

ASBMB Today

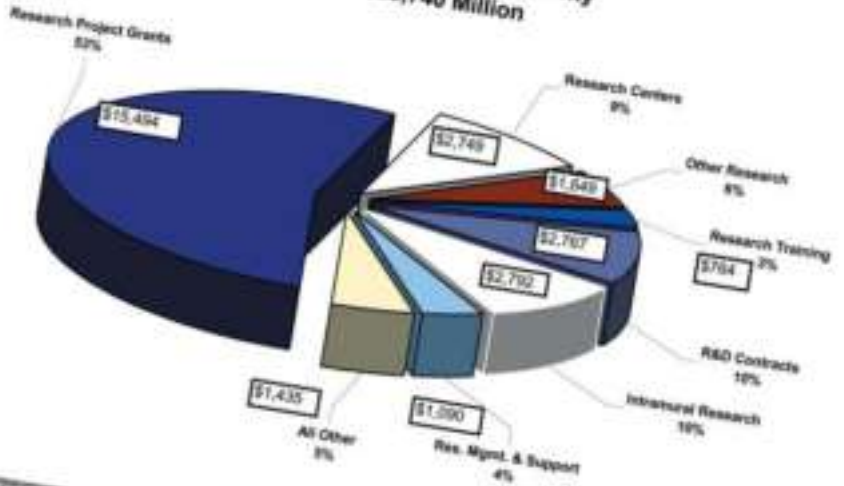
Constituent Society of FASEB
AMERICAN SOCIETY FOR BIOCHEMISTRY AND MOLECULAR BIOLOGY

2006 Budget Woes hit NIH, NSF

NATIONAL INSTITUTES OF HEALTH
Summary of Appropriations
(Dollars in millions)

Appropriation	FY 2004 Budget Authority 1/2/3/	FY 2005 Appropriation 1/4/	FY 2006 Estimate 1/	2006/2005
	Includes AIDS	Includes AIDS	Includes AIDS	\$ Change
		\$4,825	\$4,842	\$17
	\$4,739	2,941	2,951	10
	2,878	302	303	5
	36	1,173	1,177	4
	82	1,000	1,050	50
	51	1,403	1,459	56
	4,303	1,144	1,355	211
	1,905	1,270	1,278	8
	1,242	669	673	4
	653	648	648	0
	631	1,100	1,100	0
	1,025	51	3	-2
	501	34	7	-2
		1,18	1,18	0
	382	1,2	1,10	-12
	381	1,4	1,10	-12
	995	438	440	2
	428	138	139	1
		489	491	2
			300	2
			+100	-15
				1

FY 2006 President's Budget Request
Total NIH Budget Authority
\$28,740 Million



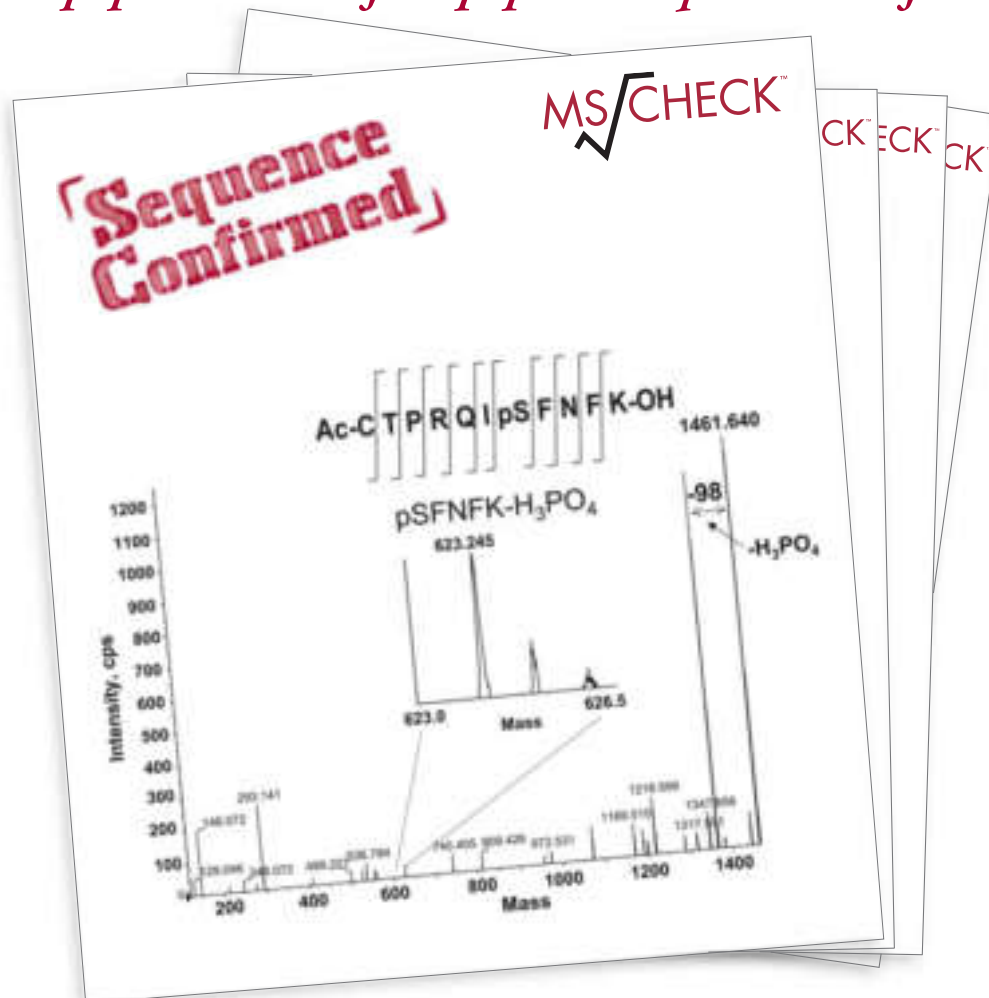
1 Totals may not add due to:
 1/ Includes funds to be transferred from the Department of Health and Human Services to the National Institutes of Health.
 2/ Reflects across-the-board reduction of \$425 million.
 3/ Comparable for transfers to NIH from the Department of Health and Human Services.
 4/ Reflects across-the-board reduction of \$425 million.
 5/ FY 2004 includes \$3,472 million NCI breast cancer research.
 6/ FY 2004 reflects real transfer from ONDCP \$3,818 million.
 7/ OD total includes Roadmap funds for distribution to ICs (FY2004 \$34.8 million).
 8/ Funds available for diabetes research in accordance with P.L. 106-554 and P.L. 106-555.

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ASBMB Today

AMERICAN SOCIETY FOR BIOCHEMISTRY AND MOLECULAR BIOLOGY

MARCH 2005,
Volume 3, Issue 12

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MOST IMPROVED MAGAZINE
COLUMNS & EDITORIALS
DESIGN & LAYOUT

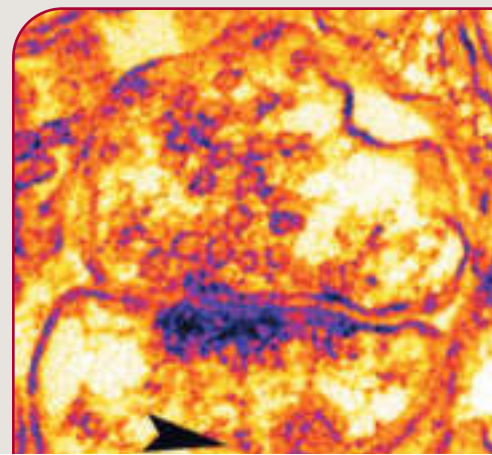


BRONZE AWARD WINNER 2003

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LETTERS

Perceived Shortage?

(The following commentary on the shortage, or lack thereof, of U.S.-born scientists responds to a letter on this topic that appeared in an earlier issue of ASBMB Today. The opinions expressed are those of the author and do not necessarily reflect those of this Society.)

Dear Dr. Warner:

I read your letter addressed to the ASBMB about the "perceived" shortage of U.S. borne scientists in the U.S. job market in the *ASBMB Today* magazine of August 2004. Despite being a foreign student in this country for over five years now, I must say that your letter presented a valid point.

Assuming for a minute that everything you mentioned in the letter is 100% true, then actually there is no shortage of qualified American scientists for various jobs in America. The employers, in the name of this unreal shortage, hire qualified foreign scientists flooding the market with job-seekers leading to the outnumbering of Americans and their eventual loss in the competition. Also according to you, the American employers should hunt down these "discarded," hidden and already-trained home-grown talents to hire, which will reduce for them the time, energy and costs of searching for and importing foreign talents and training them for new environments and jobs, even though this will deprive the employers of the "cheap labor pool" that you mentioned in the letter.

Agreed, all this makes sense. But what's next? Just mentioning that American employers should start hiring U.S. borne scientists can't be a solution. It's just an opinion.

Sincerely,

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TELL US WHAT YOU THINK

We appreciate receiving letters that are suitable for publication regarding issues of importance or commenting on articles appearing in *ASBMB Today*. Letters should be sent to the editor, John Thompson, at the address found at left. Letters must be signed and must contain the writer's address and telephone number. The editor reserves the right to edit all letters.

You've come a long way, baby! Or have you?



Dr. Judith Bond

A few decades ago, a cigarette company used the slogan "You've come a long way, baby!" to attract the longer-lived gender to smoking, a habit that was much more frequent at the time for men.

Well, these marketing schemes and other influences were successful, and lung cancer and other smoking-related diseases rose dramatically, demonstrating that women were just as vulnerable to the detrimental effects of smoking as men. There are in fact other realms in this 'men's world' that have opened up to women and are much healthier and challenging. For example, the pursuit of scientific careers.

We are in a place in time where 50% of our biomedical and life-science graduate students, medical school students, and postdoctoral trainees are women, and they are thriving as trainees. Yet far lower percentages of our tenurable faculty in the biomedical and chemical or physical sciences or in leadership positions at major universities are women. So, the question has been asked: 'why is that?'

The answer is that, in spite of a substantial amount of investigation of genetic, psychological, sociological, and environmental factors, there are no convincing data that explain the underrepresentation of women in senior positions in academia. Most of us agree there are genetic differences between men and women, and there are numerous environmental factors that shape our behavior as men and women. There are different expectations from our parents, teachers, and peers, expectations for ourselves, priorities, and encounters

with discrimination that affect the genders differentially.

However, there are numerous examples of women who have had successful, productive and satisfying careers in science. There is no question that women have the ability to be productive scientists and leaders in our profession. It does not help, however, when men in influential positions in academia question the innate ability of women to succeed in scientific careers.

In mid-January 2005, the president of Harvard University, Lawrence Summers, at a conference titled "Diversifying the Science and Engineering Workforce," at the National Bureau of Economic Research in Cambridge, Massachusetts, raised the specter that women lack the ability to succeed at the highest levels in science.

His comments offended several women in the audience, and rightly so. Comments from the president of a prestigious university that cast doubt

on the abilities of over half of our student population to succeed are irresponsible and unwarranted. There are no data that show that, despite the differences between the genders, women cannot succeed in careers in science at the highest levels. His comments will have a negative impact on young, impressionable female scientists, and could encourage discrimination.

Dr. Summers has apologized for his comments, but the damage is done. Bettie Sue Masters, Past President of the ASBMB, and I have written to Dr. Summers to suggest that some action on his part is called for. We suggested he consider personal involvement in activities promoting women's welfare, such as scholarships and fellowships, which would help promote their success in the science and mathematics fields. Female scientists have come a long way, and with encouragement and support we can go further.

Judith S. Bond, President, ASBMB

Nominations for ASBMB 2006 Awards

Nominations for the Society's 2006 Awards are now being solicited. The deadline for the receipt of nominations is May 2, 2005. Nomination for all awards should consist of a letter of recommendation, curriculum vitae minus list of publications, a list of not more than 10 of the nominee's most significant publications, and summary, not to exceed two pages, of the nominee's achievements. The Awards for which nominations are sought are:

- ASBMB-AMGEN AWARD • ASBMB-MERCK AWARD
- SCHERING-PLOUGH RESEARCH INSTITUTE AWARD •
- WILLIAM C. ROSE AWARD • AVANTI AWARD IN LIPIDS
- HERBERT A. SOBER LECTURESHIP •

For more information about the awards check the ASBMB website, www.asbmb.org. And please make sure to get your nominations to us by May 2, 2005.

by Peter Farnham, CAE, ASBMB Public Affairs Officer

NIH, NSF Do Not Fare Well in

The administration released its 2006 budget request on Monday, February 7, and the news was not good for science. Both the National Institutes of Health and the National Science Foundation received increases, but in neither case was the increase sufficient to keep up with inflation; in fact, NIH's proposed increase was the smallest in at least a decade. The NIH's budget summary is available on the NIH website at www.nih.gov/news/budget/FY2006presbudget.pdf

The NIH would receive \$28,845 million, an increase of \$196 million or 0.7% over the FY 2005 Appropriation. NIH Director Elias Zerhouni noted in remarks yesterday that his greatest priority was maintaining the basic research portfolio and trying to ensure that new and young investigators were adequately taken care of in the budget. The budget would support an estimated 9,463 competing RPGs, for \$3.6 billion, an increase of an estimated 247 competing RPGs from the FY 2005 Appropriation. The average cost of a competing RPG is about \$350 thousand. No inflationary increases are provided for direct, recurring costs in non-competing RPG's. However, where the NIH has committed to a programmatic increase in an award, the increase will be provided.

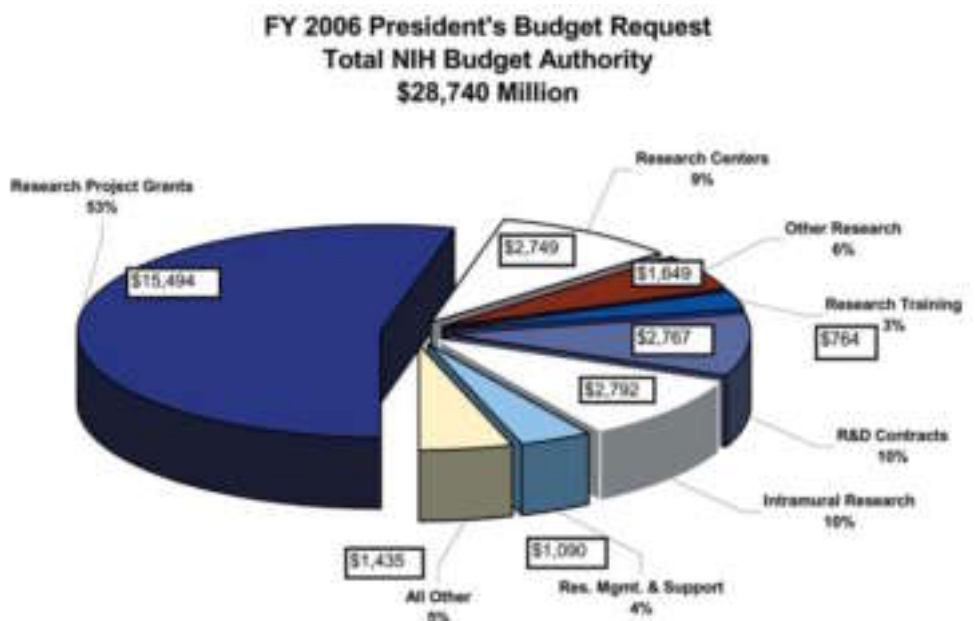
ASBMB Public Affairs Advisory Committee chairman Bill Brinkley expressed considerable disappointment with the budget proposal, telling *ASBMB Today* that "The President's proposed budget for NIH is alarming,

coming on the heels of a time when Congress has just completed the doubling of the NIH budget, a build-up designed to make significant advances in medical research to fight America's war on disease. The magnitude of the buildup brought on by the doubling of the NIH will essentially be extinguished by the President's plan for level funding. The doubling of the NIH budget and the excitement created by this remarkable build-up will have been for naught. Level funding

will mean little or no opportunities for training the next generation of scientists and for young investigators who are just beginning their careers, and applying for their first grant applications. Level funding will mean lack of adequate funding for the NIH Roadmap and other new initiatives for medical research. Ultimately, Congress, not the President, appropriates the funding for NIH. Let's hope that our "champions" on Capitol Hill will again come to the rescue of health

"This budget ignores our future economic needs and will cause irreparable harm to our country's ability to compete in the increasingly sophisticated and competitive global market place."

—Rep. Bart Gordon



Bush's 2006 Budget Request

research funding. We in the scientific community must rededicate our efforts to educate the public and Congress on remarkable opportunities in medical research and the need to maintain hope for the next generation of medical researchers."

The table on page 4 shows how the NIH budget would be spent under the President's plan.

NSF Receives Just Over 2% in President's Budget

The National Science Foundation (NSF) fared slightly better under the President's budget proposal for 2006 than NIH, receiving a proposed increase of 2.4% to about \$5.6 billion, up from \$5.47 billion received for 2005. Director Arden L. Bement Jr. described the budget climate for the coming year as "constrained," but nevertheless remained upbeat, portraying

the budget as a challenge to "leverage resources to enable science and engineering in key areas with sustained funding to meet national needs while working more productively."

The fiscal 2006 budget includes nearly a 3% increase in research and related activities (about \$113 million above 2005) to a total of \$4.3 billion, the largest amount ever for NSF's support of research. The request focuses heightened attention on core research, an area that many advocates for NSF worry gets overlooked as the agency devotes resources to various "priority areas" that amount to targeted research programs.

During his remarks, Bement said he wants to improve the success rate for NSF proposals, which has fallen from 30-33% to near 20% agency-wide. He added that improved management, a re-evaluation of the balance in the NSF portfolio between solicited and unsolicited proposals, and between individ-

ual researchers, teams, and centers will be some of the elements NSF will review

Significant cuts are proposed in education programs at NSF, amounting to over \$100 million. House Science Committee chairman Sherwood Boehlert (R-NY) was especially concerned about these cuts, saying, "As everyone knows, this is a very tight budget, with an overall cut to non-defense domestic discretionary spending. Given that context, the science programs fared relatively well. I would certainly like to see more robust increases in the science budget, particularly for the National Science Foundation ... I am especially troubled by the proposed cuts in the education programs at NSF." He noted that the committee would be reviewing the entire R&D budget at a February 16 hearing.

House Science Committee Democrats had a considerably less upbeat view, calling the proposed cuts at NSF and other science agencies "devastating." Science Committee ranking Democrat Bart Gordon (D-TN) noted that that the federal science budget overall decreased by \$877 million in the President's proposal, despite recent assurances by Office of Science and Technology Policy Director John Marburger that "this Administration understands that science and technology are major drivers of economic growth." Gordon commented, "This budget ignores our future economic needs and will cause irreparable harm to our country's ability to compete in the increasingly sophisticated and competitive global market place." ❧

House Appropriations Panels to Be Revamped?

In what one long-time House staffer characterized as "probably a done deal," new House Appropriations Chair Jerry Lewis (R-CA) was set to announce a sweeping reorganization of his committee, reducing the number of subcommittees from 13 panels to 10. Among the subcommittees on the chopping block is VA/HUD/Independent Agencies, where the National Science Foundation has resided. NSF will now move

to a newly expanded subcommittee covering Science, Commerce, and Justice. Labor/HHS, where NIH is located, is so far unaffected.

Senate appropriators are reportedly less than enthused about the Lewis proposal, but cannot prevent it in the House. In any case, Senator Arlen Specter (R-PA) has announced that he will remain as chairman of the Senate Labor/HHS subcommittee, thus keeping his jurisdiction over NIH.

NIH Issues New Conflict of Interest Rules

By Peter Farnham, CAE, ASBMB Public Affairs Officer

Department of Health & Human Services (DHHS) rules announced on February 1 impose new restrictions on the National Institutes of Health's approximately 18,000 intramural employees for such activities as teaching, writing, and consulting for pay with a variety of organizations; the amount and type of stocks they may own; and the awards they may receive. The rules are final and take effect immediately. The rules, plus a summary, are posted on the NIH website at www.nih.gov/about/ethics_COI.htm.

The new rules apply to all HHS employees, but most of the provisions are aimed at the NIH in response to the various violations of the current rules that have attracted a great deal of media and congressional attention since December 2003. There have been about 100 cases of NIH intramural employees engaging in unreported activities for which they were compensated by outside groups, such as universities, and pharmaceutical or biotechnology companies. The new rules strictly prohibit most such compensated relationships. As NIH Director Elias Zerhouni told ASBMB Today, "We needed to get this issue off the table. It was hurting us badly in the public eye."

Outside Employment

Although a few "limited exceptions" may be allowed (with prior approval), the new rules prohibit employment "including consulting and advisory or other board service, and compensated teaching, speaking, writing, or editing," with biotechnology, pharmaceutical, or medical device companies; hospitals,

clinics, health maintenance organizations or other health care providers; health insurers; health, science, or health research-related trade organizations, professional associations, or consumer or advocacy groups; and educational institutions or non-profit independent research institutes that are or recently were doing business with NIH.

NIH employees can teach a regular course at a college or university, and teach, speak or write as part of a continuing education program (although if the program is funded by a company, it must be through an unrestricted grant). They can also work with political, religious, social, fraternal, or recreational organizations; conduct clinical, medical, or health-related professional practice involving provision of care to individual patients; provide clerical or similar services; and write articles, chapters or textbooks that are subject to a peer review or substantially equivalent editorial review process (although again, if this work is funded by a company, it must be through an unrestricted financial contribution).

Employees must terminate prohibited outside activities within 30 days, but can request up to 60 days more to allow them to complete outstanding obligations.

Prohibited Holdings

In general, NIH employees who file financial disclosure reports are not allowed to own stock in biotechnology, pharmaceutical, and medical device companies involved in the research, development, or manufacture of medical devices, equipment, preparations,

treatments, or products. All other employees (and their spouses and minor children) are subject to a \$15,000 cap on holdings in such companies.

Employees may have up to 150 days to divest of holdings to comply with the law.

Awards

Senior employees, and others with official responsibilities involving awarding entities, may not receive awards with an aggregate market value of more than \$200. If the recipient is not a senior employee or does not have official duty matters involving an awarding organization, an NIH employee may accept bona fide awards for meritorious public service, if such awards have been reviewed by the Advisory Committee to the Director, meet certain criteria, and the employee has been individually approved to receive the award.

Employees, generally, may receive awards from outside sources that are nothing more than plaques or trophies of little intrinsic value, as well as free attendance and food at the event in which the employee is honored. An exception to the \$200 limit is allowed for "the most prestigious awards" such as the Nobel or Lasker prizes

New Rules Rankle

Dr. Zerhouni presided at a contentious NIH "town meeting" shortly

Continued on the next page



Dr. Elias Zerhouni


NIH Announces Enhanced Public Access Policy

On February 3, the National Institutes of Health (NIH) announced its policy on enhanced public access to publications resulting from NIH-funded research. Beginning May 2 NIH-funded investigators will be asked to submit to PubMed Central, NIH's on-line archive, an electronic version of the author's final manuscript upon acceptance for publication, if the manuscript resulted from research supported by NIH. The author's final manuscript is defined as the final version accepted for journal publication, and includes all modifications made during peer review.

The final policy reflects modifications and clarifications to the proposals released last September. NIH received more than 6,000 comments on the proposal, including comments from ASBMB. The Society did not object to the proposal since it conformed closely to ASBMB's business model for its publications, but questioned the need for the proposal and recommended that PMC simply link to final articles on publishers' websites, rather than maintain a separate repository of manuscripts.


The most significant change in the policy from that originally proposed

is that it now provides "more flexibility for authors to specify the timing of the posting of their final manuscripts for public accessibility through PMC." The proposed policy indicated a six-month delay of posting through PMC. The final policy requests and "strongly encourages" that authors specify posting of their final manuscripts for public accessibility as soon as possible, and within 12 months of the publisher's official date of final publication.

A copy of the policy can be found at: http://www.nih.gov/about/publicaccess/publicaccess_imp.pdf 

Continued from previous page

after the new rules were announced. The restrictions that seem to rankle the most among NIH employees (some of whom are ASBMB members) are those on stock ownership. Many NIH employees expressed the view that it is unfair to disallow their ownership of certain stocks because a few senior employees failed to comply with the rules. However, so far DHHS is not backing down.

In addition, certain ambiguities exist regarding the nature of allowable relationships between ASBMB and NIH employees for such activities as service on the Council and Society committees, and as editors or on editorial boards. While the ASBMB staff is generally confident that current relationships are allowed, the staff is seeking additional, specific guidance from NIH on these points. ASBMB is also taking steps to ensure that its awards are recognized and approved by NIH in advance. 

THE NATIONAL INSTITUTES OF HEALTH THIRD SYMPOSIUM ON THE FUNCTIONAL GENOMICS OF CRITICAL ILLNESS AND INJURY

April 21-22, 2005

Natcher Conference Center, Bethesda, Maryland

The topic is the application of genomic technologies to the diagnosis and treatment of critical illnesses and injuries.

For information:

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A Pathway to Blocking Autoimmunity

By reprogramming cells in the immune system, a team of scientists led by a Howard Hughes Medical Institute international research scholar has found a way to boost production of natural killer T cells, with long-term potential for fighting diseases in which the body attacks its own cells.

Natural killer T (NKT) cells maintain the immune system's balance between destruction and tolerance, a mechanism that is off kilter in autoimmune diseases such as type 1 diabetes and irritable bowel disease.

"If we can regulate the level of NKT cells, we have a chance to slow down the process of type 1 diabetes," says László Nagy,* HHMI international research scholar and Molecular Biologist at the Research Center for Molecular Medicine, University of Debrecen, Hungary. He and colleagues from the Research Center collaborated with a scientist from Albert Einstein College of Medicine in New York to do the series of experiments, which was published in the July 2004 issue of the journal *Immunity*.

After finding that a transcription factor, PPAR-gamma, is expressed in dendritic cells—the immune system's first responders—Dr. Nagy and colleagues used a drug, rosiglitazone, to increase PPAR-gamma activity. The additional PPAR-gamma activity prompted immature dendritic cells to develop into a form that could activate NKT cells specifically.

"Everyone knew that dendritic cells are derived from monocytes, and we knew there were different kinds of dendritic cells," Dr. Nagy said. "But nobody knew the regulatory events that drove dendritic cells to differentiation. We described a pathway to make

dendritic cells with a special phenotype that includes NKT cell induction."

Dendritic cells wait in peripheral tissue, such as the skin, ready to engulf foreign invaders or dying cells. Once they take up fragments of these cells, that is the antigens, they migrate to the lymph nodes, where they stimulate T cells to mount a specific immune response against that antigen. The type of immune response induced varies depending on the form of dendritic cells.

Dr. Nagy believes his group has found a way to make dendritic cells that favor recognition and tolerance of self—preventing, for example, the destruction of the insulin-producing beta cells of the pancreas that occurs in type 1 diabetes.

Once they found that PPAR-gamma was expressed in dendritic cells, the researchers profiled each gene regulated by PPAR-gamma to characterize the pathway leading to NKT activation. They were able to show that PPAR-gamma regulated the expression of a gene called CD1d, which encodes a glycoprotein responsible for the presentation of self and foreign lipids to T cells. This protein is indispensable for the generation of NKT cells.

"We think PPAR-gamma is capable of orchestrating a coordinated response whether endogenous ligands arrive from outside of the cell or are generated inside the cell."


—Dr. László Nagy

The researchers state that the work provides insight into how signals from outside the cell can influence differentiation and gene expression and is an entry point for intervention into autoimmunity by modulating CD1d expression, and NKT cell activation.

"We think PPAR-gamma is capable of orchestrating a coordinated response whether endogenous ligands arrive from outside of the cell or are generated inside the cell," Dr. Nagy said.

Previous studies with non-obese diabetic (NOD) mice, a model of type 1 diabetes, support the idea that modulating NKT cell levels can help combat autoimmunity. These studies have linked the process of beta-cell destruction and development of type 1 diabetes to the CD1d gene and NKT cells. In 2003, another research group reported that treating NOD mice with a molecule that activates PPAR-gamma substantially reduced development of type 1 diabetes.

Although the current studies were limited to cultured human cell lines, Dr. Nagy sees potential for testing the mechanism in patients. Rosiglitazone, the drug they used to activate PPAR-gamma, is already used in the United States to improve insulin sensitivity in patients with type 2 diabetes. Nagy suggested that looking for changes in the NKT cells of patients taking rosiglitazone would indicate whether the mechanism is active.

He and his colleagues continue to study the PPAR-gamma pathway, and have recently begun using mouse models to knock out relevant components—PPAR-gamma, CD1d, and NKT cells—to evaluate their impact on the pathway's function. 

**ASBMB member.*

NSF Website Redesigned



The National Science Foundation introduces a new Web site, entirely redesigned to better serve both the research and education community and the general public. The Web address remains the same: www.nsf.gov.

Through the new site, NSF hopes to more effectively explain its use of public funds, and the results derived from it, while offering a user-friendly interface for its thousands of grantees and contractors. NSF supports researchers and educators in all fields of science and engineering through competitive grants and other funding awards to more than 2,000 institutions in all 50 states. As an independent federal agency, NSF receives


public support through Congressional appropriations.

The new Web site culminates more than a year of study and analysis regarding the most current and effective ways to communicate in today's fast-paced electronic information environment. It represents the first major redesign of the NSF Web site in five years.

Some key features that are aimed at the general public:

- ❖ A help center describing the new features (www.nsf.gov/help)
- ❖ A plain-language explanation of NSF and how it works (www.nsf.gov/about/glance.jsp)
- ❖ General overviews on the types of science that NSF supports (www.nsf.gov/news/overviews)
- ❖ Results of NSF research (www.nsf.gov/discoveries)
- ❖ Examples of NSF-supported TV programs and other informal education efforts (www.nsf.gov/news/now_showing)

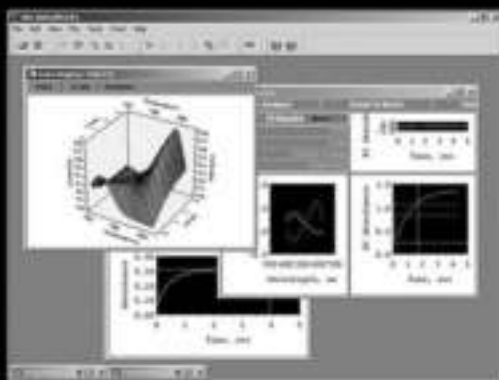
Additional features that are aimed at the science and education community:

- ❖ A new "funding" section, including an A-Z index, and upcoming due dates (www.nsf.gov/funding/)
 - ❖ A new way to find NSF employees <http://www.nsf.gov/staff/>
 - ❖ Quick access to science and engineering statistics (www.nsf.gov/statistics)
 - ❖ Consistent design to NSF directorates, divisions and programs
- Revisions and updates to the new site will be undertaken as required. 

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Nitric Oxide Sensor Found in Toxic Bacteria

By Nicole Kresge, Science Writer

In determining how a deadly bacterium recognizes and avoids its molecular toxin, structural biologists at the University of Texas Medical School at Houston (UTH) have also elucidated the origins and structure of a vital cell signaling protein, guanylyl cyclase.

The research, published on October 7 in *Science Express*, the rapid online publication forum for the journal *Science*, also offers an explanation for how the decades-old practice of treating meat with sodium nitrite prevents botulism.

Since 1925, sodium nitrite has been used as a source of nitric oxide to inhibit the growth of *Clostridium botulinum* spores and toxin production in cured meats. In fact, the name 'botulinum' comes from the Latin word for sausage, 'botulus.' However, until recently, the molecular strategies used by this bacterium to recognize and avoid nitric oxide have remained unknown.

A team of researchers led by C. S. Raman hypothesized that *C. botulinum* may use a prokaryotic version of the mammalian nitric oxide receptor, soluble guanylyl cyclase, to detect nitric oxide. To identify candidate nitric oxide sensors, Dr. Raman and his colleagues screened the *C. botulinum* genome for orthologs of the nitric oxide binding domain of human soluble guanylyl cyclase.

They discovered a gene that encodes a protein whose N-terminal

domain is similar to soluble guanylyl cyclase and whose C-terminal domain is similar to a chemotaxis protein. This suggests that binding of nitric oxide to the receptor may trigger the chemotaxis machinery and allow the bacteria to retreat from the source of nitric oxide. The researchers named the *C. botulinum* protein SONO for 'sensor of nitric oxide' because it has an extreme binding affinity for nitric oxide.

These scientists also cloned a soluble guanylyl cyclase ortholog from the eukaryotic unicellular green alga *Chlamydomonas reinhardtii*, whose chloroplasts derive from cyanobacteria. This led to the hypothesis that the mammalian soluble guanylyl cyclase may have evolved from the fusion of a bacterial SONO and a cyclase.

Dr. Raman's laboratory used X-ray crystallography to determine the crystal structure of a SONO ortholog from *Thermoanaerobacter tengcongensis*—an extremely thermophilic microbe—

and found that the protein contains a fold that had not previously been described. This new structure will hopefully provide important answers to some questions regarding mammalian soluble guanylyl cyclase, which has not yet been crystallized.

"For nearly three decades it was unclear how a gaseous molecule such as nitric oxide can activate a heme-containing enzyme to generate cyclic GMP in humans," said Dr. Raman. "Our ability to determine the crystal structure of a closely related bacterial protein (SONO) dramatically helps with solving this puzzle."

In humans, nitric oxide binding to soluble guanylyl cyclase serves as the signal to make cyclic GMP, a molecule that improves blood flow by relaxing blood vessel walls. Dr.



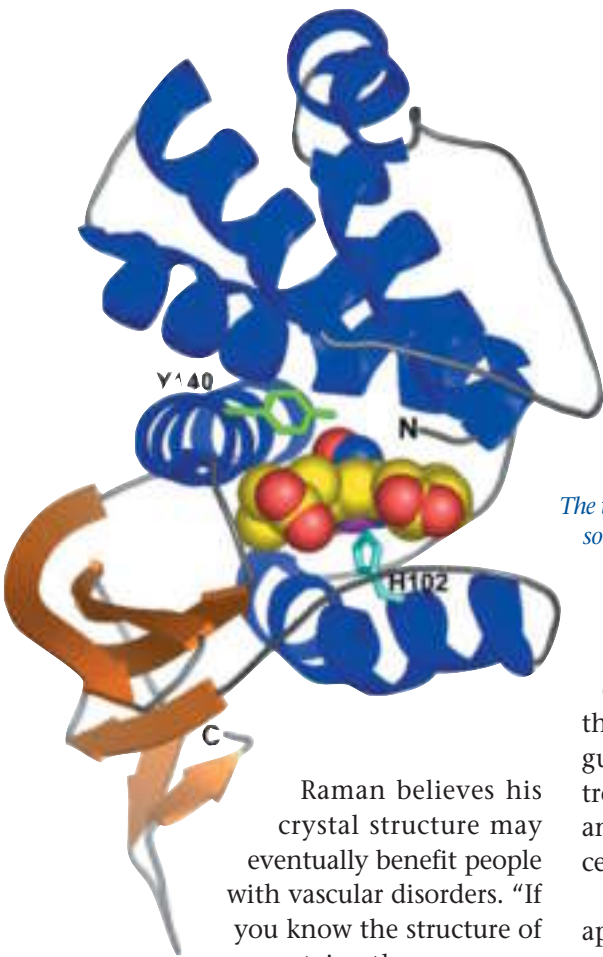
Dr. C.S. Raman

Danish Award Honors Mina Bissell

Mina Bissell,* the first biologist and the first woman to hold the rank of Distinguished Scientist at Berkeley Lab, received an honorary doctorate, the Doctor Medicinae Honoris Causa, from the University of Copenhagen. Queen Margrethe of Denmark attended the ceremony and met with Bissell and five other

distinguished honorees. Bissell has received numerous honors for her pioneering work in postulating and then establishing the important role of the microenvironment in general and extracellular matrix in particular, in regulation of both normal and malignant cell behavior.

*ASBMB member




The three-dimensional structure of SONO heme domain, the first structural relative of mammalian soluble guanylyl cyclase to be determined, reveals an archetypal topology that is different from any other protein. Image courtesy Pierre Nioche, University of Texas Medical School at Houston.

Raman believes his crystal structure may eventually benefit people with vascular disorders. "If you know the structure of a protein, then you can

develop therapeutics targeted to specific binding sites on the molecule," Dr. Raman explains. "Such therapeutic agents may allow soluble guanylyl cyclase activity to be controlled in the absence of nitric oxide, and help combat cardiovascular and cerebrovascular diseases."

The results have other potential applications as well. "Having a protein that binds nitric oxide with

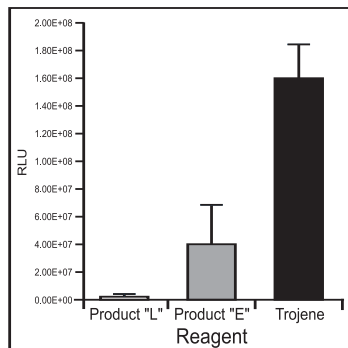
high-affinity can be instrumental in the development of new biosensors for detecting nitric oxide," says Dr. Raman. "Our protein could also be used to determine how much nitric oxide is generated in physiological settings."

Funding for this research was provided by the Pew Charitable Trusts, The Robert A. Welch Foundation, and the National Institutes of Health. 

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'Molecular Portals' in

Infinitesimal particles of gold have enabled neurobiologists to track down key molecules in the machinery of "entry points" in neurons—offering clues to the organization of a region that has thus far remained largely unknown neuronal territory.

The researchers—from Duke University Medical Center and the University of North Carolina—used electron microscopy to locate molecules tagged with targeted antibodies attached to gold particles—rendering the molecules' precise location visible.

The findings by the researchers, led by Dr. Michael Ehlers* of Duke and Dr. Richard Weinberg of the University of North Carolina at Chapel Hill, were published online August 22, 2004, in the journal *Nature Neuroscience*. Their studies aimed to understand how receptors on the surface membranes of nerve cells undergo a recycling process called endocytosis, in which the receptors are drawn into the interior of the neurons to be recycled.

These receptors are proteins that are activated by bursts of signaling chemi-

cals, called neurotransmitters, launched from another, transmitting neuron. Such activation triggers a nerve impulse in the receiving neuron. Changes in the strength of a neuron's response to such chemical signals depend on the number of receptors on the dendritic spine surface. And the strength of such connections is key to establishing the neural pathways through the brain that are the basis of learning and memory.

The neurotransmitter "receiving stations" on the neuron are mushroom-shaped dendritic spines that festoon its surface. The signaling regions between neurons are known as synapses, and the receiving membrane on the dendritic spine is known as the postsynaptic membrane.

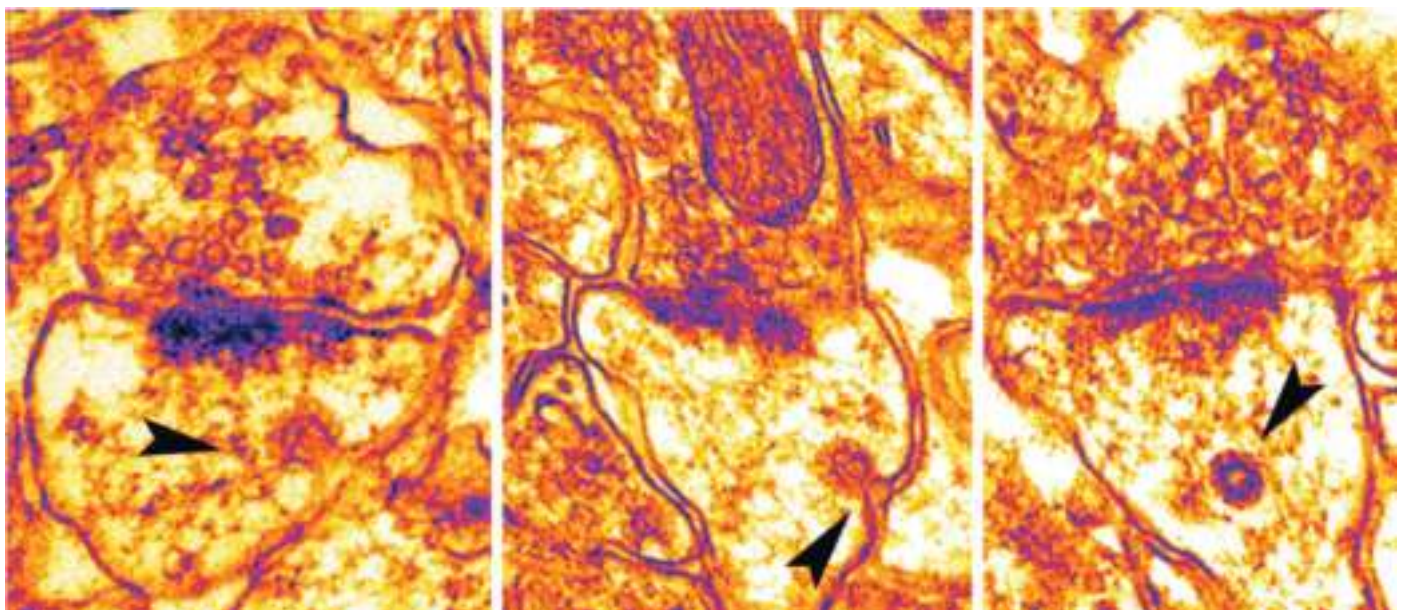
"A key mystery about dendritic spines," said Dr. Ehlers, "has been where on their surface such recycling of receptors takes place. It has been known for some time that signal reception takes place in a small region of the spine membrane known as the postsynaptic density, but the postsynaptic density comprises only 15 percent of the membrane area.

What happens in the remaining 85 percent of the spine's membrane has been almost completely unknown.

"One way that connections in our brains are weakened is by removing receptors from synapses, but where this removal occurs has been unclear. Defining this 'microanatomy' of dendritic spines is thus quite fundamental to understanding how neural connections are formed and restructured as our brains develop, change, and age."

According to Dr. Ehlers, it has been believed that receptors to be recycled "uncouple" from the postsynaptic density and move across the fatty membrane to an "endocytic zone." In this unidentified zone, molecular machinery attaches to the receptor, draws it into a bubble-like vesicle and transports it to machinery where it is either recycled or destroyed.

Endocytosis in dendritic spines occurs at specialized lateral domains. Electron micrographs show synapses from CA1 hippocampus of adult rat. Arrowheads point to coated pit assembly (left), vesicle scission (middle) and internal trafficking (right). Endocytic profiles are seen lateral to the postsynaptic density.



Brain Cells Identified



Dr. Michael Ehlers with cascading clathrin.

To attempt to map such zones, the researchers decided to trace the precise location of three key molecules known to play central roles in endocytosis:

- Clathrin, the protein that stitches together to create the vesicle like a soccer ball that buds from the membrane,
- AP-2, the adaptor molecule that grabs onto receptor cargo and attaches it to clathrin, and
- dynamin, the protein that drives the machinery that pinches the vesicle off from the cell membrane, freeing it to travel to the recycling machinery.

The researchers attached gold particles to antibodies that specifically tar-



Dr. Richard Weinberg

geted each of these proteins, and used electron microscopy to search for these molecules in rat brain tissue. Their tracking revealed that each of the molecules concentrates in specific lateral zones of the spines.

"If you think of the spine as a roughly spherical structure with the synapse at 12 o'clock, we found that these endocytic molecules concentrate at zones at 3 o'clock and 6 o'clock," said Dr. Ehlers. He said that these concentrations mark the spots at which the membrane is internalized by endocytosis and the receptors drawn in. And even when the spines are larger or smaller, the distances expand or shrink so the zones stay at the same relative positions.

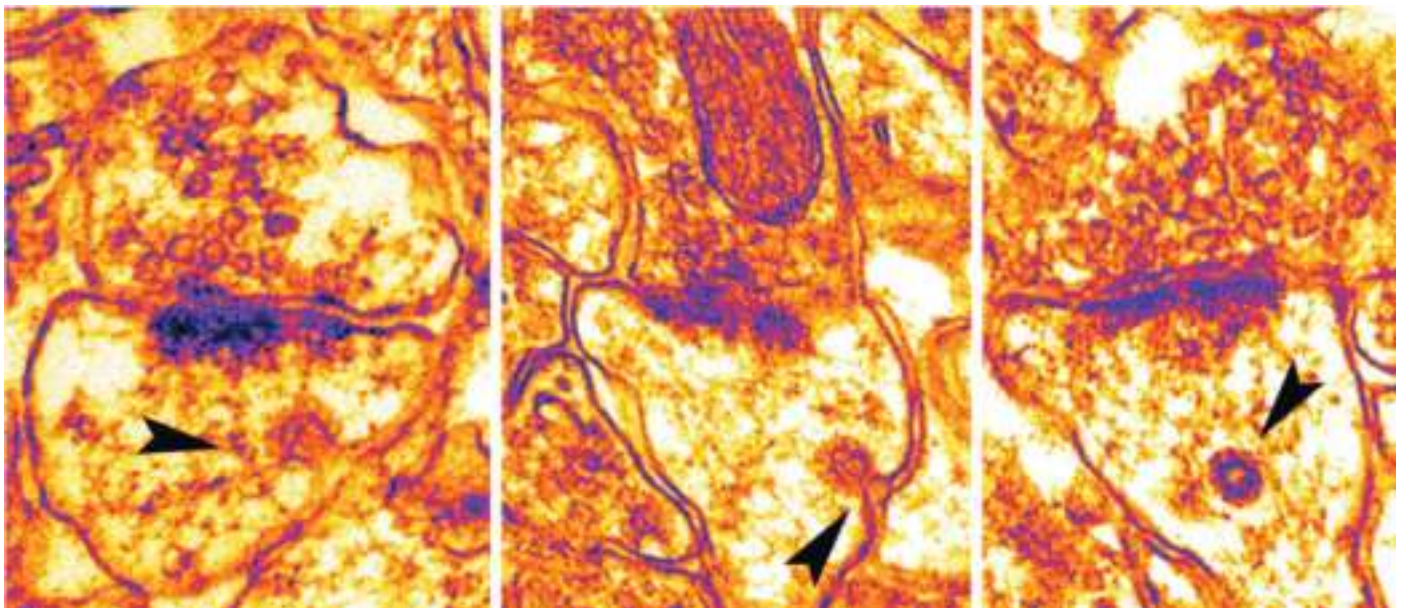
"While we still don't fully understand how this zone is established or how molecules move through this zone into the cell interior, with these findings, we are

beginning to see a level of organization that we didn't know existed," he added. "These findings imply a hidden level of organization on the dendrite that's yet to be revealed. This specialized endocytic zone is only the second known membrane specialization in dendritic spines."

The existence of zones in the postsynaptic membrane mirrors a similar organization known to exist on the presynaptic terminals on the transmitting neurons that launch bursts of neurotransmitter, and Dr. Ehlers believes that the findings of organization on dendritic spines could have broader implications in understanding signaling between nerve cells.

"It's well known that many kinds of receptors, not just neurotransmitter receptors, undergo downregulation by endocytosis," said Ehlers. "These include receptors involved in learning and memory, tolerance to medications, or reactions to drugs. I think our findings will be relevant in understanding a wide range of such processes." ❧

** ASBMB member*



Researchers Discover How Worms Sense Oxygen

A multi-institutional collaboration of scientists has learned how the nematode, *Caenorhabditis elegans*, is able to sense oxygen levels in its environment and feed in areas where the concentration of oxygen is just right.

In the process, the researchers also discovered that nematodes do not like as much oxygen as originally thought. While nematodes grown in the laboratory are kept at 21% oxygen (the ambient concentration), nematodes appear to prefer only 6% oxygen.

"It was totally unexpected that they would actually prefer 6%. We don't know why, though it probably gives them some survival advantage," said Michael A. Marletta,* Professor of Chemistry and Molecular and Cell Biology at the University of California, Berkeley, and a faculty scientist at Lawrence Berkeley National Laboratory (LBNL). "The bordering and clumping that worm experts refer to as social behavior is really the worms, in an artificial setting like a Petri dish, trying to get to an area of 6% oxygen, which they like. It's a laboratory phenomenon."

Dr. Marletta is one of the co-authors of a paper on oxygen-sensing in *C. elegans*, which appeared in the July 15, 2004, issue of the journal *Nature*. Other authors are Cornelia Bargmann, who holds a joint appointment with the University of California at San Francisco and the Howard Hughes Medical Institute, plus David Karow of UC Berkeley, Jesse Gray, Hang Lu, and Andy Chang of UCSF, Jennifer Chang of the University of Michigan, and Ronald Ellis of the University of Medicine and Dentistry of New Jersey.

Bordering and clumping is a peculiar behavior in which the nematodes cluster around the border of the Petri dish instead of spreading evenly around the surface. Dr. Marletta and his colleagues determined that the bacteria the worms feed on are at a higher density

around the border of the dish, consuming oxygen along with the worms. When oxygen levels are high, the worms pile onto the densest clumps of bacteria, because that's where oxygen levels are lowest.

"The swarm of worms and density of bacteria together lower the oxygen concentration in that immediate environment," Dr. Marletta explained. "We found that when we lower the oxygen concentration to 6%, the worms disperse in three minutes."

At high concentrations, oxygen is toxic and corrosive. Worms avoid high



oxygen presumably to avoid damage to their cells, although oxygen sensors also may help them find food.

The investigators determined that nematodes use a homolog of the enzyme guanylate cyclase to detect oxygen. By knocking out seven predicted soluble guanylate cyclases in the worm, they were able to show that one gene (*gcy-35*) was acting as an oxygen detector, primarily steering worms away from too much oxygen. Dr. Marletta and his colleagues also determined that guanylate cyclase is found in three separate neurons that innervate the pseudocoelom of the worm—thereby providing a connection to the outside world.


In humans and other animals, guanylate cyclase, is found in smooth muscle. Nitric oxide binds to and activates guanylate cyclase, catalyzing the formation of cyclic GMP, which relaxes

and dilates blood vessels. Nitric oxide also activates guanylate cyclase in the brain, where it is involved in learning and in memory.

"When we took apart the guanylate cyclase protein to study nitric oxide signaling, we found that the binding site is a heme molecule," said Dr. Marletta. "However, whereas the heme molecule in hemoglobin cannot discriminate between oxygen or nitric oxide, the heme molecule in guanylate cyclase only binds with nitric oxide. Somehow, nature engineered a way for the guanylate cyclase to screen out the oxygen, which is usually present in much higher concentrations than nitric oxide."

Dr. Cornelia Bargmann speculates that the oxygen-sensing system used by *C. elegans* may be used by other animals who must avoid low-oxygen environments, including fish. Humans may also have such a detector to trigger hyperventilation during exercise or exposure to anoxic environments.

"We are immersed in a 21% oxygen atmosphere all the time, and our blood stream and lungs maintain the optimum oxygen levels in our tissues. So, we take oxygen levels for granted," noted Dr. Bargmann. "Many other animals on the planet live in water or the soil, such as *C. elegans*. And since oxygen diffuses much more slowly in those environments, they must evolve ways to sense oxygen and react to changes in oxygen levels."

Dr. Marletta and his research team have already begun structural studies that they believe will enable them to predict whether a given guanylate cyclase enzyme will be an oxygen or a nitric oxide sensor. A better understanding of how these enzymes are able to selectively bind to nitric oxide or oxygen could have implications for biology, including research into human cardiovascular diseases. 

*ASBMB member

Minority Affairs Committee Sessions at EB 2005

The ASBMB Minority Affairs Committee (MAC) will present two sessions during EB 2005. The first session entitled, Mentoring Young Scientists, is co-chaired by MAC chairperson, Juliette B. Bell from Fayetteville State University, Fayetteville, North Carolina, and Tom Landefeld from California State University, Dominguez Hills, California. It will be held on Monday, April 4 from 9:55 a.m. until 12:15 p.m.

This session will focus on the critical role that mentoring plays in the success of young scientists, and its impact in developing and nurturing interest in scientific research careers. This is particularly important for minorities, where the numbers who earn advanced degrees and go on to pursue careers in the sciences are abysmally small. In this session, presenters will discuss mentoring from their perspectives, share their experiences as mentors, and give some tips on effective mentoring.

Speakers include Frank Talamantes from Texas Tech Health Science Center who will discuss the history of mentoring and what characteristics make a good mentor in his presentation, "How to carry out effective mentoring." In his talk, "Mentor advice for success at different levels of your science career," John Alderete, also from the University of Texas Health Science Center, recommends that young scientists choose no less than three mentors. He also offers his advice, as a mentor, on career development.


The final speaker in this session, Faith Zamamiri-Davis, approaches mentoring from the perspective of the person being mentored in her talk, "The importance of being mentored...correctly". She will discuss "the highs and lows of mentoring relationships" throughout her graduate and postdoctoral training, with a focus on suggestions on how to get the most out of a mentoring relationship. The overall goal of this session is to help

both mentors and protégés identify ways of building strong and fruitful mentoring relationships. Audience participation and discussion are encouraged.

This session will be followed immediately by The Minority Scientists Mixer from 12:15 p.m.- 1:15 p.m. in the Convention Center, Terrace. During the mixer, minority students and scientists will have the opportunity to meet MAC members, session speakers, and other ASBMB members.

The evening of April 4 will be rounded out by the ASBMB Graduate/ Postdoctoral Travel Award Symposium, chaired by ASBMB-MAC Chairperson, Juliette Bell. This symposium will feature oral presentations by selected travel award winners followed by a poster session featuring all of the travel awardees. Concurrent with the graduate/postdoctoral travel award poster session, the undergraduate poster session will be held. Philip Ortiz, the chair for this session.

On Tuesday, April 5, ASBMB-MAC will present its second session entitled "World Health: Malnutrition" co-chaired by Philip Ortiz of Empire State

University and Dr. Kristie J. Lancaster of New York University. This session will feature scientists who will present their latest findings on the issue of nutrition around the world. 

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.

Jin-Hun Jung

University of California Riverside

Kevin Marley*

Oregon State University

Guofei Zhou

Northwestern University

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

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Nobel Laureate Agre to Have New Leadership Role at Duke

Peter C. Agre will join Duke University Medical Center in July as Vice Chancellor for Science and Technology. Dr. Agre shared the 2003 Nobel Prize in Chemistry with Roderick MacKinnon, Professor and HHMI Investigator at Rockefeller University, for discoveries concerning channels in cell membranes.

In this newly created post, Dr. Agre* will help guide the development of Duke's biomedical research enterprise in ways that will further enhance its efforts to support and attract the world's top scientists and students. In addition, he will lead an effort to assess healthcare needs on a global scale, and ensure that Duke's research programs are positioned to address those needs.

His appointment was announced by Victor J. Dzau, Chancellor for Health Affairs at Duke and President and CEO of the Duke University Health System, who stated, "Peter is one of the most accomplished physician-scientists of our era, but he is even further distinguished by his passion to improve the lives of people throughout the world. His interests span not only science and medicine, but also human rights and the education of children in math and science."

In his role as vice chancellor for science and technology, Dr. Agre will work closely with the chancellor for health affairs, the deans of the medical and nursing schools, and with faculty to develop strategies for the future direction of science as well as the



DUKE UNIVERSITY MEDICAL CENTER

opportunities that will be enabled by rapidly evolving technologies.

"After many years as a bench scientist, I've become increasingly interested in contributing to science in a broader way," said Dr. Agre. "The work I'm about to begin at Duke will help to shape the next generation of scientists, who will determine whether our nation will continue to lead the world in science and medicine."

Duke's newly appointed Vice Chancellor received his medical doctorate from Johns Hopkins University School of Medicine in 1974. He took a residency in internal medicine at Case Western Reserve University and a fellowship in hematology/oncology at the University of North Carolina at Chapel Hill. In 1981, he returned to Hopkins where he progressed through the ranks of the departments of medicine and cell biology. In 1993 he joined the department of biological chemistry as a full professor. In 2003, he shared the Nobel Prize in Chemistry for revealing the molecular basis for the movement of water into and out of cells.


In addition to his scientific talents, Dr. Dzau said he sought Dr. Agre's expertise as a champion and critic of scientific and medical issues that have important societal implications. He said that he asked him to expand those efforts as part of his role at Duke. Mak-



Dr. Peter C. Agre

ing advocacy an institutional priority, he said, is needed to fill a void that exists nationally.

"Too often, academic medical centers and universities have been silent on issues that are important to the future of our society," said Dr. Dzau. "As leaders of these institutions, I think we have an obligation to express our views and step into the public debate on important issues. I have asked Peter to use his position at Duke to do precisely that."

"Peter's broad interests, ranging from scientific to humanitarian, will make him an invaluable resource to the entire Duke University community, President Brodhead and I look forward to having Peter serving as a senior adviser to the provost, the deans and students across the campus." 

* ASBMB member.


Elizabeth Nabel Is New Director of National Heart, Lung, And Blood Institute

Elias Zerhouni, Director of the National Institutes of Health, has appointed Dr. Elizabeth G. Nabel as director of the National Heart, Lung, and Blood Institute (NHLBI). Dr. Nabel, who was previously the Scientific Director of Clinical Research in the NHLBI intramural program, began her new appointment February 1.

"Dr. Nabel is a leading scientist and recognized expert in the development of novel genetic and cellular therapies for cardiovascular disease. Her research on vascular biology and the regulation of smooth muscle cell growth has provided important insights into the development of heart disease," said Dr. Zerhouni in announcing the appointment. "As both a researcher and a clinician, she brings a well-rounded scientific background and strong management skills to this position. She has championed the concept 'from bench to bedside.' This effort to bring research advances into clinical practice continues to be a focus of the NHLBI and of NIH."

Dr. Nabel will oversee an annual budget of almost \$3 billion and a staff of approximately 850. The Institute provides leadership for a national research program on heart, lung, blood, and sleep diseases and disorders. Since 1993, the Institute has been the home of the National Center on Sleep Disorders Research and, since 1998; it has had responsibility for the NIH Women's Health Initiative. Institute-funded research is conducted in Bethesda, Maryland in the NHLBI's intramural laboratories and throughout the country by institutions and individuals supported by research grants and contracts. In addition, the NHLBI conducts educational activities, including the development and dissemination of materials for health professionals, patients, and the general public, with a strong emphasis on prevention.

A cardiologist who has taken care of many patients with cardiovascular disease, including women with heart disease, she joined NHLBI in 1999 as Scientific Director of Clinical Research. Among her many accomplishments as Scientific Director, she initiated a cardiothoracic surgery branch, a state of the art training and research program in cardiovascular surgery. Her lab, which has published more than 200 papers, has studied factors involved in the regulation of vascular smooth muscle cell growth and vascular inflammation. This research has opened up new avenues for therapeutic targets for vascular diseases.

Dr. Nabel has received numerous awards, including the ASBMB Amgen-Scientific Achievement Award. 

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ANNUAL REVIEWS

Intelligent Synthesis of the Scientific Literature

by John D. Thompson, Editor

California Supreme Court to Decide Genentech/City of Hope Dispute

California's Supreme Court has stepped into a high-stakes dispute over whether Genentech Inc. should have to pay \$500 million to a former research partner, the City of Hope National Medical Center, which has accused it of systematically withholding royalties on a breakthrough gene-splicing method. Five of the court's seven justices voted to grant a hearing on Genentech's appeal of a lower-court ruling that upheld a Southern California jury's \$500 million damage award in 2002 to the City of Hope.

City of Hope and Genentech, then a fledgling biotech company in South San Francisco, collaborated starting in 1976 on methods to insert human genes into fast-growing bacteria and make them produce medically useful proteins, like insulin. City of Hope claims principal credit for that development which led to the first drugs made by the emerging biotech industry.

The partners signed a contract in which Genentech held the patents and was to pay royalties on its products. Over the next 20 years City of Hope alleges that Genentech engaged in a "campaign of concealment and misdirection to cheat City of Hope out of hundreds of millions of dollars."

Genentech said it had paid everything it owed, but the lower court found in 2002 that City of Hope was entitled to another \$300 million in royalties. Finding that Genentech had also violated a legal duty to protect City of Hope's interests in the scientific

innovations, the jury added \$200 million in punitive damages.

Genentech's appeal challenged the entire damage award but focused on the punitive damages, which it called a dangerous precedent.

The company said the case was a contract dispute, in which punitive damages, normally awarded for per-

sonal injuries and economic harm caused by fraud or malice, are improper. Allowing the jury verdict to stand will invite punitive damage claims in all royalty disagreements, risking "real injury to a vital sector of the California economy," Genentech attorney Jerome Falk said in court papers.

Inpharmatica Partners with Pfizer

Inpharmatica Ltd, a drug discovery company, has announced a series of agreements with Pfizer that provide Pfizer with access to four core components of Inpharmatica's PharmaCarta gene to candidate technology platform.

Inpharmatica will use its proprietary technology for target druggability assessment; while Pfizer will gain access to StARLIT, a database containing 20 years of curated medicinal chemistry information on compound structure and bioactivity linked to targets; to DrugStore, a curated database of all known drugs, linked with their targets; and to Admensa, Inpharmatica's proprietary technology for assessing the absorption, distribution, metabolism, and excretion characteristics of therapeutic compounds and compound libraries.

PharmaCarta is Inpharmatica's gene to candidate platform, which bridges the gap between biology and chemistry. PharmaCarta facilitates target selection through druggability

assessment linked to electronic identification of potential compounds biased for good characteristics.

Founded in 1998, Inpharmatica Ltd is a drug discovery company using predictive technologies to improve speed and productivity. Focusing on highly druggable targets, its proprietary platform, PharmaCarta, is an integrated suite of informatics-based technologies capable of rapid gene to candidate operations. Inpharmatica's lead discovery program is focused on generating pre-clinical candidates against 16 novel nuclear receptors - proteins widely considered to be both druggable and of high therapeutic interest. Other significant portfolio targets include novel secreted proteins/antibodies, ion channels, P450 enzymes, metalloproteinases and progesterin receptors.

Inpharmatica employs some 100 professionals at its UK locations in London and Cambridge, with business development headed in North America.

Playing Follow-the-Leader in Stem Cell Research

California voters' passage, last November, of a \$3 billion measure to create an institute for regenerative medicine based on embryonic stem cell research, has created a follow-the-leader game in northeastern states.

New Jersey kicked off the game in 2004, with a plan to create the New Jersey Institute for Stem Cell Research, a joint project of the University of Medicine and Dentistry of New Jersey and Rutgers University. The state's budget allocated \$6.5 million that is to be included in a \$10 million public/private stem cell fund, designed to attract top researchers from around the world. An additional \$50 million in public and private funds would be used to support the institute in the following 5 years.

Then, in mid-January, the New York State Senate's Democratic

leader, David Paterson, proposed the budgeting of \$1 billion for stem cell research and the creation a New York stem cell institute. State Senator Liz Kreuger (D) followed up with an announcement that she would introduce a bill to support embryonic and adult stem cell research and ban human cloning.

Just two weeks after the New York senators announced plans to enter the contest, Connecticut legislators introduced a bill that endorses research on embryonic and adult stem cells, and Governor Jodi Rell said she would take between \$10 and \$20 million from the state's budget surplus to promote stem cell research in the state.

Commenting on all this, New York's Senator Kreuger told *The Scientist*. "California has almost started a range war over scientists."

EU Commissioner Urges Easing of Rules on GM Crops

The European Union's new Agriculture Commissioner, Mariann Fischer Boel, has given signs of a major shift in EU policies toward genetically modified (GM) crops, telling a German newspaper recently that she believes the EU should issue guidelines for acceptable distances between GM and non-GM crops.

Currently, the European Union leaves it up to member states to regulate the sowing of GM crops so they do not contaminate adjacent non-GM fields. Coexistence of GM and non-GM farm fields is highly controversial in several EU nations, including Germany, and Fischer Boel's predecessor, Franz Fischler, is said to have simply avoided the issue.

In an interview with the daily *Berliner Zeitung*, Fischer Boel said that GM and

non-GM fields must be separated to avoid GM contamination. However, she opined that: "Regulations must not be so hard that the producers of GM crops have no chance to come to market."

Some German political observers have seen Fischer Boel's comments as a veiled reference to that country's strict new GM law, which holds planters of GM crops liable for economic damages to adjacent non-GM fields even if they followed planting instructions and other regulations. Many GM crop supporters see that law as an indirect attempt to stop GM planting in Germany.

Schroeder's main opposition parties, the CDU/CSU and the FDP, both issued statements applauding Fischer Boel's initiative.

Could Genomics Add to Growing Healthcare Bill?

Rampant inefficiency, inappropriate incentives, and advancing medical technology are all fueling the U.S.'s exploding medical bill, which has jumped from 2% to 16% of the GDP over the past 20 years. In a few years, genomic diagnostics and related treatments will be adding substantially to those costs, according to an executive of a diversified consulting firm Capgemini Vice President Peter R. Kongstvedt, speaking at the World Health Care Congress (WHCC) earlier this week.

Kongstvedt, whose company has a focus on controlling healthcare costs, pointed out that doctors already prescribe gene tests for breast cancer risk. At one end of the spectrum he stated, "some doctors recommend the test only for Jewish women with a family history of breast cancer." However, he added, "Other doctors are prescribing it for all women." Determining the true value of testing to any woman, he noted, is an important part of controlling the nation's spiraling healthcare bill. In this accord, he advised that genomic test developers think more, and earlier, about the cost and value of their potential products.

Discovery of Key Protein's Shape Could Lead to Improved Bacterial Pneumonia Vaccine

Scientists at St. Jude Children's Research Hospital have discovered that the shape of a protein on the surface of pneumonia bacteria helps these germs invade the human bloodstream. This finding, published December 16, 2004, online by the *EMBO Journal*, could help scientists develop a vaccine that is significantly more effective in protecting children against the disease.

The St. Jude researchers determined the shape of a large, paddle-like molecule that *Streptococcus pneumoniae* bacteria use to latch onto cells lining the throat and lungs. The protein, CbpA, binds to a molecule on the cell called pIgR, which takes antibodies from the bloodstream on one side of the cell and transports them to the other side. There it releases the antibody at the lining of the throat and lungs. If a pneumococcus bacterium is hovering on the lining of the respiratory tract, this germ binds to pIgR and pushes this antibody shuttle back through the cell to the bloodstream. Once at the other side of the cell, the pneumococcus breaks free of pIgR and enters the blood, where it can multiply and infect the body.

S. pneumoniae is the only bacterium known to use CbpA to invade human cells by binding to pIgR, according to Dr. Richard W. Kriwacki,* associate member of St. Jude Structural Biology and senior author of the *EMBO Journal* report. "The fact that we now know the structure of this important protein means we can begin to develop a vaccine that is more effective in children than those that are currently available," he explained. "Using CbpA as the key part of a new vaccine against *S. pneumoniae* would solve a problem that now hinders our ability to protect children

from this infection," added Elaine Tuomanen, Chair of Infectious Diseases and Director of the Children's Infection Defense Center at St. Jude, who is co-author of the *EMBO Journal* paper.

Current pneumonia vaccines designed to protect adults against more than two dozen strains of *S. pneumoniae* do not work in young children. Adult vaccines are composed of pieces of carbohydrates naturally appearing on the surface of these bacteria. When used in a vaccine, these pieces of carbohydrate stimulate the immune system to make antibodies against the real carbohydrate targets on the bacteria. The problem with such vaccines is that the immune systems of very young children (younger than two years) do not naturally respond to carbohydrates. Pneumococcus vaccines for children must instead be modified by binding those carbohydrates to special proteins that stimulate the immune systems of young children.


"However such vaccines are so complex that they can carry carbohydrate targets for only a few specific strains of pneumonia bacteria," Dr. Tuomanen said. "Children are always under-protected, since there are so many different strains of these bacteria."

"CbpA is a very large protein," she noted. "Now that we know what it looks like and how it's put together, we can pull it apart to see if smaller pieces of it can be used to make a vaccine that triggers production of antibodies against the CbpA. Since all the *S. pneumoniae* strains need CbpA to invade the bloodstream, we can widen the protection of a vaccine to all 90 types of pneumococcus by just adding CbpA, or a piece of CbpA."

The discovery of the structure of CbpA was a two-step process that

included studies of how this protein works, followed by determination of its structure using powerful tools. Previous work by another team suggested that CbpA binds to pIgR. However, that finding was made in "test-tube" experiments without using actual bacteria. So the St. Jude team developed pneumococcus bacteria that had mutated CbpA in order to prove that live bacteria with mutated CbpA could not bind to pIgR on cells.

"Our work confirmed that the pneumococcus uses CbpA to bind to human cells," said Beth Mann, a research specialist in the Tuomanen lab who developed the bacteria carrying mutated CbpA. Mann showed that the long, paddle-shaped extensions of the protein must be folded in a specific way in order for CbpA to work.

The discovery of the actual shape of CbpA was made using nuclear magnetic resonance (NMR) spectroscopy and circular dichroism (CD). NMR combines radio wave emissions and a powerful magnetic field to determine the three-dimensional structure of proteins suspended in solutions, whereas CD measures differences in the absorption of different wave lengths of polarized light by molecules to determine certain broad features of their overall shape. It also detects transformations in structure when the protein interacts with another molecule. "This work required that we develop new NMR methods in order to determine the shape of this protein, which undergoes changes as it interacts with pIgR," said Dr. Rensheng Luo, a post-doctoral fellow in St. Jude Structural Biology and Infectious Diseases and first author of the paper. 

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The American Society for Biochemistry for Molecular Biology is pleased to announce the support of two meetings in 2005 and two meetings in 2006. Mark your calendars and watch for more details in *ASBMB Today* and on our website, www.asbmb.org/meetings.



Fe-S Proteins: Biogenesis, Structure and Function

May 19-22, 2005 • University of Wisconsin, Madison
Organizers: Elizabeth A. Craig, Helmut Beinert, Patricia Kiley, and Richard Eisenstein, University of Wisconsin, Madison



14th International Conference on Cytochromes P450: Biochemistry, Biophysics, and Bioinformatics

May 31-June 5, 2005 • Hyatt Regency Hotel, Dallas
Organizers: Julian A. Peterson, and Sandra E. Graham, U.T. Southwestern Medical Center, Dallas, Texas



Transcriptional Regulation by Chromatin and RNA Polymerase II

Meeting in 2006
Organizer: Ali Shilatifard, Saint Louis University School of Medicine

DNA Structure, Genomic Rearrangements, and Human Disease

Meeting in 2006
Organizers: James R. Lupski, Baylor College of Medicine, and Robert D. Wells, Texas A&M University System Health Science Center



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Britain's Need for Foreign Students

By John D. Thompson, Editor

In the U.S. we have an ongoing debate about whether there are or are not enough U.S. born scientists (see letter page 2), and whether problems in obtaining visas are stemming the flow of foreign students to U.S. universities, in Britain the problem is that age old one—money.

According to a report in the January 15 issue of *The Economist*, the tuitions paid by foreign students from nations outside Britain and the European Union (EU) are crucial to keeping the UK's universities afloat. These foreign students pay £8,000 (about \$15,000) a year, while the universities get only about £5,000 (\$9,400) in fees and government subsidies from the typical stu-

dent from the EU or UK. That £3,000 difference, according to authorities such as Ivor Crewe, of the lobbyist group Universities UK, and Sir Howard Davies, Director of the London School of Economics, is essential to the nation's universities. The importance of foreign money is epitomized by one university in Middlesex, where fees from foreign students cover a fifth of the school's budget, and are expected to soon exceed the funding from British students.

As UK institutions look to the future, they can take comfort from what is happening on this side of the Atlantic. The U.S., regarded as Britain's biggest competitor for international students, is see-

ing hordes of potential students turning elsewhere because of stricter policies and lengthy delays in obtaining visas. This seen as having a favorable impact on the UK, where the demand from Chinese students is huge and has been increasing at an annual rate of 50%.

Britain's current advantage in attracting foreign students may, however, prove fleeting. Competition is on the way. European universities have begun an aggressive marketing campaign to attract post-graduate students from overseas, while China is attracting increasing numbers of students from other Asian countries, while at the same time seeking to entice foreign universities into opening Chinese campuses. 

UK Spurns Open Access

The British government said early last month that it had no intention to require researchers to deposit copies of their papers in free-access repositories.

"The government should be supporting the best and most cost-effective way possible to channel scientific outputs, and at the moment it is not demonstrable that the 'author pays' model is the better system," the government said in its second response to criticisms of its earlier statements. "The action the government has decided on is to facilitate a level playing field, which will enable authors who wish to publish in author-pays journals to do so. This includes working with the Research Councils UK (RCUK) on a common policy that allows scientists to publish in an author-pays journal when they want to do so."

"The government recognizes the potential benefits of institutional repositories and sees them as a signifi-

cant development worthy of encouragement," the response said. "But it believes that each institution has to make its own decision about Institutional repositories depending on individual circumstances."


Last July, the House of Commons Select Committee on Science and Technology published a report on the status and future of scientific publishing in the UK. The committee's report recommended that the government fund the establishment of a network of institutional repositories where all research articles originating in the United Kingdom would be deposited and available to read for free.

In November, the government responded, by stating that it had no intention of requiring researchers to deposit copies of their publications in free-access repositories. That response drew strong criticism from open-access advocates and from the committee itself, particularly over the government's

focus on the "author-pays" model of journal publishing, rather than the idea of open-access repositories.

"The government has not decided against the author-pays model, but does not want to force a premature transition to a different system," the new report says. "To strongly endorse or reject the author-pays approach would not be in the interests of allowing the market itself to evolve to meet the needs of authors and the wider academic community."

Peter Suber, an advocate of open access who is based at Earlham College in Richmond, Ind., told *The Scientist* that the government's latest response suffers from the same shortcomings as the first.

He declared that by giving its primary attention to open access journals, a secondary issue in the committee report, it had ignored the primary recommendation of the report on open access archives, without answering any of the committee's points, 

Career Opportunities

EDITOR-IN-CHIEF OF THE FASEB JOURNAL

The Federation of American Societies for Experimental Biology (FASEB)

The position of Editor-in-Chief (EIC) of The FASEB Journal will become available as early as July 1, 2005, but needs to be filled no later than January 1, 2006. A search committee has been appointed by the FASEB Board and the FASEB Publications Committee to initiate the search for a distinguished scientist to head this interdisciplinary journal. Candidates should have a Ph.D., M.D., or an equivalent academic degree, broad experience in experimental biological and biomedical sciences, and prior experience in editorial activities related to these scientific fields. The appointment would be for a five-year term, with potential reappointment. The EIC would report to the Board of Directors of FASEB through the FASEB Publications and Communications Committee but he or she would have extensive flexibility in selecting the Associate Editors, the Editorial Board, and future directions for the Journal. Candidates interested in the position should submit a statement of interest, along with their curriculum vitae and the names of three references to Donald A. Fischman, M.D., Chair, FASEB J. Search Committee, C/O Ms. Lynn Willis, Managing Editor, FASEB J, 9650 Rockville Pike, Bethesda, MD 20814-3998; or by email to llwillis@faseb.org. The application deadline is May 1, 2005.

DOW Endowed Professor of Chemistry

The West Virginia State University Department of Chemistry and Division of Agricultural, Consumer, Environmental, and Outreach Programs solicits applications for the newly endowed position, the Dow Endowed Chemical Company Professor of Chemistry Research and Education.

Qualifications: Candidates for this new position will have a Ph.D. in biochemistry. Both postdoctoral research and experience in securing externally-funded grants are desired. This is a non-tenure track position, renewable for up to 5 years. However, this position could evolve into a tenure track position.

Duties and Responsibilities: The successful candidate will be expected to interact with members of the Departments of Biology & Chemistry, researchers in Land Grant Programs and to strengthen the corporate partnership between Dow Chemical Company and

West Virginia State University. The successful candidate is expected to teach both a biochemistry lecture and laboratory course annually, participate in outreach educational activities, and to establish a research program in her/his area of expertise. This research should complement ongoing activities within one of the programs sustained in the USDA 1890 Land-Grant Plan of Work: applied, industrial, or environmental microbiology and biotechnology; horticulture and alternative agriculture; environmental biology or environmental chemistry; aquaculture. This research will attract external funding and active participation by undergraduate and graduate students. This is a joint teaching and research appointment.

Salary: Commensurate with experience.

Closing Date: Screening of applicants will begin February 15, 2005 and will continue until the position is filled. The successful candidate should be prepared to start by August 15, 2005.

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Calendar of Scientific Meetings

APRIL 2005

American Society for Biochemistry and Molecular Biology Annual Meeting in Conjunction with EB2005

April 2–6 • San Diego, CA

Nobel Laureates Michael S. Brown and Joseph L. Goldstein will open the ASBMB Annual Meeting with the Herbert Tabor/Journal of Biological Chemistry Lecture.

Contact: ASBMB 2005, 9650 Rockville Pike, Bethesda, MD 20814-3008; Ph: 301-634-7145; Email: meetings@asbmb.org
Website: www.asbmb.org/meetings

The 46th ENC Experimental Nuclear Magnetic Resonance

April 10–15 • Rhode Island Convention Center, Providence, RI

Contact: ENC, 2019 Galisteo Street, Building I Santa Fe, New Mexico 87505 (USA); Ph: 505-989-4573
Fx: 505-989-1073; E-mail: enc@enc-conference.org
Website: www.enc-conference.org

MAY 2005

Bone Quality: What Is It and Can We Measure It?

May 2–3 • Hyatt Regency Bethesda, Maryland

A Scientific Meeting Sponsored by the National Institute of Arthritis and Musculoskeletal Skin Diseases (NIAMS) and the American Society for Bone and Mineral Research (ASBMR)
Ph: 202-367-1161; Email: asbmr@smithbucklin.com
Website: www.asbmr.org/bonequality.cfm

EuroMedLab 2005—16th IFCC-FESCC European Congress of Clinical Chemistry and Laboratory Medicine

May 8–12 • EuroMedLab, Glasgow, UK

Contact: Jordanhill Campus Southbrae Drive Glasgow 2, UK
Email: euromedlab2005@meetingmakers.co.uk
URL <http://www.glasgow2005.org>

From Gene to Genome: Heredity and Society

May 26–28 • Palais de Congrès, La Grande Motte, France

Contact: Christophe Schwob; Ph: +33 4 95 09 38 00
Fx: +33 4 95 09 38 01; Email: c.schwob@mcocongres.com
Website: www.genetogenome.org

14th International Conference on Cytochromes P450: Biochemistry, Biophysics, and Biochemistry

May 31–June 5 • The Hyatt Regency Hotel, Dallas, Texas
Focusing on such topics as Structure, Regulation, Protein-Protein Interaction, Bioinformatics, Functional Genomics, and Biophysical Investigations of Cytochromes P450 and their associated enzymes. Includes a CME course on Drug-Drug Interactions and P450 Polymorphisms and hands-on computer workshops.
Regular Registration by April 1, Late posters by April 1.
Contact: Sandra Graham; Ph: (001) 214 648-7628
Fx: (001) 214 648-8855; Email: Sandy@P450Dallas2005.US
Website: www.P450Dallas2005.US

JUNE 2005

7th Annual Plant Sciences Institute Symposium; Meristems 2005

June 2–5 • Iowa State University, Ames, Iowa

Abstracts due April 1, 2005; Registration Deadline May 2, 2005
Student Travel Grants: Applications due April 1, 2005
Contact: Plant Sciences Institute Symposia, Symposium Office, 3208 Molecular Biology Building, Iowa State University, Ames, Iowa 50011-3260; Ph: 515-294-7978; Fax: 515-294-2244
Email: pbmb@iastate.edu
Website: www.bb.iastate.edu/~gfst/phomepg.html

International Society For Stem Cell Research 3rd Annual Meeting

June 23–25 • San Francisco Marriott

Abstract Submission closes February 25.
Submission for oral and poster presentations will be via the ISSCR website. Ph: 847/509-1944; Fax: 847/480-9282
Email: isscr@isscr.org; Website: www.isscr.org

Glycoproteomics—Protein Modifications for Versatile Functions

June 28–30 • Dubrovnik, Croatia

For information: Email: glauc@pharma.hr; Ph: 385 1 4818 757
Website: bmb.pharma.hr/glyco2005/

JULY 2005

30th FEBS Congress — 9th IUBMB Conference, 2005 The Protein World; Proteins and Peptides: Structure, Function and Organization; Science is Fun: A Conference for Your Creativity

July 2–5 • Budapest, Hungary

Contact: Ms. Franciska Morlin, Chemol Travel Congress Dept. H-1366 Budapest, P.O.Box 28, Hungary
Ph: +36-1-266-7032, Fx: +36-1-266-7033
Email: incoming@chemoltravel.hu; www.febs-iubmb-2005.com

7th International Symposium on Biocatalysis and Biotransformations

July 3–8 • Delft, Netherlands

Contact: Biotrans 2005 Secretariat, Department of Biotechnology, Julianalaan 67 2628 BC, Delft, The Netherlands
Email: biotrans2005@tnw.tudelft.nl
Website: www.biotrans2005.bt.tudelft.nl/

FASEB Summer Research Conference on Transport ATPases: Genomics, Mechanisms, and Relevance to Disease

July 16–21 • Saxtons River, Vermont

Poster Sessions, Discussions, Young Investigator Forum
Organizers: Alan Senior & Kathleen Sweadner.
Applications will be available in March; Website: src.faseb.org.

Pathobiology of Cancer

July 17–24 • Snowmass Village Resort, Colorado
For information: Email: meetings@aacr.org
Website: www.aacr.org; Ph.: 215-440-9300

BioScience2005 – From Genes to Systems

July 17–21 • Glasgow, UK
Poster abstract deadline: April 15, 2005, Early registration deadline: May 23, 2005, For more information: BioScience2005, Biochemical Society, c/o Commerce Way, Colchester, Essex CO2 8HP
Ph: +44 (0)1206 796351; Fx : +44 (0)1206 798650
Email: info@BioScience2005.org; www.BioScience2005.org

Gordon Research Conference on Molecular & Cellular Biology of Lipids

July 24–29 • Kimball Union Academy, New Hampshire
Email: www.grc.uri.edu/05sched.htm#GRC

AUGUST 2005

Ninth International Congress on Amino Acids and Proteins

August 8–12 • Vienna, Austria
For Information: Prof.Dr.Gert Lubec, FRSC (UK)
Medical University of Vienna, Dept. of Pediatrics, Div. of Basic Science, Währinger Gürtel 18, A 1090 Vienna, Austria
Email: gert.lubec@meduniwien.ac.at
Ph: 0043.1.40400 3215; Fax: 0043.1.40400 3194
Website: fens.mdc-berlin.de/calendar/?id=485&action=read

2005 International Gap Junction Conference

August 13-18 • Westin Resort and Spa, Whistler, BC, Canada
Website: www.gapjunctionconference.org
Abstract And Registration Deadline: April 1
Contact: Dale W. Laird, University of Western Ontario, London, Ontario, Canada, N6A-5C1; Ph: 519 661-2111 x86827
Fax: 519 850-2562; Email: dale.laird@fmd.uwo.ca

7th International Symposium on Mass Spectrometry in the Health and Life Sciences: Molecular and Cellular Proteomics

August 21-25 • Fairmont Hotel, San Francisco
This symposium will integrate mass spectrometry perspectives with the needs of the biomedical sciences, including: Sub-cellular separation strategies and sample handling • Analysis and automation technologies • Protein identification and quantitation • Studies of covalent modifications • Modulation of biological function • Protein machines and assemblages and organelles • Deciphering protein networks and systems • Mining genome and proteome databases • Bioinformatics.
For further information contact the symposium office:
Phone: (415) 476-4893; Fax: (415) 502-1655
Email: sfms@itsa.ucsf.edu
Website : http://ms-facility.ucsf.edu/symposium

SEPTEMBER 2005

Second World Congress on Synthetic Receptors

September 7–9 • Salzburg Congress Centre, Salzburg, Austria
Abstract Deadlines: 25 March 2005 (oral and poster papers)
For information: Conference Secretariat, Elsevier, The Boulevard, Langford Lane, Kidlington, OxfordOX5 1GB, UK
Tel: +44 (0) 1865 843691; Fax: +44 (0) 1865 843958
Email: jm.seabrook@elsevier.com
Website: www.syntheticreceptors.elsevier.com

Strategies for Engineered Negligible Senescence [SENS], 2nd Conference

September 7–11 • Queens' College, Cambridge, England
Conference organizer: Aubrey de Grey
Email: ag24@gen.cam.ac.uk
Website: www.gen.cam.ac.uk/sens2/CSBMCB

14th Annual Growth Factor and Signal Transduction Symposium: Integration of Structural and Functional Genomics

September 22 – 25 • Iowa State University, Ames Iowa
Ph: 515-294-7978; Email: gfst@iastate.edu
Website: www.bb.iastate.edu/~gfst/homepg.html

International Conference on Enzyme Technology RELATENZ 2005

September 20–23 • Varadero, Matanzas, Cuba
Contact: Autopista a Varadero km 3 ?
Matanzas, C.P.44740, Cuba
Email relatenz.umcc@umcc.cu
Website: www.umcc.cu/EnzymeTechnology/relatenz.htm

American Society for Bone and Mineral Research [ASBMR] 27th Annual Meeting

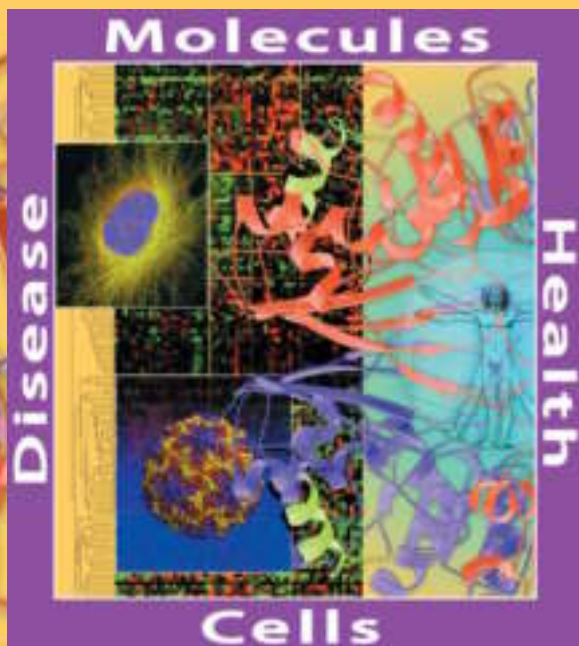
September 23–27 • Gaylord Opryland Resort and Convention Center, Nashville, Tennessee
Abstract Submission Deadline: April 27, 2005
For more information call (202) 367-1161
Email: asbmr@smithbucklin.com; Website: www.asbmr.org

OCTOBER 2005

North Carolina RNA Society's Symposium on RNA Biology VI: RNA, Target and Tool Theme: Small RNAs and RNPs.

October 21-22 • North Carolina Biotechnology Center, Research Triangle Park, NC. 2005
Deadline for registration and abstract submission: July 1
Email: stu_maxwell@ncsu.edu.
Website: http://www.med.unc.edu/pmbb/nc-rna-soc.html

See You in San Diego!



2005 ASBMB Annual Meeting

Held in conjunction with EB 2005

April 2-6, 2005

San Diego, CA

Meeting Organizers

Dennis R. Voelker, National Jewish Medical Research Center

Cecile Rochette-Egly, IGBMC, Strasbourg

and the 2005 ASBMB Program Planning Committee

Meeting Themes

Dynamics of Protein—

Protein Interactions (Bumping in the Night)

Chair: Ben Margolis, HHMI, Univ. of Michigan

DNA Replication and Interactive Repair and Recombinational Processes

Chair: Charles S. McHenry, Univ. of Colorado Health Sciences
Center

Coordinate Regulation of Transcription

Chair: Cecile Rochette-Egly, IGBMC, Strasbourg

Interactions and Functions of Glycoconjugates

Chair: Mark A. Lehrman, Univ. of Texas Southwestern
Medical Center

Integration and Organization of Signaling Pathways

Chair: Alex Toker, Beth Israel Deaconess Medical Center

Minority Affairs Committee Symposia

Chair: Phillip A. Ortiz, Empire State College

Biochemistry and Molecular Biology of Lipids

Chair: Charles O. Rock, St. Jude Children's Research Hospital

Organelle Biogenesis and Dynamics

Co-Chairs: Carla Koehler, UCLA and Danny Schnell, Univ. of
Massachusetts, Amherst

Proteolysis and Disease

Chair: Charles Craik, Univ. of California, San Francisco

Catalysis: Structure, Function, and Evolution

Chair: John A. Gerlt, Univ. of Illinois, Urbana-Champaign

Metabolic Regulatory Circuits

Chair: M. Daniel Lane, Johns Hopkins Univ. School of Medicine

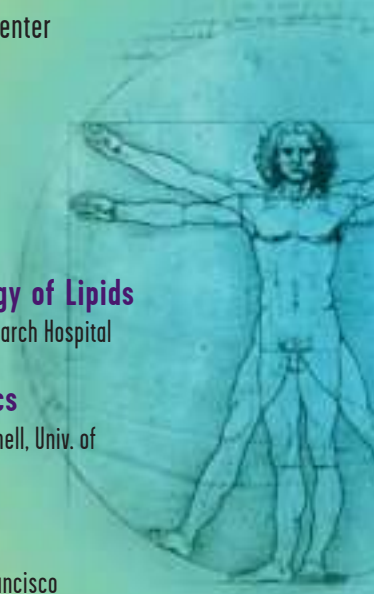
Genomes and Proteomes

Chair: Andrew J. Link, Vanderbilt Univ.

Education in the Biomolecular Sciences:

The Next Generation

Co-Chairs: Judith G. Voet, Swarthmore College and Marion O'Leary,
California State Univ. at Sacramento



Experimental
Biology

2005

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