studying genetic mutations have focused instead on the cell replication process, in which damaged and unrepaired DNA within multiplying cells can be copied before cells divide and passed along to a new generation of cells. Most of the cells within organisms are no longer replicating, however, and instead spend their time manufacturing proteins.

ASBMB member Paul W. Doetsch, Professor of Biochemistry and Radiation Oncology at Emory University School of Medicine, lead author Damien Bregeon, an Emory postdoctoral fellow, and their colleagues discovered that in *E. coli* cells, two of the most frequently occurring spontaneous DNA damages that cells in all organisms are exposed to on a daily basis cause transcriptional mutagenesis (TM). TM occurs when cells with damaged DNA produce bad messages during transcription that lead to the creation of mutant proteins.

During transcription, cells make an RNA copy of the combinations of base sequences that make up the genes on the DNA molecule. This RNA copy serves as a blueprint for manufacturing particular proteins. One type of spontaneous genetic damage occurs in non-dividing cells when cytosine (C), one of the four amino-acid bases (A, T, G, and C) spontaneously changes to uracil (U). This common substitution causes genetic miscoding that can lead to TM and the manufacture of mutant proteins during transcription.

A second type of genetic damage is caused by 8-oxoguanine, another base substitution that frequently results from the formation of oxygen radicals during normal cellular metabolism.

“These base substitution errors have very important implications for the biological consequences of genetic damage in non-dividing cells,” Dr. Doetsch pointed out. “In some cases this miscoding could cause a cell to manufacture a mutant protein that controls cell division, which could take the cell from a non-growth state to a growth state and contribute to malignant transformation in the case of mammalian cells. Transcriptional mutagenesis in neurons could lead to neurodegenerative diseases.”

Scientists already have learned that some genetic damages may block the transcription process, which is a signal for DNA repair molecules to move in and correct the mistake. When the DNA repair machinery is defective, however, the non-dividing cells are capable of continuing transcription despite the erroneous coding messages.

The Emory scientists present direct evidence that mutated proteins can be manufactured through this transcription pathway. They analyzed cells that were completely normal with respect to their DNA repair mechanisms as well as cells with various components of their DNA repair machinery eliminated. For some of the damages, when the repair machinery was intact, TM was very low, indicating that the purpose of DNA repair systems in non-dividing cells is to eliminate TM, Dr. Doetsch explained.

“Not only does this research show that genetic damages are capable of causing TM, it also identifies specific components of the cellular machinery whose job it is to repair damage from uracil and 8-oxoguanine to prevent TM from occurring,” said Dr. Doetsch. “The extent to which TM might occur for different kinds of genetic damages will depend on the cells’ ability to repair damage before the transcriptional errors occur. This research also may allow us to devise explanations for physiological changes that occur in non-dividing cells exposed to damaging environmental agents.

“A number of studies, culminating in this one, show that DNA damages leading to TM are an important event that may account for the deleterious effects of unrepaired genetic damage. Although our study was in *E. coli*, very similar systems operate to repair genetic damage in human cells, thus this is a very important model for helping understand the mechanisms in non-dividing cells that can cause the manufacture of mutant proteins as a result of genetic damage to cells.”

The ASBMB Minority Affairs Committee: Past and Present

By Dr. Thomas D. Landefeld

Professional scientific societies have long represented the best collection of scientists in a given discipline. In fact, for many years, being accepted into one of these societies was somewhat similar to receiving a promotion or tenure in an academic setting as the criteria were quite stringent. Although this is not generally the case now, the societies are still comprised of what many consider the “best of the best” in their discipline.

At the same time, the membership of these professional groups has included very few ethnic minorities. With the changing face of society, this lack of diversity in scientific societies is a major concern. The ASBMB, known as the ASBC at the time, established the Committee for Equal Opportunities for Minority Groups (CEOMG) in the 1970s, designed specifically to increase the cultural diversity of scientists working in the areas of biochemistry and molecular biology, which in turn represent a large segment of researchers in the biomedical sciences arena. The mission of the CEOMG was to increase the participation, visibility and status of minorities in the Society. These goals continue to inspire the current ASBMB Minority Affairs Committee (MAC). Historically, ASBMB has had a strong group of committee members with a commitment to make a difference in the support of minority scientists, not only within ASBMB but also in the entire scientific community.

The MAC Committee, in its various names, has been through some structural changes since its inception. After

a period of time, the activities of the committee were transferred to the Outreach Task Force, which was a subgroup of the ASBMB Human Resources Committee. The Outreach group took on the task of identifying “minority affairs” needs within ASBMB and, as a result, there was once again a presence of a minority-focused session at the annual meeting. These sessions included scientific symposia as well as other important activities such as a “minority scientists” reception. However, there was still the need for a specifically-designated minority affairs committee, not only to do even more in this area, but also to demonstrate ASBMB’s true commitment to diversity. ASBMB recognized this need and re-established the MAC in 2000.

Since that time, the MAC has sponsored a panel session at each of the ASBMB Annual meetings, the last two of which have been part of the Experimental Biology Meeting. The presentations by the panelists have been very well received by a diverse audience and have been posted on the ASBMB Website. A session on “Obesity and Minority Populations” is planned for the 2004 ASBMB meeting in Boston. In addition, MAC has been involved with the minority affairs committees of other EB Societies in scheduling a joint session at the 2002 EB Meeting and again for the 2004 EB Meeting. Another important focus of MAC has been in the recruitment of minority scientists, particularly as students, to ASBMB. This effort has been facilitated by an ASBMB booth at the annual Society for the Advancement of Chicanos and Native Ameri-

cans in Science (SACNAS) Conference and the Annual Biomedical Research Conference for Minority Students (ABRCMS) as well as a discounted membership fee for the students.

The MAC now consists of five members, chaired by Phillip A. Ortiz, Area Coordinator of Math, Science and Technology at Empire State College. The other members are Juliette Bell, Professor of Natural Sciences at Fayetteville State University; Thomas D. Landefeld, Associate Dean and Professor of Biology at California State University, Dominguez Hills; K.V. Venkatachalam, Associate Professor of Biochemistry at Nova Southeastern University; and the newest member, Faith Zamamiri-Davis, Postdoctoral Research Associate at St. Jude’s Children’s Hospital.

“As a graduate student, I benefited from the travel awards and poster sessions sponsored by the MAC and am excited to be able to contribute my perspectives and experience to the committee now,” says Dr. Zamamiri-Davis. “As the first postdoctoral representative on the committee, I hope to provide representation for minority postdocs and collaborate with other members of our committee in developing new strategies to diversify ASBMB membership and target emerging young scientists.”

The re-establishment of MAC has resulted in concerted efforts to increase the participation, visibility and status of underrepresented minorities in ASBMB, and in doing so, contribute to efforts to address the overall under representation of minorities in all sciences. ❧

Steven Almo to Receive 2004

Dr. Steven Almo, of the Department of Biochemistry, Albert Einstein College of Medicine, has been selected to receive the 2004 ASBMB-AMGEN Award. This award is made to a new investigator, with no more than 15 years experience since receipt of a doctorate, for significant achievements in the application of biochemistry and molecular biology to the understanding of disease. Nominations must be originated by Society members but the nominees need not be ASBMB members. The Award consists of a silver and crystal commemorative sculpture, stipend, and transportation and expenses to present a lecture at the ASBMB Annual Meeting. Recent recipients have been Wesley Sundquist in 2003, Joan and Ronald Conaway in 2002, Tyler Jacks in 2001, Masashi Yanagisawa in 2000, and in 1999 Patrick J. Casey.

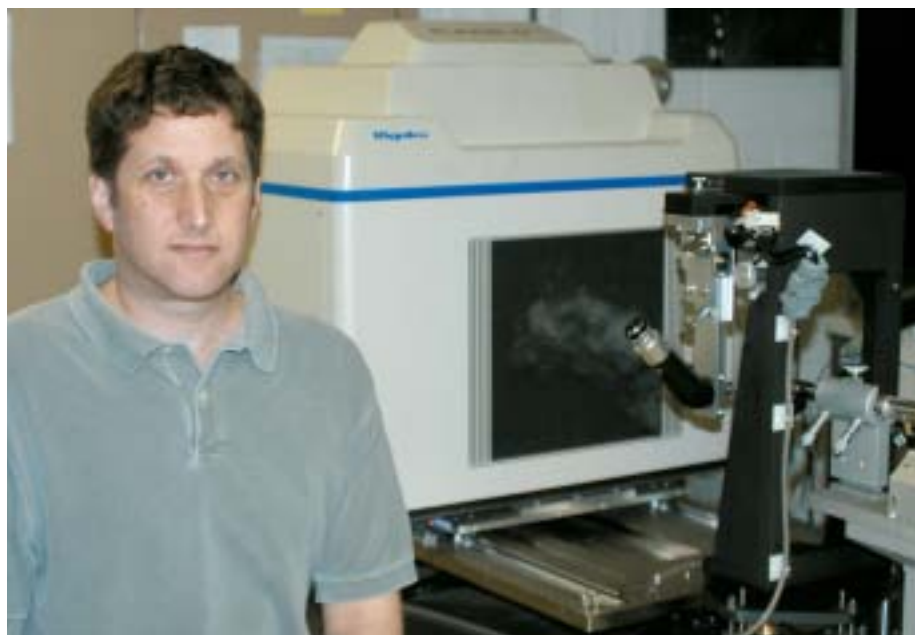
"Dr. Almo has achieved a position of world-leadership in structural biology by developing a unique program in the cytoskeleton and functional analysis of contractile and allergenic proteins," wrote Vern Schramm, Professor and Ruth Merns Chair in Biochemistry at the Albert Einstein College of Medicine of Yeshiva University. "His vision for the future is to lead an initiative for the determination of structures of cellular protein complexes. Since his appointment at the Albert Einstein College of Medicine in 1992, his research program has been a leader in the fields of the structural biology of the cytoskeleton and the structural basis for the immune response. He has been a primary investigator in the New York program in Structural Genomics."

Dr. Almo is a structural biochemist whose scientific effort and research philosophy represent the paradigm for the future of structural analysis. His focus

on problems of significance to human health is best exemplified by his recent work on the co-stimulatory molecules that modulate the T cell response of the adaptive immune response. His group solved the structures of the molecules responsible for attenuating the T cell response, including CTLA-4 and B7, as well as the receptor-ligand complex formed by these molecules. The CTLA-4/B7 complex represents the first atomic view of a co-stimulatory receptor-ligand complex, and has provided novel insights into the atomic and molecular mechanisms that modulate T cell reactivity. Based on significant sequence similarity to other T-cell proteins, this structure provides an excellent model for the stimulatory CD28/B7 and ICOS/B7H receptor-ligand complexes. In particular, this structure highlighted potential mechanisms responsible for the localization/compartimentalization of these receptor-ligand pairs and the organization of discrete complexes of signaling molecules at the T cell/APC interface.

Dr. Almo is now using these structures to produce biochemically defined receptor and ligand mutants that will ultimately be expressed in the appropriate knockout/transgenic mouse model to provide the first *in vivo* structure-function correlations for the co-stimulatory molecules. This general atoms-to-animal strategy represents one of the most powerful future uses of structural information and his approach is expected to serve as the paradigm for future structural biology studies.

His group has also recently solved the structure and characterized the ligand binding properties of PD-I, the major co-stimulatory molecule responsible for controlling peripheral tolerance. These studies indicate that PD-I operates through mechanisms that are distinct from the other co-stimulatory molecules. As these receptor-ligand pairs directly regulate T cell responsiveness (both up and down), these molecules provide the opportunity for clinical intervention to modulate the immune response for a broad range of



ASBMB-AMGEN Award winner Steven Almo.


ASBMB-AMGEN Award

human diseases, including auto-immunity, graft versus host disease, graft rejection, as well as the development of peptide-based vaccines for the treatment of cancer. Importantly, clinical trials are currently being pursued in all of these areas, highlighting the major clinical relevance of these molecules.

The second major area of work in Dr. Almo's lab is the structural and biochemical analysis of the molecules that regulate the actin cytoskeleton and contractile and motile cellular processes. He is a recognized leader in this field and has successfully solved the high resolution structure of a wide range of actin regulatory proteins including those involved in actin polymerization, actin filament severing and the proteins responsible for the bundling and crosslinking of individual filaments into higher order structures. Consistent with his atoms to animals theme, Dr. Almo has already used these structures to design *in vivo* experiments that have revealed novel

mechanistic features of cytoskeletal regulation. To pursue the structural characterization of complexes not amenable to traditional approaches, he has been closely involved in the development of a novel protein footprinting technology that is amenable to multi-component assemblies of any size and any complexity.

While the majority of Dr. Almo's *in vivo* studies have been performed in yeast, he has recently begun to generate knockout mouse models to examine the complex behavior of cytoskeletal regulatory proteins in a mammalian system. In particular, he is close to completing an inducible knockout model of *mts1*, a protein that regulates myosin filament assembly, and which is a major determinant of metastatic potential. This model system will provide a unique opportunity to examine the direct effects of mis-regulation of the acto-myosin cytoskeleton on the motile and invasive properties involved in tumor metastasis.

Dr. Almo is a national leader in NIH-sponsored structural initiatives. He is a founding member of the New York Structural Genomics Research Consortium, one of the nine NIH-funded National Centers charged with the development of a high throughput structure discovery pipeline to provide a useable model for all individual protein structures. In addition, he has taken a leadership role in organizing the National Effort on Structural Proteomics, which promises to establish the infrastructure for the large-scale structural characterization, at the EM and X-ray levels, of the multi-component protein assemblies that are the ultimate effectors of normal and pathological cellular function. This initiative will provide an unprecedented structural database that delivers unique insight into biological function and mechanism, and will serve to drive the next generation of biological and biomedical discovery. 

NIH Meeting ...


Continued from page 6

that there must be a strong emphasis on mathematical models. One critical component of future computing infrastructure, he said, will be improved access to the proper algorithms and an investment in tools that deliver better data points.

Stephen J. Katz, Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases, said, "This is an area where our institute needs help. Bones need to be better assessed for quality, not just density. There is a need to create a resource that will use computational biology to better understand fractures and how to treat them."

Lawrence Tabak, Director of the National Institute of Dental and Craniofacial Research, noted that biomedical computing enters the mouth in the form of biometric and tissue engineering approaches to restore function and form. He suggested that computational methods might help make saliva—which holds clues to everything from antibody and hormonal levels to signs of illicit drug use—a more convenient diagnostic tool. "In saliva veritas," he declared, "saliva tests can help predict the tendency for both oral and systemic diseases." He said that he envisions a massive health surveil-

lance network based on quick oral diagnostics.

At concurrent sessions on "Networked Science" and "Scientific Data Integration," participants expressed some concern about how the NIH will accomplish the data networking and integration challenges ahead. "The community needs to represent what they see in a rigorous way that's relevant and useable," meeting Cochair Richard Morris, of the National Institute of Allergy and Infectious Diseases, told *The Scientist*, "and when they collect data, the network must be much more reliable than it currently is." 

William C. Rose Award Honors Sunney Chan's Commitment to Young Scientists

The 2004 William C. Rose Award will be presented to Sunney I. Chan, Professor, Department of Biochemistry, California Institute of Technology, at the ASBMB Annual Meeting, June 12-16, in Boston. The Award recognizes outstanding contributions to biochemical and molecular biological research, and a demonstrated commitment to the training of younger scientists as epitomized by the late Dr. Rose. It consists of a plaque, a stipend, and transportation to the ASBMB Annual Meeting to present a lecture.

Dr. Chan, who for the past six years has been building the Institute of Chemistry in the Academia Sinica on Taiwan, first as Director and then as Vice President of the academy, will be honored for a career that includes a remarkable combination of research, mentoring, and community service.

His career reflects a remarkable combination of research, mentoring and community service that fulfills the objectives of the Rose Award to recognize "outstanding contributions to biochemical and molecular biological research and a demonstrated commitment to the training of younger scientists," wrote Douglas C. Rees, Professor, Division of Chemistry and Chemical Engineering at Caltech, in nominating Dr. Chan for the Award.

"Dr. Chan's research is stunning in its breadth and significance, with his most recent work emphasizing the novel application of spectroscopic and biophysical methods to the characterization of complex membrane proteins such as cytochrome *c* oxidase and the particulate methane monooxygenase,"

noted Dr. Rees. "These studies have served as the training ground for 82 Ph.D. students, 51 postdoctoral fellows, and uncounted numbers of undergraduates, who now populate the ranks of scientists in universities and industries around the world and who represent a remarkably diverse range of research interests."

Dr. Chan's most recent research interests have been broadly based in the area of physical biochemistry, with particular emphasis on bioenergetics and the structure and function of membrane proteins, magnetic resonance spectroscopy, and bioinorganic chemistry. Over the past several years he has developed a very promising approach to study protein folding using photochemical methods to rapidly initiate folding to study early folding events.

The breadth of his interests may be appreciated when you consider that after receiving his undergraduate degree in chemical engineering; he moved into physical chemistry for his graduate work on microwave spectroscopy, and then to post doctoral in physics doing molecular beam NMR studies. From this "hard-core" chemical physics background, he then moved into biophysical chemistry, where he used NMR methods to provide the first observation of base-stacking of nucleic acids in aqueous solution and to analyze the structure and dynamics of lipid bilayers.

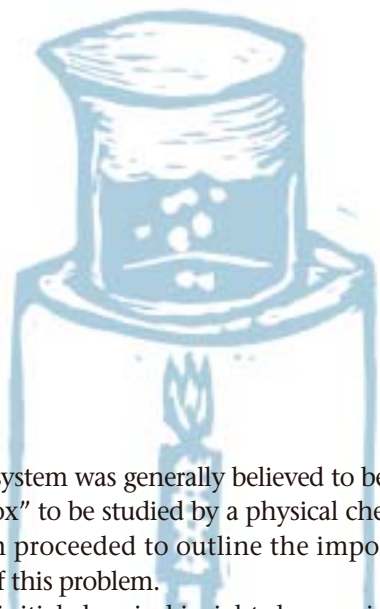
From this interest in membranes, Dr. Chan then began to shift his focus to



William C. Rose Award recipient Sunney Chan.

membrane proteins, and carried out a beautiful series of biochemical and spectroscopic studies that probed the metal center structure and proton-pumping mechanism of cytochrome *c* oxidase, with more recent efforts focused on the structure and mechanism of the copper-containing, membrane bound methane monooxygenase in methanotropic bacteria that catalyzes methane oxidation to methanol.

"When I began working with Professor Chan as a graduate student," wrote Gary Brudvig, Professor, Department of Chemistry, Yale University, "his interests were moving into the area of structure and function of membrane proteins. My work involved studies on the enzyme cytochrome *c* oxidase. When I arrived in 1976, this protein was poorly characterized chemically



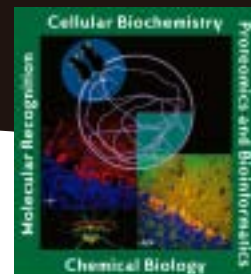
and the system was generally believed to be too much of a "black box" to be studied by a physical chemist. However, Dr. Chan proceeded to outline the important chemical aspects of this problem.

Those initial chemical insights have guided the work of Dr. Chan's group on cytochrome *c* oxidase and related systems over the past 20 years. His ideas and his group's experiment results set a high standard in this field. By combining elegant isotopic manipulation with first-rate magnetic resonance spectroscopy, Dr. Chan obtained structural information on the four metal centers that mediate electron transfers, proton pumping and O₂ reduction in cytochrome *c* oxidase. The recent publication of the x-ray crystal structure of cytochrome *c* oxidase confirmed much of the spectroscopic studies, including the bis-cysteine and bis-histidine ligation of CU_A, the histidine axial ligation of heme a₃ and the distance between heme a₃ and Cu_B.

"Dr. Chan's contributions to training future scientists go beyond his research lab," noted Lynmarie Thompson, Associate Professor of Chemistry and Molecular and Cellular Biology at the University of Massachusetts. "He enriched the life of Caltech undergraduates in many ways. Sunney was also my course advisor, and he always had time to provide guidance when I asked for it, giving me a list of laboratories to explore before choosing one for undergraduate research, a list of graduate schools to apply to, etc. But he went beyond providing excellent advice and was very generous with his time for his students, which made us feel that our lives and careers were important to him. I remember one occasion when he invited all of his advisees into his home and he cooked a full Chinese dinner for us."

"During the time that I was at Caltech," recalled Dr. Thompson, "Sunney also served as the MOSH, the Master of Student Houses. This is an incredibly time-consuming job providing support and encouragement for Caltech undergraduates who, as you can imagine, can be very intense individuals! Sunney again gave generously to this role, fulfilling needs ranging from the very serious job of counseling students through extreme personal difficulties, to the lighter job of participating in Caltech social functions." ☺

ASBMB TRAVEL AWARDS AVAILABLE!



"A Molecular Exploration of the Cell"
ASBMB Annual Meeting
and 8th IUBMB Conference
June 12 - 16, 2004
Boston, Massachusetts

ASBMB Graduate Minority Travel Awards

The ASBMB has been awarded a grant through the Minority Access to Research Careers (MARC) program, administered by the National Institute of General Medical Sciences, NIH, to support a portion of the expenses of minority graduate students to attend the ASBMB/IUBMB 2004 Meeting in Boston. A special scientific session will be held Monday evening, June 14, 2004 in which all recipients of this award must present a poster. Several awardees may also be chosen to make short oral presentations in this session. Applicants must be members of a minority group currently under-represented in science (i.e., African American, Hispanic American, Native American, or Pacific Islander). An applicant must submit an abstract to be presented at the meeting. Successful applicants will be reimbursed up to \$1,000 for their expenses. Only U.S. citizens or permanent residents qualify for the award. Students already funded by the MARC Program are not eligible.

ASBMB Graduate or Postdoctoral Travel Awards

Fellowships are available to assist graduate or postdoctoral fellows attending the ASBMB/IUBMB 2004 Meeting in Boston. Applicants must submit an abstract to be presented at the meeting. A special scientific session will be held Monday evening, June 14, 2004 in which all recipients of this award must present a poster. Several awardees may also be chosen to make short oral presentations in this session. U.S. residency is not required for this award. Successful applicants will be reimbursed up to \$750 for their expenses and the advanced registration fee.

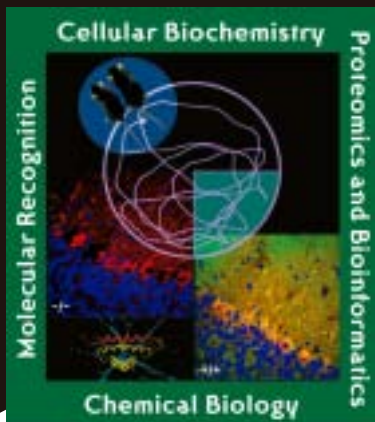
ASBMB Undergraduate Travel Awards

Funds are available to assist undergraduate students participating in the Undergraduate Poster Competition on Monday evening, June 14, 2004 during the ASBMB/IUBMB 2004 Meeting in Boston. The undergraduate student must be the first author of the poster. U.S. residency is not required for this award. Spring 2004 college graduates are eligible. Applicants may receive up to \$300 to defray their expenses. Registration for undergraduates is free and available on-site.

ASBMB Undergraduate Faculty Travel Awards

The ASBMB will award 20 travel fellowships of \$500 each. The fellowships, awarded competitively, are for faculty at undergraduate institutions who are primarily involved in undergraduate teaching at institutions which have limited travel resources. In order to receive funding, all recipients are required to return a brief survey after attending the ASBMB/IUBMB 2004. U.S. residency is not required for this award.

Applications available on-line at
www.faseb.org/meetings/asbmb04
Applications are due January 23, 2004.



REGULATION OF GENE EXPRESSION AND CHROMOSOME TRANSACTIONS MEETING

Organized by **Joan W. Conaway**,
Stowers Institute for Medical Research

PLENARY LECTURE:

How checkpoints respond to replication perturbations
Teresa S. Wang, *Stanford Univ. Sch. of Med.*

"A Molecular Exploration of the Cell"
**ASBMB Annual Meeting
and 8th IUBMB Conference**
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Boston, Massachusetts

DNA Replication

Replication initiation and cell-cycle control in mammalian cells.

Chair, Anindya Dutta, *Univ. of Virginia*

DNA replication and genome stability: Lessons from budding yeast

John F.X. Diffley, *Cancer Res.UK London Res. Inst.*

Selection, activation and regulation of eukaryotic origins of replication

Stephen P. Bell, *MIT*

Transcription Networks

Using chromatin immunoprecipitation coupled with genomic microarrays to identify target genes for human transcription factors

Chair, Peggy J. Farnham, *Univ. of Wisconsin-Madison*

Michael Cole, *Princeton Univ.*

Michael Snyder, *Yale Univ.*

Transcription Regulatory Mechanisms

Dynamics of RNA polymerase II transcription

Chair, Marc Timmers, *Univ. Med. Ctr.-Utrecht, The Netherlands*

Mapping protein-protein interactions in the transcription preinitiation complex using photocrosslinking and artificial proteases

Steve Hahn, *Fred Hutchinson Cancer Res. Ctr.*

Analysis of the mechanisms of regulation of yeast RNA polymerase II transcription

Tony Weil, *Vanderbilt Univ.*

Chromatin Dynamics

Histone modifying complexes that regulate transcription

Chair, Jerry Workman, *Stowers Inst. for Med. Res.*

Functional analysis of complexes that modulate chromatin structure and regulate transcriptional memory

Robert E. Kingston, *Massachusetts Gen. Hosp., Harvard Med. Sch.*

From nucleosome to heterochromatin, their formation and maintenance

Genevieve Almouzni, *Institut Curie*

Signaling to the Nucleus

Nuclear retinoid receptor phosphorylation and transduction of the retinoid signal

Chair, Cecile Rochette-Egley, *Strausbourg*

STAT3: Transcriptional control studies and cancer therapy

James E. Darnell, Jr., *The Rockefeller Univ.*

Chromatin modification and rapid gene induction

Louis C. Mahadevan, *Oxford Univ.*

Additional Speakers will be chosen from the abstracts submitted to the ASBMB Regulation of Gene Expression and Chromosome Transactions topic categories.

Travel Awards Available for Undergraduates, Graduates, Postdoctoral Fellows and Undergraduate Faculty

More Information:

ASBMB Meetings Office

9650 Rockville Pike

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Tel: 301-634-7145

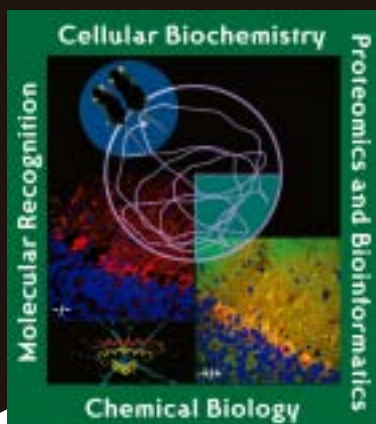
Fax: 301-634-7126

Email: asbmb@asbmb.faseb.org

www.asbmb.org

www.faseb.org/meetings/asbmb04

Abstract Deadline: February 11, 2004



"A Molecular Exploration of the Cell"

**ASBMB Annual Meeting
and 8th IUBMB Conference**

June 12 - 16, 2004

Boston, Massachusetts

Additional Speakers will be chosen from the abstracts submitted to the ASBMB Genomics, Proteomics and Bioinformatics topic categories.

Travel Awards Available for Undergraduates, Graduates, Postdoctoral Fellows and Undergraduate Faculty

More Information:

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GENOMICS, PROTEOMICS AND BIOINFORMATICS MEETING

Organized by **Charlie Boone**, *Univ. of Toronto*
and **Michael Snyder**, *Yale Univ.*

Orfeomics and Interaction Networks

Chair, Charlie Boone, *Univ. of Toronto*

Michael Snyder, *Yale Univ.*

Marc Vidal, *Dana Farber Cancer Inst.*

Brenda J. Andrews, *Univ. of Toronto*

Macromolecular Machines

Chair, Brian Chait, *Rockefeller Univ.*

Proteomic and genetic dissection of the yeast transcription apparatus

Jack Greenblatt, *Univ. of Toronto*

Phosphoproteome

Chair, Kevan Shokat, *UCSF*

Donald F. Hunt, *Univ. of Virginia*

Direct imaging and profiling of proteins in tissues using mass spectrometry to aid diagnosis and treatment of disease and to identify therapeutic targets

Richard Caprioli, *Vanderbilt Univ.*

Bioinformatics: Comparative Genomics

Claire Fraser, *Inst. for Genomic Research, Rockville, MD*

Amos Bairoch, *Swiss Inst. of Bioinformatics*

Ford Doolittle, *Dalhousie Univ., Nova Scotia*

Proteomics and Medicine

Proteomic and functional genomics in translational breast cancer research

Chair, Julio Celis, *Danish Cancer Society*

Molecular pathway analysis in cancer using proteomics

Sam Hanash, *Univ. of Michigan*

Steven A. Carr, *Millennium Pharmaceuticals, Inc.*

Bioinformatics and Networks

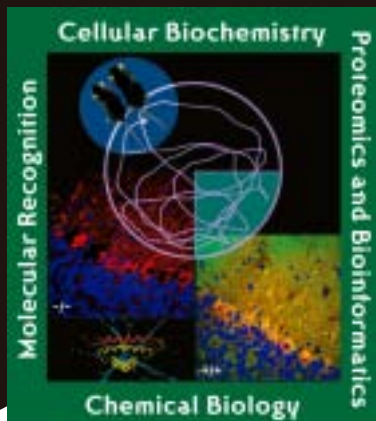
Chair, David Eisenberg, *UCLA*

Mark B. Gerstein

David Sabatini

www.faseb.org/meetings/asbmb04

Abstract Deadline: February 11, 2004



"A Molecular Exploration of the Cell"
**ASBMB Annual Meeting
and 8th IUBMB Conference**
June 12 - 16, 2004
Boston, Massachusetts

Additional Speakers will be
chosen from the abstracts
submitted to the ASBMB
Protein Structure, Catalysis and
Dynamics topic categories.
Abstract deadline: 2/4/04

Travel Awards Available for
Undergraduates, Graduates,
Postdoctoral Fellows and
Undergraduate Faculty

More Information:
ASBMB Meetings Office
9650 Rockville Pike
Bethesda, MD 20814
Tel: 301-634-7145
Fax: 301-634-7126
Email: asbmb@asbmb.faseb.org
www.asbmb.org

PROTEIN STRUCTURE, CATALYSIS AND DYNAMICS MEETING

Organized by **Susan Taylor, UCSD**

PLENARY LECTURE

Site-Directed Drug Discovery

James A. Wells, Sunesis Pharmaceuticals, Inc., S. San Francisco

Molecular Assemblies I

Chair, **Mike Rosen, Univ. of Texas, Southwestern**

Eva Nogales, HHMI, UC, Berkeley

Peter E. Wright, Scripps Res. Inst.

Jamie Williamson, Scripps Res. Inst.

Molecular Assemblies II

Chair, **Mike Rosen, Univ. of Texas, Southwestern**

Katryn Rittinger, NIMR, MRC, London

Dynamics of Catalysis I

Chair, **T.K. Harris, Univ. of Miami Med. Ctr.**

Joseph A. Adams, UCSD

Lewis E. Kay, Univ. of Toronto

Dynamics of Catalysis II

Chair, **Rowena G. Matthews, Univ. of Michigan**

John Kuriyan, UC, Berkeley

Joseph T. Jarrett, Univ. of Pennsylvania

David Barford, Inst. of Cancer Res., London

Ligand-Receptor Dynamics

Chair, **Heidi Hamm, Vanderbilt Univ.**

Andrew Hincks, Univ. of Texas, San Antonio

Kathryn M. Ferguson, Univ. of Penn Sch. of Med.

John J.G. Tesmer, Univ. of Texas at Austin

Tethering and Targeting of Proteins

Chair, **Lewis C. Cantley, Beth Israel Deaconess
Med. Ctr.**

Benjamin J. Neel, Beth Israel Deaconess Med. Ctr.

Michael Yaffe, MIT

www.faseb.org/meetings/asbmb04

Abstract Deadline: February 11, 2004

Cancer Biologists and Cardiologist Take New Look at Aggressive Tumors

Collaboration between a University of Iowa cardiologist and cancer biologists at the University's Holden Comprehensive Cancer Center, the Scripps Research Institute in California, and Kanagawa Cancer Center Hospital and Research Center in Japan utilized a multidisciplinary approach to learn more about how aggressive cancer cells function and how they differ from poorly aggressive cancer cells. The study, which appeared in the September 1, 2003, issue of *Cancer Research*, may also suggest potential new therapeutic targets for cancer treatment.

Previous studies had found that aggressive tumor cells express genes that are more normally associated with other cell types, including endothelial cells that line blood vessels. Also, aggressive cancer cells are able to form vascular-like, fluid-conducting networks, an ability known as vasculogenic mimicry that resembles the behavior of embryonic cells that form primitive vascular networks. Tumors that have fluid-conducting networks are much more aggressive than tumors that do not have those networks.

The study focused on a few of the genes that are expressed by aggressive, but not by poorly aggressive, tumor cells. These genes normally are involved in regulating anticoagulant, or blood-clotting, activity in endothelial cells. The study suggests that the expression of these genes by aggressive tumor cells provides the cells with anticoagulant capabilities that are similar to those in blood vessel cells.

"Essentially our observations indicated that the aggressive melanoma tumor cells behaved in a similar manner as do endothelial cells that form blood vessels," said Mary Hendrix, the

Kate Daum Research Professor of Anatomy and Cell Biology and Department Head, who is an ASBMB member and former FASEB President.

The finding that tumor cells have anticoagulant properties similar to endothelial cells prompted the researchers to analyze whether there was blood flow within these tumors in extravascular spaces lined by tumor cells.

University of Iowa Cardiologist Robert Weiss, Associate Professor of Internal Medicine, used Doppler imaging to ana-




Dr. Mary Hendrix

lyze blood flow within tumors. The researchers saw an exchange of blood from the normal vasculature (blood vessels) at the periphery of the tumor through tumor-cell-lined extravascular spaces within the aggressive tumor.

Although the precise role of the extravascular intra-tumoral network remains unclear, one possibility might be that the meshwork may provide a nutritional exchange for aggressive tumors that might prevent cell death within the tumor.

The observation that aggressive tumor cells over-express key anticoagulation pathway genes may help to explain how blood could flow through aggressive tumors prior to the growth of new blood vessels within the tumor compartment.

"This is yet another example of the plasticity of aggressive melanoma tumor cells in that they can mimic other cell types, such as endothelial cells, and our study provides a mechanistic example of how they do it," Dr. Hendrix said. She added that this

"chameleon-like" ability of aggressive tumor cells raises some clinically important issues. "This plasticity represents a clinical challenge in trying to detect aggressive tumor cells, but it also provides new insights on how we might target them more effectively." 

ASBMB Welcomes New Ph.D.s

ASBMB extends its congratulations to these individuals who recently received their Ph.D. degrees. In recognition of their achievement, ASBMB is presenting them with a free one-year membership in the Society. The new Ph.D.s are listed below with the institution from which they received their degree.

Stephane Angers,
University of Montreal

Christina R. Bourne,
University of Oklahoma Health Sciences Center

Suresh Guruswamy,
University of Oklahoma Health Sciences Center

Shalaka Metkar,
University of Mumbai, India

Michael A. Morgan,
Hannover Medical School

Oluwakemi Obajimi,*
UHI Millennium Institute in the United Kingdom

Devon Taylor,
The Graduate Center, City University of New York

Li Zhang,
The Graduate School, City University of New York

**Candidates with an asterisk were previous Associate members who met the requirements for a free one-year membership.*

Enzyme Revealed as Key to Fungus's Ability to Breach Immune System

A newly discovered mechanism by which an infectious fungus evades the immune system could lead to novel methods to fight the fungus and other disease-causing microbes, according to Howard Hughes Medical Institute investigators at Duke University Medical Center.

Disruption of a key enzyme in the fungus *Cryptococcus neoformans*, a common cause of infection of the central nervous system in patients such as organ transplant recipients who lack a functioning immune system, led to a significant loss of fungal virulence in mice. That loss stemmed from the fungus's inability to launch a counterattack against components of the innate immune system.

The Duke-based team led by HHMI geneticist and ASBMB member, Joseph Heitman, Director of Duke's Center for Microbial Pathogenesis, and HHMI biochemist Jonathan Stamler, also an ASBMB member, reported their findings in the November 11, 2003, issue of *Current Biology*. The work was funded by the National Institutes of Allergy and Infectious Diseases and the Burroughs Wellcome Fund.

The "fungal defense" enzyme, flavohemoglobin, which catalyzes the oxidation of NO to nitrate is prevalent among many bacterial and fungal pathogens, and Dr. Heitman

noted that the findings in *Cryptococcus* are likely relevant to other infectious microbes. New drugs that target these enzymes might therefore represent effective treatments for a wide range of infectious diseases, he added.

The human immune system uses a two-pronged mechanism to fight infection: a rapid innate response and



Dr. Jonathan Stamler



Dr. Joseph Heitman

a slower adaptive response that depends on the production of antibodies. Key components of the innate immune system are macrophages that engulf and kill invading pathogens by using a combination of oxidants, including hydrogen peroxide, nitric oxide and related molecules.

"The body must rely on macrophages of the innate immune system to protect itself before the adaptive immune system can respond to invasion," Dr. Heitman noted. "While much is known about how pathogens defend themselves against hydrogen peroxide produced by the macrophages, this study is the first biologically relevant test of what microbes do to counteract nitric oxide and promote infection."

The researchers found that a mutant *C. neoformans* strain lacking the flavohemoglobin enzyme failed to break down nitric oxide in laboratory cultures. Fungus with the enzyme deficiency also ceased to grow when in the presence of nitric oxide, whereas ordinary fungus survived normally.

Mice infected with the flavohemoglobin-deficient *C. neoformans* survived for five days longer than those infected with the normally virulent strain. In contrast, the normal and mutant fungal strains were equally virulent in mice whose immune cells could not produce nitric oxide, the team reported.

The mutant fungus also failed to grow normally in laboratory dishes containing macrophage cells, further implicating the innate immune system in the loss of virulence exhibited by fungi lacking flavohemoglobin.


Dr. Stamler reported, "We found that a mutant *C. neoformans* strain lacking the flavohemoglobin enzyme failed to break down nitric oxide in laboratory cultures. Fungus with the enzyme deficiency also ceased to grow when in the presence of nitric oxide, whereas ordinary fungus survived normally. A second enzyme, S-nitrosoglutathione (GSNO) reductase, also had a protective role. Thus both NO and GSNO are evidently produced by the mammalian host to fight infection"

"By disabling either the fungal nitric oxide defense system or the immune system's ability to produce nitric oxide, we were able to tip the balance one way or the other, in favor of the fungal infection or the host," Dr. Heitman explained. "That raises the possibility that we could treat infectious disease with drugs that either inhibit fungal defense enzymes or increase the innate immune system's ability to mount a nitrosative attack."

"The production of nitric oxide and other nitrosants serves as both

an immediate early innate immune defense mounted prior to adaptive immunity, and likely also functions in aspects of controlling infections during long term latency for facultative intracellular pathogens,” he added. “Our work reveals for the first time in a true physiological context the role of specific enzymatic defenses in a ubiquitous human pathogen.

“Specifically, the enzymes flavo-hemoglobin denitrosylase and S-nitrosoglutathione reductase were shown to promote fungal virulence, and to act specifically in defense against nitrosative challenge. We expect this to be a broadly deployed pathogenic defense mechanism, and to play central roles in virulence in bacteria, fungi, and parasites.

“These findings raise the possibility of enhancing the host production of nitrosative stress as an adjunct to antimicrobial therapy and there has been a report in the *Lancet* (February 22, 2003) that low arginine levels, the metabolic precursor in NO production, are correlated with increased severity and risk of cerebral malaria in children in Africa. Thus, even simple diet supplementation might have an impact on the course of infectious disease, as is known to be the case with vitamin A supplementation and risk of death from measles infection. The importance of our findings is to provide insight into the physiological functions of this broadly conserved family of NO detoxifying enzymes, specifically in a role during infection by a common pathogenic fungus, *Cryptococcus neoformans*.” 


Mathematical Modeling Predicts Cellular Communication

From the moment its life begins, the fate of a multicellular organism depends on how well its cells communicate. Proteins act as molecular switchboard operators to keep the lines of communication open and the flow of cellular messages on track. But charting the protein interactions, signaling pathways, and other elements that regulate these networks is no small feat. There are many players that interact in complicated ways. Furthermore, these efforts have been hampered by the lack of quantitative data—measurements of signal duration, amplitude, and fluctuation—on these regulatory pathways.

In a combination of mathematical modeling and precise quantitative measurements, ASBMB member Marc Kirschner, of Harvard Medical School, and Reinhart Heinrich, of Humboldt University, Berlin, and colleagues focused their efforts on a well-studied signaling pathway, the Wnt pathway, which plays a role both in various stages of embryonic development and in carcinogenesis. Like most signaling pathways, Wnt is highly conserved. Consequently, developing tools that elucidate the Wnt pathway not only provide insights into this important pathway but have implications for understanding communication pathways in animals from jellyfish to humans.

In order to develop their model, the researchers needed to know the concentrations of the various signaling components. When they measured the concentrations of the principal scaffold proteins (which bring other components in a pathway together by

providing an interaction surface), axin and APC, they found that these two proteins were present in dramatically different concentrations, with axin at very low levels relative to the other signaling components and APC at similar concentrations to other signaling components. With this information in hand, and after refinements based on additional experiments, they were able to develop a model that could not only simulate the behavior of the main players in the pathway—with or without a Wnt signal—but which also suggested why the two scaffold proteins are present in different concentrations. The low level of axin here may help the pathways retain their modularity, preventing the Wnt pathway from interfering with the other pathways.

These findings demonstrate that modeling can offer powerful new insights into the workings of complex signaling systems, cutting through the static to pick up important signals even in those pathways that are well understood. The results have important implications for developmental biology and human disease. The Wnt pathway is often activated during carcinogenesis. Mutations in several of these signaling proteins have been linked to colon cancer, which suggests that cancer can develop when signals in the Wnt circuitry somehow get crossed. By predicting how quantitative factors may influence the behavior of signaling networks, mathematical models such as this could shed light on the role that breakdowns in cellular communication play in carcinogenesis. 

Bone Marrow Fusion With Nerve

Bone marrow cells can fuse with specialized brain cells, possibly bolstering the brain cells or repairing damage, according to research from the Stanford University School of Medicine. Whether stem cells can be reprogrammed or not is the subject of some controversy. Marked cells can be found in various organs after transplantation, and there is a need to know whether they have differentiated into cells characteristic of that tissue, or fused with preexisting cells there.

Do adult stem cells transform from bone marrow cells into other cell types, such as brain, muscle or liver cells, or do they fuse with those cells to form a single entity with two nuclei? This question has been at the heart of

an ongoing debate, the answer to which has major implications for the potential use of certain stem cell types in tissue repair and gene therapy. This research shows that for complex brain cells called Purkinje cells, fusion is the normal pathway.

ASBMB member Helen Blau, the Donald E. and Delia B. Baxter Professor of Pharmacology, said the next step is to learn under what circumstances bone marrow cells fuse with Purkinje cells. "If you know what those signals are, you could deliver the signal to damaged tissue and recruit the body's own bone marrow cells to treat disease." She hopes these recruited bone marrow cells may be a way of repairing damage caused by

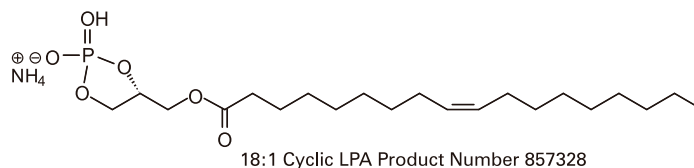
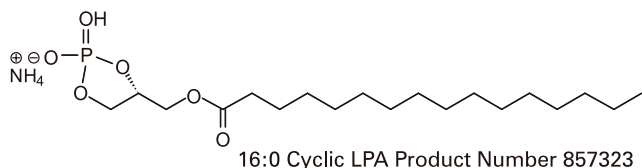
injury, stroke or such illnesses as Parkinson's disease.

Dr. Blau had previously shown that transplanted bone marrow cells can wind their way up to the brain in humans where they take on characteristics of Purkinje cells—large cells in the part of the brain that controls muscular movement and balance. She had also shown that mature cells in a lab dish can fuse with other cell types and take on characteristics of those cells.

In her most recent work, published in the October 16, 2003, issue of *Nature Cell Biology*, Dr. Blau showed that the bone marrow cells in mice fuse with existing Purkinje cells and activate genes normally made in Purkinje cell nuclei.

"I think that fusion might be a really

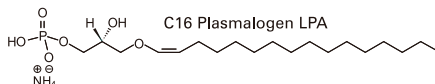
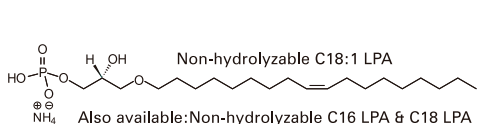
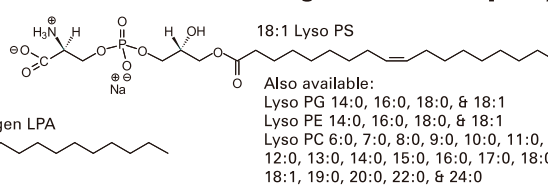
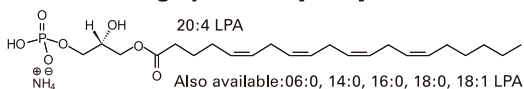
Synthetic Cyclic LPA's - another first for Avanti



A novel bioactive lipid, cyclic phosphatidic acid (cPA), was isolated originally from myxoamoebae of a true slime mold, *Physarum polycephalum*, and has now been detected in a wide range of organisms from slime molds to humans. It has a cyclic phosphate at the sn-2 and sn-3 positions of the glycerol carbons, and this structure is absolutely necessary for its activities. This substance shows specific biological functions, including antimetastatic regulation of the cell cycle, regulation of actin stress fiber formation and rearrangement, inhibition of cancer cell invasion and metastasis, regulation of differentiation and viability of neuronal cells, and mobilization of intracellular calcium. Although the structure of cPA is similar to that of lysophosphatidic acid (LPA), its biological activities are apparently distinct from those of LPA. In the present review, we focus mainly on the enzymatic formation of cPA, the antimetastatic regulation of the cell cycle, the inhibition of cancer cell invasion and metastasis, and the neurotrophic effect of cPA.

Murakami-Murofushi, K., A. Uchiyama, Y. Fujiwara, T. Kobayashi, S. Kobayashi, M. Mukai, H. Murofushi, and G. Tigyi. (2002). Biological functions of a novel lipid mediator, cyclic phosphatidic acid. *Biochim Biophys Acta* 1582:1-7.

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Cells May Repair Brain Damage


important biological mechanism,” explained Dr. Blau. She said researchers previously considered fusion to be less medically important than the idea that bone marrow cells may be able to change fates entirely, but she disagrees with that assessment. “Fusion might be a sophisticated mechanism for rescuing complex damaged cells,” Dr. Blau stated.

She and senior research scientist Dr. James Weimann transplanted mice with bone marrow cells that had been genetically altered to produce a fluorescent green protein. Over the course of the next 18 months (75 percent of a

mouse’s life span) they looked for signs of fluorescent green cells in the animals’ brains.

Over time, the group found an increasing number of Purkinje cells that glowed green under a microscope. Looking closely at these cells, they found two nuclei—one from the original Purkinje cell and one from the fused bone marrow cell. They also found that the compact nucleus of the bone marrow cell expanded over time to take on the appearance of the more loosely packed Purkinje cell nucleus.

The bone marrow nucleus in the fused cell also acts like a Purkinje cell nucleus, they found. When the group transplanted mice with bone marrow cells that only glow green when Purkinje cell genes are active, they found normal-looking Purkinje cells that glowed green. This showed that the bone marrow cells had fused with Purkinje cells and activated Purkinje cell genes.

Other Stanford researchers who participated in the study include postdoctoral scholar Clas Johansson and research associate Angelica Trejo. 

Study Of Primitive Life Form May Provide Clues To Biological Processes In Higher Organisms

Primitive microorganisms provide important clues as to how all creatures employ a basic regulatory mechanism to conduct the business of life. ASBMB member Peter Kennelly, Professor of Biochemistry at Virginia Polytechnic Institute, is studying a primitive organism discovered in acidic hot springs at Yellowstone National Park to find clues about that mechanism in higher organisms. A \$400,000 NSF grant supports Dr. Kennelly’s investigations into the process of protein phosphorylation.

In higher organisms, thousands of phosphorylated proteins are linked together in networks that coordinate the multiple chemical events that take place inside each cell and modify these processes in response to changes in the environment.


While the great size of these networks provides them with a high capacity to process a broad spectrum of environmental factors and select appropriate responses, it also renders

them difficult to study, Dr. Kennelly said. Microorganisms carry out many of the same basic processes as higher organisms, but they do so with a much smaller set of molecular machinery.

“If you consider living cells to be a molecular puzzle, a microorganism puzzle contains from 10 to as many as 100 times fewer pieces than the human puzzle,” Dr. Kennelly said. “Solving the first puzzle will be much faster than the second. More importantly, the parallels between microbial and human puzzles mean that completing the first puzzle will make solving the second one easier and faster.”

The Kennelly lab is studying *Sulfolobus solfataricus*, an extremophile from the Archaea. Extremophiles live in conditions far more stressful than other life forms can endure.

Dr. Kennelly and his students aim to identify the proteins that are controlled by phosphorylation in *Sulfolobus solfataricus*, the protein

kinases that are responsible for phosphorylating them, and the protein phosphatases that remove the phosphate groups. The project will utilize a variety of approaches, including genomics, enzymology, molecular biology and mass spectroscopy. Ultimately, he hopes to not only identify all the pieces in the phosphorylation network, but to also dissect the functional relationships between them. The end product will be a molecular map that can be used as a guide to the solving the more complex systems in more biologically complicated organisms. 

Correction

On page 20 of the November issue the recipients of the 2002 ASBMB-Merck Award were erroneously identified as Dr. Robert G. Roeder and Dr. Robert D. Kornberger. It was Dr. Roger D. Kornberg, and not Robert D. Kornberger, who shared the 2002 award with Dr. Roeder.

by John D. Thompson, Editor

Britain Maps Plans for Biotech Innovation

Britain as a global leader in the bioscience industry is the vision of a report issued in mid-November of last year by a consortium of the UK government and the country's BioIndustry Association (BIA).

The report, *Biotech Innovation and Growth (BIGT)*, is the result of a seven-month project launched by Lord Sainsbury, Parliamentary Under Secretary of State for Science and Innovation, and Lord Hunt, then a Minister at the Department of Health, in partnership with the BioIndustry Association (BIA). The mandate of the BIGT was to take a strategic approach to the future of the bioscience industry in the UK.

The BIGT's vision is that by 2015 the UK will have secured its position as a global leader in bioscience. This means the nation will boast: a diverse, self-sustaining bioscience sector, with a core of large, profitable companies; the most efficient and effective setting for conducting clinical trials in the world; and a healthcare system, regulatory regime and business environment that support bioscience innovation.

The report envisions two significant benefits for the UK in achieving this vision:

Improved national health, through improved clinical performance and early access to innovative medicine.

Increased national wealth: enhanced Gross Domestic Product by maintaining and supporting a high growth, high margin, high value-added, knowledge-based industry.

The UK is currently number two in the global bioscience industry, after the

United States. The UK biotech sub-sector includes over 400 companies, employing over 25,000 people and generates revenues of £3 billion. The UK industry also has what it regards as an impressive number of drugs in its pipeline with 194 in development and 23 in phase III clinical trials.

Among other recommendations, the BIGT report advises establishing a national clinical trials agency in the

United Kingdom to allow collaboration between the National Health Service and industry. It also calls for supportive regulations particularly for drug development, appropriate funding, and a sufficient supply of scientists. The group also advised the government to establish a network of bioprocessing centers of excellence across the United Kingdom to develop the biomanufacturing sector.

Cumbre, University of Wisconsin Publish Data on Bacterial RNA Polymerase Inhibitor

Cumbre Inc., a privately held biopharmaceutical company, announced the publication of a research paper in the October 24, 2003, issue of *Science* entitled "A new class of bacterial RNA polymerase inhibitor affects nucleotide addition." The paper describes the identification and characterization of the "CBR703" class of inhibitors through combined efforts in biochemistry, genetics and structural modeling with contributions from both Cumbre researchers and scientists from the University of Wisconsin-Madison.

Co-author Robert Landick, Ph.D., an ASBMB member and Professor of Bacteriology at the University of Wisconsin-Madison, whose laboratory is primarily focused on studies of regulatory mechanisms that control gene expression in bacteria, commented, "The Cumbre RNA polymerase inhibitors are a major breakthrough. They give us a power-

ful new tool to study the mechanism of the central enzyme in the process of gene expression. At least as importantly, they also hold great promise for the development of new antibiotics that target bacterial pathogens, which is now a high-priority need in both medicine and bio-defense."

A. Simon Lynch, Ph.D., Cumbre's Director of Research, added, "We are excited about the development potential of the CBR703 series, and are pleased to be able to contribute to the RNA polymerase research community through provision of a novel experimental tool. We hope that ongoing efforts to determine high resolution X-ray structures of RNA polymerase-inhibitor complexes will both aid Cumbre's antibiotic development program and yield additional insight regarding the fundamental processes underlying the transcription elongation cycle."

Genentech Exec Says Stock Option Expensing May Harm Small Companies

During testimony November 12 before the Senate Subcommittee on Securities and Investment, Walter K. Moore, Vice President for Government Affairs at Genentech Inc., said that proposed accounting rules mandating that companies expense employee stock options will be detrimental to biotechnology firms—particularly small, biotech start-up companies, which often use stock options as an enticement for employee recruitment.

Under current accounting standards, companies are permitted but are not required to expense employee stock options. The Financial Accounting Standards Board (FASB), however, is considering a proposal that would require all companies to expense the options.

Such a proposal would “greatly impact all companies that use broad-

based employee stock options without providing investors with consistent, comparable and reliable financial information,” Moore stated in testimony submitted to the Senate panel.

Proponents of the proposed changes in the FASB accounting standards argue that stock option expensing will provide investors with a clearer understanding of a company’s financial health. However, Genentech’s position

is that the proposal would seriously hinder small, start-up biotechnology companies, which frequently offer stock options as part of an employee’s overall compensation package

Moore told Senate panel members that existing problems with current option valuation methods applied by the FASB must be addressed or new models must be developed before wide scale accounting changes are implemented.

Creating Biobased Plastics from Corn

Creating environmentally friendly plastics, fibers and films from a corn byproduct is one focus of a new research project between South Dakota State University (SDSU), Iowa State University (ISU), and Midwest Grain Processors Corp., an ethanol company.

The study is funded by a \$1 million joint grant from the U.S. Department of Agriculture and the Department of Energy. Approximately half of the grant goes to SDSU, and the rest to ISU. The project is one of only 19 selected for funding from among 400 applications.

Associate Professor of Agricultural and Biosystems Engineering James Julson, SDSU coordinator for the sub-contract, said the goal is to develop value-added products from distillers’ dried grains (DDG), a byproduct from the production of ethanol from corn.

“Development of value-added products from DDG is crucial to the future profitability of the ethanol industry,” he explained. “There are potentially high-value oils and proteins which are not converted to ethanol by the yeast. They may provide beneficial nutrition or health benefits for humans.”

The two-year research project calls for first extracting those high valued oils and proteins from the DDG. Scientists then will use thermal gasification on the remaining DDG product to produce “syngas,” a mixture of carbon monoxide and hydrogen. That syngas serves as feedstock for anaerobic fermentation in which microorganisms feed on the carbon monoxide to produce the biopolymer polyhydroxyalkonates, or PHAs, which have potential applications in the manufacture of degradable plastics, synthetic fibers and films.

Euros Missing

The € symbol for euros was inadvertently dropped from the article “Germany Pumps Extra Funding into Biotech Firms” in the December issue of *ASBMB Today*. The € should have appeared before expenses in euros which should have read as, for example: Federal Minister of Education and Research Edelgard Bulmahn announced a commitment to spending an extra €100 million (\$117 million) on the sector in the next four years, with the money being directed to small- and medium-sized biotech companies.

Calendar of Scientific Meetings

FEBRUARY 2004

Second International Conference on Ubiquitin, Ubiquitin-Like Proteins, and Cancer

February 5-7 • University of Texas M. D. Anderson Cancer Center, Houston

To allow for the optimal exchange of ideas, the conference will be limited to 175 attendees, who will be selected based on past contributions and/or newly developed interests in this field. In addition to the invited speakers, all attendees are encouraged to present posters and some will be invited to present them at the podium. Due to the limited number of attendees, you are encouraged submit online applications prior to the November 15, 2003 deadline. Contact: Amy Heaton; Ph: 713-745-6826 email: aheaton@mdanderson.org; website: <http://www.sentrin.org>

Biophysical Society 48th Annual Meeting

February 14-18 • Baltimore, Maryland

Abstract Deadline: October 5, 2003

Early Registration Deadline: December 12, 2003

Ph: 301-634-7114; Fx: 301-634-7133

Website: <http://www.biophysics.org/annmtg/site-index.htm>

50th Anniversary Gordon Conference on Isotopes in Biological and Chemical Sciences

February 15-20 • Ventura, California

Chair: David N. Silverman, Vice Chair: Charles L. Perrin

Email: silvrnmn@ufl.edu

Website: <http://www.grc.org/programs/2004/isotopes.htm>

The 1st Gordon Research Conference on The Biology of 14-3-3 Proteins

February 22-27 • Ventura, California

Chairs: Haiyan Fu & David Klein, Vice-Chair: Alastair Aitken

Email: hfu@emory.edu

Website: <http://www.grc.org/programs/2004/14-3-3.htm>

Association for Biomolecular Resource Facilities 2004 Annual Meeting

February 28-March 2 • Portland, Oregon

Abstract Deadline: November 21, 2003

Early Registration Deadline: January 16, 2004

Ph: 301-634-7010; Fx: 301-634-7014; Email: marcella@faseb.org

Website: www.faseb.org/meetings/abrf2004

MARCH 2004

Oxygen Club of California 2004 Congress

Co-sponsored by the Linus Pauling Institute and the Society of Free Radical Research International

March 10-13 • Santa Barbara, California

Contacts: Enrique Cadenas (cadenas@usc.edu); Lester Packer (packer@usc.edu); Website: <http://www.oxyclubcalifornia.org>

APRIL 2004

7th International Conference on Plasma Membrane Redox Systems and their Role in Biological Stress and Disease

April 14-17 • Asilomar State Park and Conference Center, Pacific Grove, California

Website: <http://redox.cfs.purdue.edu>

Experimental Biology 2004

April 17-21 • Washington, DC

Deadline for Submission of Abstracts: November 12, 2003

Website: <http://www.faseb.org/meetings/eb2004/>

Xth International Symposium on Amyloid and Amyloidosis

April 18-22 • Tours, France

A transdisciplinary meeting that will

address basic as well as clinical aspects of this field

Deadline for Receipt of Abstracts: December 15th, 2003

Abstracts must be submitted in English and only via the web via <http://www.colloquium.fr/isaa2004> where you will find all the necessary information for submission.

COLLOQUIUM-ISAA2004, 12 rue de la Croix-Faubin

75557 PARIS cedex 11 (France); Ph: +33 (0)1 44 64 15 15

Fx: +33 (0)1 44 64 15 16; email: isaa@colloquium.fr

MAY 2004

FEBS Lecture Course on Cellular Signaling & 4th Dubrovnik Signaling Conference

May 21-27 • Dubrovnik, Croatia

Application Deadline: March 1, 2004

The FEBS Lecture Course on Cellular Signaling and 4th Dubrovnik Signaling Conference are meeting jointly so that students who participate at the FEBS Lecture Course will also be able to attend all seminars and will have special tutorial sessions organized for their education.

TOPICS: Signaling cascades, Protein kinases and phosphatases, Cell compartmentalization and signaling, Receptor endocytosis and trafficking, Structural biology, GTPase signaling and diseases, Molecular targets for cancer therapy, Proteomics, Diabetes and Cardiovascular diseases

website: <http://www.icst.irb.hr>

JUNE 2004

American Society for Biochemistry and Molecular Biology Annual Meeting and 8th IUBMB Conference

June 12-16 • Boston, Massachusetts

Contact: Kelly Gull; Ph: 301-634-7145; Fx: 301-634-7126

Email: kgull@asbmb.faseb.org; Website: www.asbmb.org/meetings

JULY 2004

**4th ANNUAL CONFERENCE OF FOCIS [Federation of
Clinical Immunology Societies]**

July 18-23 • Montréal, Canada
Abstract submission: January 23, 2004
Travel Award applications (FOCIS): January 23, 2004
Early Registration: April 30, 2004
Website: www.immuno2004.org

AUGUST 2004

**12th International Conference on Second Messengers
and Phosphoproteins**

August 3-7 • Montreal, Canada
Contact: smp2004@eventsintl.com
Website: <http://www.secondmessengers2004.ca>

8th International Symposium on the Maillard Reaction

August 28-September 1 • Charleston, South Carolina
For detailed information about the meeting, including abstract
submission, a call for papers and deadlines.
Website: <http://Maillard.chem.sc.edu>
Email: Maillard@mail.chem.sc.edu

SEPTEMBER 2004

Stem Cell Biology: Development and Plasticity

September 16-19 • Scheman Continuing Education Building
Iowa State University Ames, Iowa.
Deadlines: Abstracts due July 16, 2004; registration deadline:
August 16, 2004
Travel Grants: Students may apply for travel grants (applica-
tions due July 16, 2004).
Contact: Growth Factor and Signal Transduction Conferences
Symposium Office, 3208 Molecular Biology Building, Iowa
State University, Ames, Iowa 50011-3260
Ph: 515-294-7978; Fx: 515-294-2244; Email: gfst@iastate.edu
Website: <http://www.bb.iastate.edu/~gfstlhomepg.html>

NOVEMBER 2004

4th International Congress on Autoimmunity

November 3-7 • Budapest, Hungary
Deadline for Receipt of Abstracts: June 20, 2004
Contact: 4th International Congress on Autoimmunity Kenes
International—Global Congress Organisers and Association
Management Services, 17 Rue du Cendrier, PO Box 1726,
CH-1211 Geneva 1, SWITZERLAND
Ph: +41 22 908 0488; Fx: +41 22 732 2850
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This is an ongoing project; please advise us whenever a student in your department earns the Ph.D., so that we can make this free membership offer to him or her.



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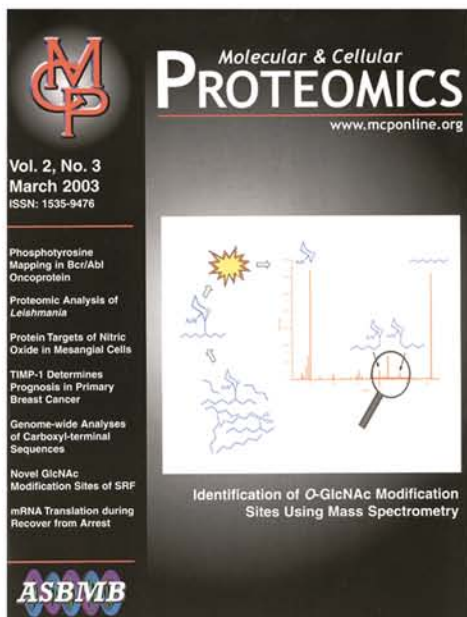
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