MARCH 2004

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ASBMB Today

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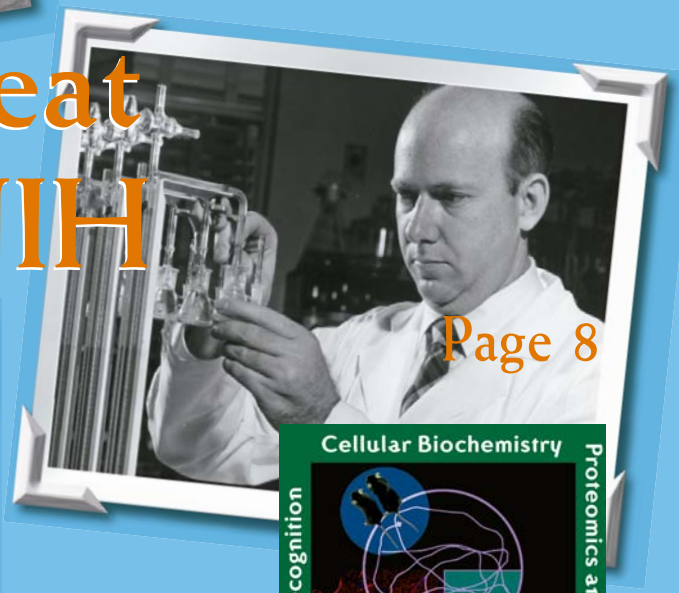
AMERICAN SOCIETY FOR BIOCHEMISTRY AND MOLECULAR BIOLOGY

ALSO IN THIS ISSUE



# The Stadtmans: 53 Years of Great Chemistry at NIH



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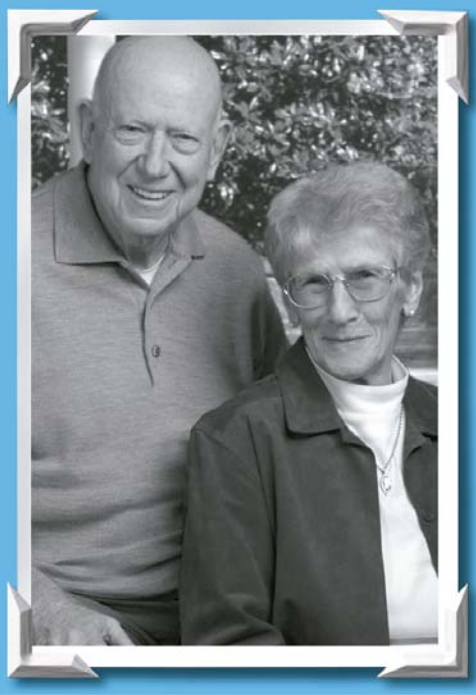

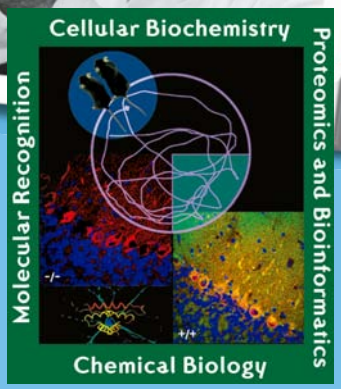


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ASBMB Annual Meeting
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June 12-16, 2004
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# ASBMB Today

AMERICAN SOCIETY FOR BIOCHEMISTRY AND MOLECULAR BIOLOGY

MARCH 2004,
Volume 2, Issue 12

## features



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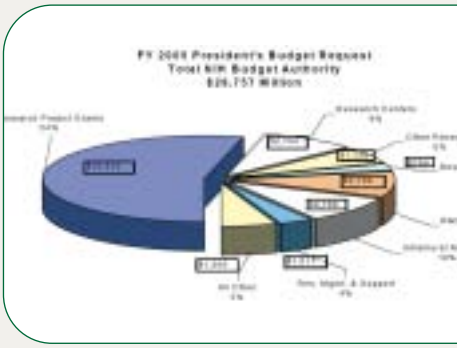

ON THE COVER:



THE EXCEL AWARDS FOR EXCELLENCE IN ASSOCIATION PUBLISHING

SOCIETY OF NATIONAL ASSOCIATION PUBLICATIONS SNAP

BRONZE AWARD WINNER 2004

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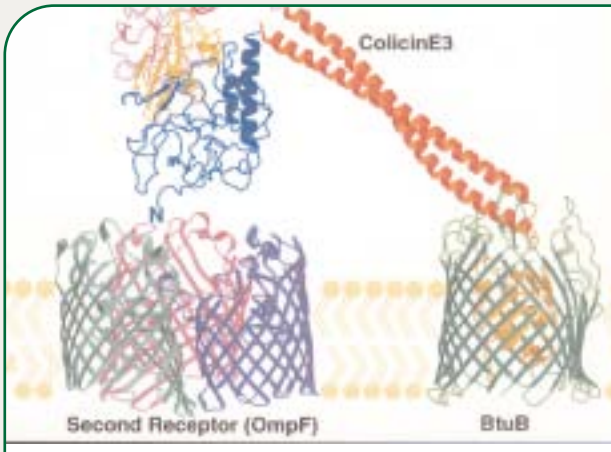

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**Comments**

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# From the ASBMB President

**Fellow Society Members:**

For the past 8 months we have been engaged in the process of a search for a successor to Mr. Charles C. Hancock as Executive Officer of ASBMB. The process was carefully planned and executed in two stages. A Search Committee, chaired by Dr. Vern Schramm and consisting of officers, journal associate editors, committee chairs and others, reviewed a slate of 81 applicants. Eight finalists were interviewed in December 2003, and from these, four finalists were selected. At their direction, I named a subcommittee of ASBMB Council, who then interviewed these finalists in Bethesda on January 28, 2004. After these interviews, a decision was made to recommend the final candidate to Council during a teleconference meeting on February 17, 2004, in which every voting member of Council (13) participated.

I am pleased to announce the selection of Ms. Barbara A. Gordon as Executive Officer of ASBMB. Ms. Gordon has served ASBMB for 31 years in various capacities, most recently as Deputy Executive Officer and Interim Executive Officer. During her interviews, she impressed the various representatives of the Society with her management plan in view of changes in the Presidency, the Council, the publishing environment, the funding of science, and the many new initiatives that ASBMB is embarking upon. Ms. Gordon maintained that the Society, through its Council, needs to set and adhere to its own course, to be facilitated through the executive offices, and she plans to work with Council to hire the appropriate support staff and organize the offices to bring these plans to fruition, as they are developed. A more complete story about Ms. Gordon will appear in the April issue of *ASBMB Today*.

I hope you will join me in welcoming Ms. Barbara Gordon to her new position and pledge *your* support of her efforts to achieve the goals of ASBMB in becoming an even greater force in the national and international biomedical research arena than it was in its previous 100 years.

Bettie Sue Masters
President

# Ask Not

## What the ASBMB Can Do for You, But Rather Ask What You Can Do for the ASBMB!

**Together we can do so much more than we can do as individuals.**

Scientists join professional societies for many reasons. A most meaningful reason is to be part of a community of scientists united in the quest for knowledge. A second reason is to lend support to an organization that promotes goals that benefit members in the short- and long-range. Other reasons cited include receiving specific benefits such as reduced rates to journal subscriptions and meeting registrations, or seemingly peripheral reasons such as insurance plans, credit cards, discounts and vacation tours. As do other societies, the ASBMB has a substantial list of "Member Benefits." A look at our web page (www.asbmb.org) reveals:

- Free subscriptions to the *Journal of Biological Chemistry On-Line* with "CiteTrack"
- Free subscriptions to *Molecular and Cellular Proteomics On-Line*
- Reduced rates on other scientific publications such as *Journal of Lipid Research*, *Biochemistry & Molecular Biology Education*, *Annual Review of Biochemistry*, *Trends in Biochemical Sciences (TIBS)*
- Free subscriptions to *ASBMB Today* and *The Scientist*
- Free access to AAAS' *Science Now* and *Science's NextWave*
- Discounts on ASBMB meeting registration fees
- Fellowship Travel Awards, Career Networking and Employment Assistance
- Public Policy Activities—information and a chance to be involved
- Free copy of the FASEB Member Directory
- Free Public Relations materials

Our experience is that there is much, much more that accrues for its members than the above list. That list recounts some of the incentives and privileges. Yes, some like the "CiteTrack" message that alerts you to articles of direct interest to you, the discounts and free subscriptions, and *ASBMB Today* magazine that keeps you informed about special public policy issues, projects and people. But of considerable importance is the fact that you can keep abreast of the pulse of the profession, and you can participate in activities at whatever level you choose. The Society has a talented, dedicated, enthusiastic staff that produces the journals, manages the meetings, supports the Education and Professional Development activities (especially undergraduate curriculum and affiliate network development), the Minority Affairs Committee (meetings programs and opportunities for underrepresented minorities), and the Public Affairs Advisory Committee. This last committee keeps abreast of policies and procedures that will affect the funding and practice of science (especially when members of Congress turn their attention to issues such as peer-review, cloning, and visas for foreign trainees and visitors). Overall though, it is the efforts of the scientists themselves who volunteer their time, thoughts, energy, and talents that really make a difference in realizing our mission:

'Promoting understanding of the molecular nature of life processes'

We are very much enriched by our colleagues who participate in ASBMB committees and plan activities. For example:

- The Education and Professional Development Committee assists undergraduate faculty and students in setting up curricula for undergraduate majors in Biochemistry and Molecular Biology (BMB), supports regional networks for BMB interactions, and organizes a session at our national meetings.
- Council members oversee all the Society activities, and initiate and approve strategic plans.
- Members of the Minority Affairs Committee develop strategies to ensure that the society is a welcoming forum and to address the problems and sensitivities of underrepresented groups.
- The Publications Committee deals with issues that affect the quality, fairness and impact of our journals.
- Members of the Meetings/Programs Committee are responsible for the organization and implementation of our annual meetings.
- Members of the Public Affairs Advisory Committee cooperate with their counterparts in FASEB and other groups to inform Congressional and other federal leaders and state agencies of issues that directly affect us (e.g., funding and regulations on cloning).
- Finance Committee members strive to use our resources wisely, and to keep the Society solvent and in concert with the changing models of online publishing and meetings.

These volunteers represent your interests.

We need you. Let us know the activities to which you can make a contribution. Send an email message

*Continued on p. 22*

by Peter Farnham, CAE, ASBMB Pulic Affairs Officer

# NIH, NSF Increases in '05 Budget

The Bush administration dropped the other shoe on February 2, and released a budget for basic scientific research that confirmed the disquieting rumors that had been circulating in Washington for weeks beforehand. Both the National Institutes of Health and the National Science Foundation are to receive increases for the coming fiscal year that barely meet projected inflation levels.

For NIH, the news is particularly unfortunate. After last year's increase of barely over 3 percent, NIH would get an increase of only 2.6 percent for fiscal 2005, continuing the erosion of the effects of the doubling program completed in 2003. NIH would receive $28.757 billion under the president's proposal, a $729 million increase over fiscal 2004. The total number of new and competing research project grants would be 10,393, the same as the projected total for fiscal 2003 and a slight increase over the number now projected for 2004. Although many academic researchers view the number of new and competing grants each year as a quick numerical method of measuring NIH's health, this is a highly imperfect measure because the number of grants can be manipulated.

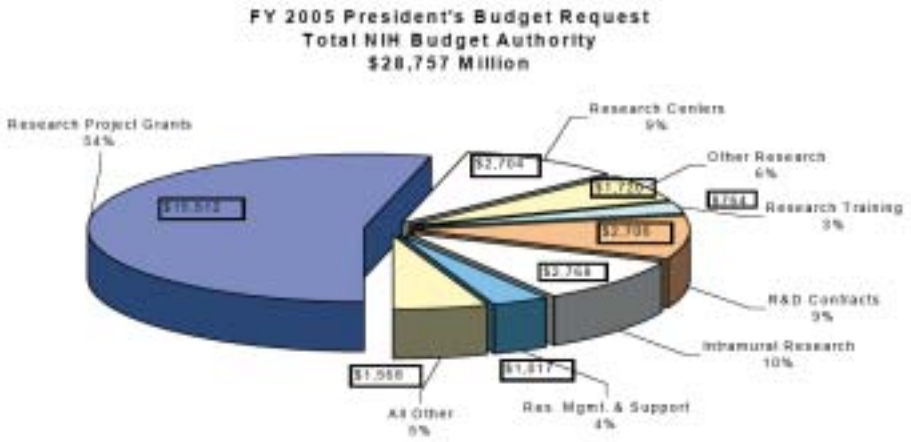
For example, many in the biomedical research community expected the number of new and competing grants to decline this year by as many as 1,500, to around 9,000 or so. That did not happen. Last year NIH projected the total number of new and competing grants for FY 2004 to be 10,509. This figure has been reduced in the 2005 budget submission to just over 10,100. This would indicate that the number such grants for 2005 has actually increased over fiscal 2004, rather than declined. However, the increases all grants get in their second, third, and fourth years are being severely curtailed under the 2005 budget. The NIH budget calls for noncompeting research project grant awards to increase by 1.9 percent, while competing awards would increase in size by 1 percent. Overall, NIH grants will increase by only 1.3 percent this year, well below the 4.6 percent projected rate of biomedical inflation, and also well below the increase most continuing renewal grants have received in the past.

In effect, the administration is keeping the number of new grants up by reducing the size of future annual increases. The result is to give most researchers some of the needed money, rather than giving fewer researchers all the money they need.

"For science, the NIH budget is a disaster," said one well-informed NIH observer. However, he noted that in the context of the President's budget as a whole, NIH is a winner. Since domestic discretionary spending increases only about 1 percent overall, for NIH to increase by 2.6 percent makes it one of the few agencies to do relatively well in the budget proposal. "The problem we need to address is that there is not enough money in the budget overall," the observer added.

NSF would receive a total of $5.745 billion for fiscal 2005 under the president's proposal. Former NSF Director Rita Colwell, who resigned effective February 21, said the funds will "address frontiers of knowledge and innovation that will strengthen economic growth and prosperity nationally." The NSF will increase about 3 percent overall. Most directorates at NSF increase by just over 2 percent, although research overall increases 4.7 percent. Unfortunately, this increase comes at the expense of the Education and Human Resources Directorate, which is hit with a whopping 17 percent decrease, as the President has proposed that the Math and Science Partnerships program be eliminated, with the funds for it being transferred to support research.

According to NSF, five priority areas are slated to receive more than $537 million in 2005. Support for Nanoscale Science and Engineering will increase



# Barely Meet Inflation Level

by 20 percent, while support for Biocomplexity in the Environment, Mathematical Sciences, and Human and Social Dynamics will continue at 2004 levels. The new budget asks $20 million to start NSF's Workforce for the Twenty-First Century program which is to focus on U.S. citizens and broader participation.

The fiscal 2005 budget seeks funding for six major research facilities, as well as a 10.7 percent increase in funding for NSF's integrative research and education centers programs, including six new Science and Technology Centers (STC). This raises overall funding for STCs by about $30 million to $72.4 million in 2005. Other major increases will be directed toward chemistry centers, Long Term Ecological Research projects, Mathematical Sciences Research Institutes, Nanoscale Science and Engineering Centers and Centers for Social, Behavioral and Economic Sciences.

NSF is also requesting $363 million for Organizational Excellence, a key strategic goal planned for 2005, which agency officials describe as equal and complementary to NSF's other goals of people, ideas and tools. "We have been an innovator in sound business practices, having received the President's Quality Award for Management Excellence and two green-light ratings from OMB for financial management and e-government," Dr. Colwell said. "Yet, for the past two decades—not years—we have kept the same basic staffing level despite significant increases in workload, steadily rising numbers of proposals and greater numbers of high-dollar, multidisciplinary projects that require sophisticated monitoring and evaluation." In particular, the increased investment will help upgrade NSF's operational systems to ensure their continued reliability, security, and user friendliness, she said.

The former NSF director also noted, with approval, the National Science Board's December 2003 report that called for a $19 billion increase in the NSF budget to address unmet scientific research and educational needs.

# Budget Will Emaciate Science, Says Science Committee Chair

*Sherwood Boehlert (R-NY),*

Sherwood Boehlert (R-NY), Chairman of the House Science Committee, commenting on the NSF's R&D budget, declared, "The budget chapter on R&D (in the president's budget proposal) includes the quotation that 'Science is a horse. Don't worship it. Feed it.' The budget does not reflect that advice. After a few years of spending at the levels proposed in this budget, science would be an emaciated, old, grey mare, unable to produce any new ideas or young scientists."

In additional observations about the NSF budget, Boehlert continued, "We need to remember that the decade of unprecedented economic growth that began in 1992 and that lasted into this new century was a result of previous investments we had made in science and technology, particularly in areas such as information technology and the health sciences. If the current recovery is to be sustained, we need to invest now in R&D. A healthy investment in R&D is the only way to ensure that our economy will continue to create jobs over the long term.

"Yet basic and applied research in this budget would increase at less than the rate of inflation. And while we are still reviewing the specific budgets of individual agencies, some glaringly bad decisions already stand out. Primary among them is the proposal to move the Math and Science Partnerships from the National Science Foundation (NSF) to the Department of Education. We will fight that decision tooth-and-nail. For some reason, the remaining, close-out money proposed for the Partnerships is moved to the research account of NSF, where it artificially inflates what would otherwise be a mediocre rise in research spending."

# NIBIB and CDRH Sign Interagency Agreement Establishing Joint Laboratory

The National Institute of Biomedical Imaging and Bioengineering (NIBIB) at the National Institutes of Health and the Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration signed an interagency agreement recently to establish a joint Laboratory for the Assessment of Medical Imaging Systems (LAMIS). The purpose of this joint effort is to assess and optimize high-resolution, high-dimensional medical imaging systems.

***"The joint agreement will provide us with another avenue for exploring innovative and high-quality technologies and interdisciplinary research that will lead to improved healthcare."***

—NIBIB Director Roderic Pettigrew.

The goals of LAMIS are to develop evaluation methodology based on advanced statistical tools, determine fundamental limitations imposed on imaging systems, characterize and optimize medical imaging systems and components, build consensus, provide advanced image evaluation methods, and develop an environment conducive to rapid deployment of improved imaging systems and components to the patient community. In addition, optimal hardware designs and approaches for image reconstruction and extracting features will be pursued.

"The joint agreement with CDRH is an exciting opportunity for the NIBIB, and will provide us with another avenue for exploring innovative and high-quality technologies and interdisciplinary research that will lead to improved healthcare. The CDRH medical imaging program is stellar, and we are proud to collaborate with an organization of this caliber," said NIBIB Director Roderic I. Pettigrew.

"CDRH welcomes this opportunity to collaborate with NIBIB," said CDRH Director David W. Feigal. "Not only will this new agreement strengthen the imaging programs of both organizations, but it will also benefit the public by leading to the earlier availability of safe, effective medical imaging technologies."

To carry out the mission of the new laboratory, a multidisciplinary team of clinicians, scientists, and mathematicians/statisticians will be assembled. The team will work with visiting scientists and trainees—from graduate and medical students to senior researchers and clinicians. Visitors to the laboratory will apply assessment methods developed by the group to their own problems, and carry with them the principles and tools for longer-term use when they leave.

## The NIH Director's Pioneer Award Program

The National Institutes of Health (NIH) invites nominations for the NIH Director's Pioneer Award (NDPA), a key component of the NIH Roadmap for Medical Research.

The goal of the program is to stimulate high-risk, high-impact research by enabling exceptionally creative investigators from multiple disciplines—including biomedical, behavioral, social, physical, chemical and computer science; engineering; and mathematics—to develop and test groundbreaking ideas relevant to NIH's mission.

In fiscal year 2004, the NDPA program will fund 5-10 awards of up to $500,000 direct costs per year for 5 years.

The program is not intended to support ongoing research projects or expand the funding of persons already well supported. Investigators at early stages of their careers and those who have not previously applied for NIH support are especially encouraged.

Nominations will be accepted from March 1, 2004 through midnight April 1, 2004, Eastern Standard Time.

For more information or to submit a nomination, visit the NIH Director's Pioneer Award Web site at: http://www.nihroadmap.nih.gov/highrisk/initiatives/pioneer.

# NSF Director Colwell Resigns

Rita R. Colwell resigned as National Science Foundation Director effective February 21, the NSF announced in early February. She will assume the position of Chairman of Canon U.S. Life Sciences, Inc. upon her retirement from the Foundation.

Serving as Acting NSF Director until a permanent director is appointed is Arden L. Bement, currently Director of the National Institute of Standards and Technology. Bement has been a member of the National Science Board, NSF's oversight body, for many years.

"I am extremely grateful to have had the opportunity to lead NSF through two Administrations and major transformational changes," Colwell said. "During the past five and a half years, our budget has increased by 68 percent, our merit review system has been recognized throughout government as the gold standard for responsible use of public funds, and our programs have helped U.S. science and engineering evolve into the flexible, robust and diverse endeavors that they must become to keep America preeminent at the frontier of research and education."

"Thanks to Dr. Colwell's leadership, vision and dedication, the National Science Foundation has become a model for management excellence among federal agencies," said President Bush. "I deeply appreciate her service to the nation, and am pleased that American science will continue to benefit from her talent."

During Dr. Colwell's tenure at NSF, grant size increased from an annual average of $80,000 in 1998 to $142,000 at present. She urged and obtained substantial increases in graduate-student stipends, and called for expanded opportunities for minorities and women in the nation's science and engineering communities.

During her term, NSF also received the highest achievement ratings of any federal agency in performance on the President's Management Agenda and was named a "model" agency by the White House.

Dr. Colwell is a microbiologist and internationally recognized expert on cholera and other infectious diseases. She took office at NSF in August 1998, and was the first life scientist to head the agency. Previously, she held many advisory positions in the U.S. Government, non-profit science policy organizations, and private foundations, as well as in the international scientific research community. She also was President of the American Association for the Advancement of Science and the American Society for Microbiology. She has authored or co-authored 16 books and more than 600 scientific publications. She produced the award-winning film, "*Invisible Seas*," and has served on editorial boards of numerous scientific journals.

## NIH Launches New Virtual Career Center

The National Institutes of Health has launched a new Virtual Career Center (http://www.training.nih.gov/careers/careercenter/index.html), developed by the intramural Office of Education (OE). It is designed to meet the needs of the NIH community as well as students and professionals in science and medicine, from the college level to postdoctoral and beyond. The Virtual Career Center is arranged into four major areas of interest for individuals seeking information on careers and employment: exploring career options, continuing education, employment options and opportunities, and the job search process. The site is highly selective, guiding users to a range of resources on the web.

## NSF-funded Survey of Changing Conceptions of the Gene

Changes in our understanding of the structure and function of genes have occurred through the concept's one hundred year history but have accelerated rapidly in recent years. The Representing Genes project, funded by NSF, is an interdisciplinary group of researchers examining the current status of the concept and how researchers in different fields have reconceived it to meet their particular needs. We aim to gather the views of the widest possible range of biological researchers and ask for your assistance in completing a web-based survey based on a series on intriguing cases in contemporary genomics. Please take the opportunity to be part of this project.

The survey is posted at: http://surveyweb.ucsur.pitt.edu/sw/wchost.asp?st=gene and will remain accessible through the end of March.

# The Stadtmans

## 53 Years of Great Chemistry

A special exhibit at the National Institutes of Health (NIH) celebrates 53 years of achievements by an outstanding couple, Earl and Thressa Stadtman, who between them have trained more than 100 postdoctoral fellows, including two Nobel laureates.

Their scientific accomplishments in the fields of Vitamin B12 and selenium biochemistry (Terry) and aging, fatty acids and amino acids (Earl) might have been enough to justify all the attention, but NIH officials have said the Stadtmans' legendary mentoring may have had a greater impact.

The Stadtmans went out of their way, they said, to follow the advice of Fritz Lipmann, Earl's mentor at Massachusetts General Hospital in Boston and a 1953 Nobel laureate in medicine.

"In his opinion, the most important thing was to maintain a good environment in which all the individuals that participated in the research had a familial feeling and liked and interacted socially and scientifically with one another," Earl Stadtman said. "I have always listened to that. I've always adhered to that."

Dozens of the scientists they trained gathered at NIH this past January to honor Earl and "Terry" Stadtman at the opening of an exhibit to celebrate their extraordinary 53-year careers that the Stadtmans. Terry, 83, and Earl, 84, who have said they will continue for as long as they can, are currently working on basic research into enzymes, which control all the chemical reactions in living organisms and determine how long and how well those organisms live. The NIH Stadtman exhibit is on line at http://www.history.nih.gov/exhibits/stadtman.

Speaking at that celebration, Arthur Kornberg, a 1959 Nobel laureate in medicine and emeritus professor of biochemistry at Stanford University, told the gathering that a scientific genealogist would find that despite having no children, the couple are near the top of a large "family tree" of proteges.

Barbara Alving, acting director of the National Heart, Lung and Blood Institute, called the Stadtmans "treasures" and said that scores of young research fellows who worked in their labs have gone on to excel in many fields.

Among those young people were many who became prominent scientists, among them two Nobel laureates, Michael Brown and Stanley Prusiner, the CEO of a major pharmaceutical company, P. Roy Vagelos, and about a dozen members of the National Academy of Sciences.

What developed into such a remarkable string of accomplishments began somewhat inauspiciously in a 1943 California lab, when Earl, then a young research assistant, spotted Thressa Campbell and, thinking she was a new dishwasher, asked her out to dinner. She agreed and only later during dinner, did she reveal that she too was a research assistant. One with a more advanced degree than her future husband's.

Photo Credit: Thressa and Earl Stadtman

*Thressa and Earl Stadtman in 1949, both receiving Ph.D. degrees from the University of California, Berkeley. Unable to overcome the barrier of the anti-nepotism rules in academia, they elected to come to the National Institutes of Health in 1950.*

His reaction? "Intimidated," she said.

Intimidated or not, the two proceeded to romance, a marriage, and extraordinary 53-year careers at the NIH, where each runs a biochemistry laboratory and train some very fortunate young scientists.

They came to Bethesda in 1950 as a young married couple and developed a unique way of conducting research and training scientists—their colleagues call it the "Stadtman way."

The "Stadtman way" refers not only to the extraordinarily high standard of rigor they set in biochemical research, but also to their generous sharing of

# at NIH

credit in publications with more junior scientists.

In 1950, at a time when most universities had anti-nepotism rules that did not allow more than one family member to work in the same department, the Stadtmans were looking for academic positions in which they could both work at the same professional level. Typical of the difficulties they encountered, was the comment Earl received from a University of Chicago administrator whose job offer he had rejected because there was no offer of employment for Thressa. That official told Earl, "If your decision is to be based upon simultaneous academic staff appointments for both you and Mrs. Stadtman, it may mean that you are closing your opportunities for an academic career, since I believe that the policy of the University of Chicago in this regard is no different from that of most other universities."

Photo Credit: Earl Stadtman

*Earl Stadtman in 1953, using Warburg apparatus in his laboratory at the National Institutes of Health*

At NIH, however, married couples could be employed and in September 1950, Thressa and Earl arrived on the main campus of NIH in Bethesda, where they began their laboratory work in Building 3. Here Thressa continued studies on the bacterial degradation of cholesterol while Earl continued his research on fatty acid metabolism. In the next five-plus decades, they racked up a string of formidable accomplishments.

Photo Credit: Thressa Stadtman

*Thressa Stadtman in 1953, doing an experiment in her laboratory at the National Institutes of Health.*

## Vitamin B12 Biochemistry

Signs of vitamin B12 deficiency in humans include fatigue, nausea, and weight loss. It can lead to pernicious anemia and neurological disorders. Investigating the role of vitamin B12 in metabolic processes is an essential step for understanding these clinical symptoms.

In the 1950s and 60s, Thressa tackled two problems: how amino acids are broken down into smaller pieces in the absence of oxygen and how methane gas is produced by some bacteria living in oxygen-free conditions. She showed that vitamin B12 is required for several enzymes that functioned in these processes. Thressa and her co-workers discovered 5 of the 12 known vitamin B12-dependent enzymes.

## Selenium Biochemistry

Selenium, a chemical element, had long been known for its toxic effects before it was recognized in the 1950s as an important nutrient for animals. Numerous studies now relate dietary intake of selenium to the reduction of cancer risk and maintenance of redox

Photo Credit: Office of NIH History

*Earl and Thressa Stadtman in 2003 on the NIH campus. Both members of the National Academy of Sciences, they are working full time in the laboratory and enjoy their lives making important discoveries in biochemistry and mentoring young scientists.*

balance in mammals. Thressa pioneered the field of selenium biochemistry by identifying many selenium-containing enzymes in cells and explaining the function of selenium in these proteins. She discovered in 1972 that selenium is required for synthesis of an enzyme called glycine reductase and showed that the selenium is incorporated into the protein. The essential selenium moiety in this protein was identified as the amino acid, selenocysteine, which later was shown to be present in most selenoenzymes.

## Fatty Acids Metabolism

The building blocks of fats are chain-like molecules called fatty acids, which are readily made in the body. By the late 1940s, biochemists had generally adopted a hypothesis that the capacity to make fatty acids is the unique property of specialized cellular systems, or particulate organelles. Earl, however, dispelled this hypothesis once and for all by demonstrating that enzymes extracted from certain bacteria can catalyze the synthesis of fatty acids in vitro, outside the living body.

Earl also showed that Coenzyme A (CoA) is involved in the synthesis of fatty acids as a carrier of the small molecular fragment called "acetyl." Among many coenzymes-molecules needed for the proper function of enzymes-CoA has most notable metabolic functions. Its derivative, acetyl-CoA, is an essential substance involved not only in making fats, as Earl showed, but also in breaking down fats, carbohydrates, and proteins to generate energy in cells. In 1952, Earl successfully carried out the first "net synthesis" of acetyl-CoA in vitro, which means that he accomplished it by using only basic materials (acetyl phosphate and CoA) and the enzyme he had discovered (phosphotransacetylase). Overall, Earl's research helped establish the "energy-rich" nature of acetyl-CoA.

## Cyclic Cascade Systems in Metabolic Regulation

In the 1960s and 70s, Earl and his co-workers discovered some mechanisms of controlling the production of amino acids. They examined glutamine synthetase, the enzyme that catalyzes the synthesis of an amino acid called glutamine. They showed that, in *E. coli*, its biosynthetic activity is regulated not only by glutamine, but also by other molecules that use glutamine as a nitrogen source. The regulation of glutamine synthetase is an example of cumulative feedback inhibition. Its activity is almost completely switched off when all final products are bound to the enzyme.

In addition, Earl and his co-workers discovered that glutamine synthetase can also be controlled by a process called cyclic cascade reversible covalent modification, which involves the attachment and detachment of certain molecules at specific positions of the enzyme. They showed that this regulatory process provides large signal amplification and fine tuning of the enzyme's activity.

## Protein Oxidation and Aging

Our bodies use oxygen to burn nutrients for energy. Most of the oxygen we breathe is reduced to water in this energy-generating process, but some turns into oxygen free radicals or other forms of highly reactive molecules. They are "oxidizing agents" that can seriously damage cellular molecules, such as proteins and nucleic acids.

In the 1980s, Earl and his co-workers examined how damaged or inactivated proteins are removed from cells in a process called "protein turnover." Their study showed that oxidation of protein can trigger this removal process. Earl and his co-workers also

discovered that the accumulation of damaged proteins is closely associated with the aging process and may play a role in age-related diseases such as Parkinson's disease.

The NIH intramural research program is well known for its outstanding scientific and medical achievements, but equally important is its role in training biomedical researchers not only from the United States but from around the world.

As mentors of more than a hundred scientists, Thressa and Earl are respected for their rigorous training and liberal sharing of credit in publications. Researchers in their laboratory are challenged to defend every new discovery in multiple alternative ways, and they are encouraged to publish papers and assume responsibility at a unusually early stage. Indeed, Thressa and Earl have had a special touch with younger scientists on their way up.

Thressa's and Earl's mentoring was not confined to postdoctoral fellows. Several pre-doctoral researchers in their laboratory received their doctoral degrees from universities near NIH. Earl also extended his teaching activities to the NIH's evening classes, which were first administered by the Graduate School of the United States Department of Agriculture in the 1950s and subsequently by the Foundation for Advanced Education in the Sciences, a non-governmental organization chartered in 1959. Furthermore, Earl enjoyed opportunities to teach in various universities as a visiting professor.

# Growth Hormone Activates Gene Involved in Healing Damaged Tissue

**"Growth hormone is known to increase lean body mass and bone density in the elderly, but it does something else, too. It activates a gene critical for the body's tissues to heal and regenerate," says ASBMB member Robert Costa, Professor of Biochemistry and Molecular Genetics at the University of Illinois at Chicago and a member of the University's Cancer Center.**

"Growth hormone levels decline as we grow older; as a result, the Foxm1b gene stops working and our bodies are less capable of repairing damage," Dr. Costa said. In a paper published in the December issue of *Hepatology* (http://www3.interscience.wiley.com), he and his colleagues reported the results of studies on liver regeneration in aged (12-month-old) and young (2-month-old) mice, a model system for studying the molecular mechanisms the body enlists to restore tissue damaged by injury or age. The liver is the only organ in the body capable of completely regenerating from mature cells.

The scientists focused on the Foxm1b gene, which is involved in the entire life cycle of the mammalian cell, with its activity elevated in dividing cells in young mammals but diminishing in old age.

In previous studies, the researchers inserted the human Foxm1b gene in aged mice whose livers had been partially removed. These experiments showed that the gene restored levels of Foxm1b proteins and induced the animals' livers to grow back at a rate typical for young mice. Additional research detailed how the gene directs the busy molecular traffic inside cells to make them divide and multiply.

In the present study, the scientists tested the effects of human growth hormone because of its purported role in stimulating cell proliferation. Growth hormone, secreted by the pituitary gland in the brain, is responsible for growth in children and young adults, but its levels decline during aging.

"The literature had suggested that growth hormone therapy in elderly men stimulates cells to divide," said Dr. Costa, "leading to increases in muscle mass and skin thickness and greater bone density in the spine, while decreasing body fat. We wanted to find out how the hormone worked at a molecular level."

When aged mice whose livers had been partially removed were injected with human growth hormone, histological and other tests showed that the activity of the Foxm1b gene increased dramatically, as did levels of various enzymes and proteins that cause cells to divide. At the same time, the livers of these animals regenerated at a pace found in young mice. Cell proliferation peaked at just two days, and the liver was fully restored within a week.

However, complete regeneration took a month or longer in aged mice that had not received hormone injections. Without growth hormone to turn on Foxm1b, the gene remained stuck at the low level of activity found in old age, and liver cells failed to multiply rapidly enough for a quick recovery.

*Dr. Robert Costa*

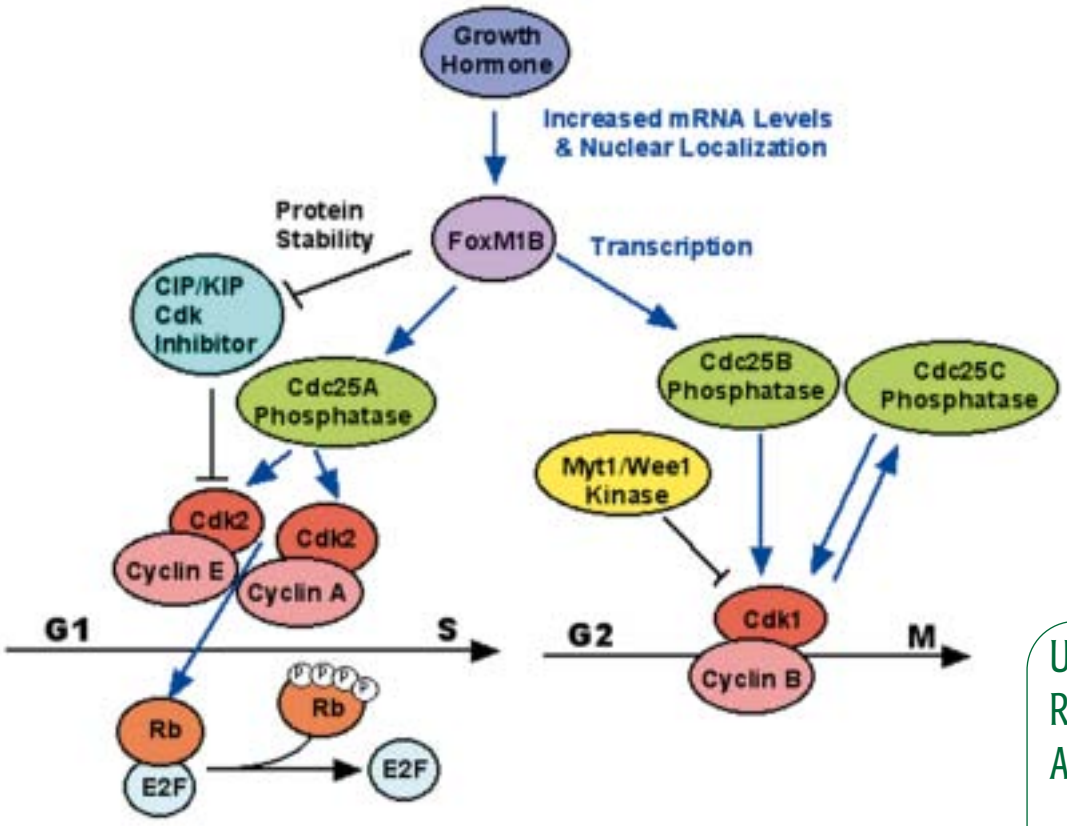



*Diagram depicting Growth Hormone stimulation of Foxm1b expression and its cell cycle target genes. The Foxm1b protein negatively regulates protein expression of the CIP/KIP (p21Cip1/p27Kip1) family of Cdk inhibitors and is required for expression of Cdc25A and Cdc25B phosphatases. Arrows represent positive regulation and lines represent negative regulation.*

Further tests were done with genetically engineered mice in whose liver cells the Foxm1b gene had been disabled. In these mice, growth hormone injections failed to stimulate recovery when the liver was partially removed.

"These results clearly demonstrate that Foxm1b is essential for growth hormone to spur liver regeneration," Costa said, but he is cautious about drawing any conclusions from his research about the merits of the therapy. "Our liver regeneration studies tell us a great deal about how growth hormone works at a molecular level, but the injections occurred only over short periods of time, giving us no information about any long-term consequences.".

While several studies have shown that prolonged growth hormone therapy has dangerous side effects ranging from diabetes to carpal tunnel syndrome, Dr. Costa surmised that short-term treatment with growth hormone could be used to speed repair after injuries or surgery in the elderly, thereby shortening recovery time.

## University of Pittsburgh Reunion at ASBMB Annual Meeting

**Attention former members of the Department of Biochemistry and Nutrition at the Graduate School of Public Health, University of Pittsburgh**

At the Boston ASBMB meeting in June, there will be a reunion of former graduate students, postdoctoral fellows and faculty, particularly those who were in the Department during the years of 1964 to 1970. The reunion will consist of a reception followed by a dinner at a restaurant in Boston. The date will either be on Monday, June 14 or Tuesday, June 15. If interested, please contact Franklin Hamilton <franklin.hamilton@mail.famu.edu>, Dennis Vance dennis.vance@ualberta.ca, or Jean Vance <jean.vance@ualberta.ca>.

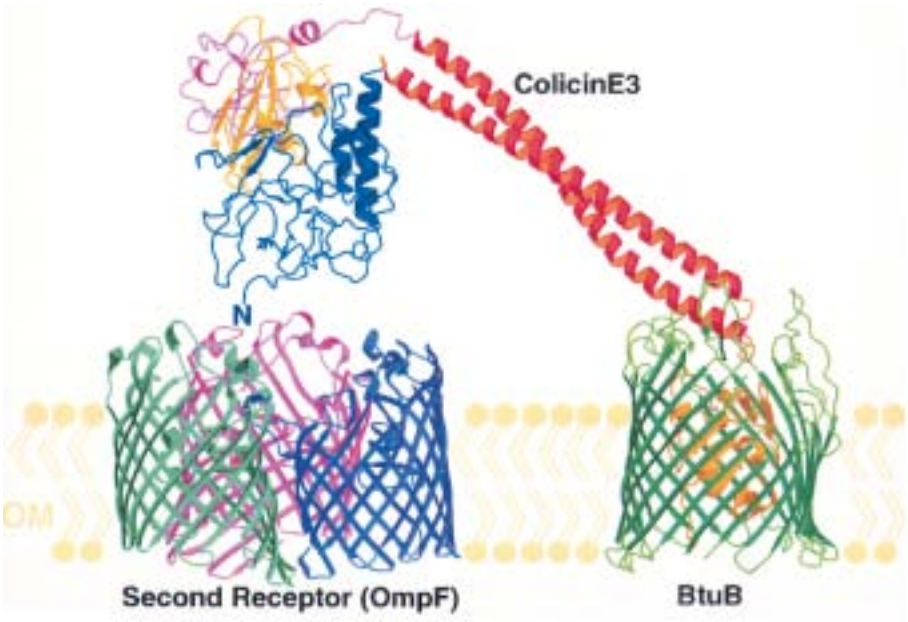
# Cells 'Go Fishing' but

When a cell needs to import a protein for an intracellular function, it sometimes uses molecule-sized fishing poles to "catch" one and "cast" it across the cell membrane, reports a research team of Purdue University biologists.

Using high-resolution X-ray crystallography, a team including ASBMB member William A. Cramer has determined the structure and surprising behavior of a protein receptor complex, or "gate," found in the outer membrane of an *E. coli bacterium*. The complex is one of thousands of such tiny gates that the cell uses to bring substances into its cytoplasm, or interior. The protein entering this gate is the cytotoxic protein, colicin. The team determined the structure of the gate with the gate opening domain of the colicin, marking a first in this field of membrane biology.

"This represents the first time we have seen a receptor complex and its corresponding importable protein up close," said Cramer, Henry Koffler Distinguished Professor of Biological Sciences in Purdue's School of Science. "While we have seen the gates before as a group, we have never seen how an individual gate works to bring a protein inside. This information could tell us a lot about our own metabolism."

An unusual aspect of the research was the nature of the protein itself. Ordinarily, a cell will admit only beneficial substances, but colic in is actually toxic to the *E. coli* once it penetrates the membrane.




*Translocon for import of colicin E3 across* E. coli *outer membrane. Extended (100 A) coiled-coil receptor binding domain (red) of the colicin E3 molecule is seen in surface complex with barrel-shaped vitamin B12 receptor (BtuB) in the* E. coli *outer membrane (right, green with orange interior). The remainder of the colicin molecule (simulated on basis of structure of M. Shoham) is poised to 'fish' for a second outer membrane protein that is porous (OmpF porin, green, blue, violet, left) and that completes the translocon. Stucture solution of complex was facilitated by prior structure of BtuB provided by M. Wiener.*

"Colicin fools the membrane, and can actually kill the bacterium once it's inside," Dr. Cramer said. "We, of course, also would like to find out how the cell ingests a helpful protein rather than a poisonous one, but this is the only protein we know that binds tightly to the receptor complex we managed to isolate for this study." Thus, the import mechanism of the cytotoxic protein is a model for cellular uptake of 'healthy' proteins.

The research, which appeared in the November 2003 issue of *Nature Structural Biology* (http://www.nature.com/nsmb/) was performed by a team including lead authors Genji Kurisu, Stanislav Zakharov and Masha Zhalnina. Also contributing was Michael Wiener of the University of Virginia's Department of Molecular Physiology and Biological Physics.

The group's work turned up some unusual details about cellular commerce, the business an *E. coli* cell conducts with the outside world through its membrane. With hundreds of protein receptors serving as gate guards, the membrane admits into the cytoplasm the nutrients the cell needs to exist. In most cases,

# Catch Killer Proteins

receptors are made to admit only one particular substance.

"If you've ever seen the game 'Perfection,' in which you have to put a number of uniquely shaped pegs into their corresponding holes before time runs out, you have a general idea of how these receptors are laid out in the cell membrane," Dr. Cramer said. "There are hundreds of receptor types, each of which is built to admit one thing—iron or sugar molecules, for example."

But while the receptor his team analyzed was made to admit the vitamin B-12, it was known that colicin could enter the *E. coli* by "parasitizing" the receptor for its own use.

"Its method, at first, seems a bit unorthodox," he said. "Colicin essentially has two parts connected to one another by a long rod, and it cannot fit through a single hole in the membrane. So once it finds its first hole, it has to go fishing for another."

One of the colicin's segments binds to the vitamin B-12 receptor, while its tail end remains hanging from the membrane like a long fishing rod. The B-12 receptor then essentially swings the tail around until it finds what it needs—the second receptor that can admit the rest of the colicin.

"This two-receptor approach may appear to be a strange way to do business," explained Dr. Cramer, "but we theorize that it is actually the norm, rather than the exception, when it comes to getting proteins across membranes."

While this is the only example thus far of how a protein uses receptors, he said that evidence for the theory lies in the organization of the receptors in the membranes themselves.

"Receptors tend to lie together in clusters," Dr. Cramer explained. "Biologists have long found a concentration of one type of receptor mixed in with a few other types, much as elephants and giraffes congregate on the plains, while other species are found in the forest. But here, it's not terrestrial ecology at work. We think the receptors lie close together because proteins need more than one to get inside."

***"Strength, endurance, health—they are all essentially metabolic processes, and figuring out how these processes change as we age will almost certainly depend on figuring out how membrane proteins do their jobs."***
***—Dr. William Cramer***

Membrane proteins have proven to be notoriously difficult to study.

"However, if we can find out more about how these membrane proteins work, we may gain fundamental insights into how your body obtains energy from the environment," Dr. Cramer said. "Strength, endurance, health—they are all essentially metabolic processes, and figuring out how these processes change as we age will almost certainly depend on figuring out how membrane proteins do their jobs."

Members of his research team are affiliated with several research centers at Purdue, including the Markey Center for Structural Biology, the Bindley Bioscience Center at Discovery Park, the Interdepartmental Program in Biochemistry and Molecular Biology, and the Purdue Cancer Center.

Funding for this research was provided mainly by NIH.

## 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.

**Wai-Ki Ip**
Chinese University of Hong Kong

**Matthew J. Oberley**
University of Wisconsin Medical School

**Deborah Zies***
University of Florida, Gainesville

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

# New Insight on How Anthrax Bacteria Can Evade Host's Immune Response

Biologists at the University of California, San Diego (UCSD) have determined how toxin produced by anthrax bacteria blocks a person's normal immune response, a discovery that could lead to new treatments for anthrax infection.

In a paper published in the January 15 issue of *The Journal of Immunology* (http://www.jimmunol.org/) the UCSD scientists show why, in the presence of anthrax toxin, human immune cells fail to respond normally to lipopolysaccharide (or bacterial endotoxin)—a component of the cell walls of many bacteria including that which causes anthrax, *Bacillus anthracis*. Bacterial invasion, or the presence of lipopolysaccharide, usually causes immune cells known as macrophages to release cytokines that signal the presence of an invader. This causes large numbers of immune cells to arrive at the site of infection and destroy the bacteria. By blocking this host immune response, anthrax bacteria are able to multiply unchecked. According to the Centers for Disease Control, approximately 75 percent of people infected with inhalation anthrax die, even with all possible medical care and antibiotics.

***According to the Centers for Disease Control, approximately 75 percent of people infected with inhalation anthrax die, even with all possible medical care and antibiotics.***

"Although it was known for quite some time that anthrax toxins can suppress cytokine production, the mechanism by which *Bacillus anthracis* escapes the immune response isn't really understood," said ASBMB member Michael David, Professor of Biology at UCSD, who headed the research team. "We have identified a protein molecule targeted by the anthrax toxin and determined where it acts in the sequence of steps involved in immune response."

Macrophages have special receptors on their surfaces that bind to lipopolysaccharide. The binding of lipopolysaccharide to this receptor sets off a sequence of events inside the macrophage, in which a series of proteins activate one another in turn. This cascade of proteins ultimately turns on cytokine genes, causing the macrophage to churn out large quantities of cytokines.

There are two separate, sometimes cooperating, routes in the cell by which series of proteins activate one another to switch on production of cytokines. One route has been recognized for a long time, but researchers were sometimes puzzled when cytokine production was turned on or off without the proteins along this route being activated or deactivated. This puzzle was resolved when the David group and others simultaneously identified the second route, the IRF3 pathway. The anthrax toxin targets the IRF3 pathway by cleaving MKK6—one of the proteins in the series along the route. The cleavage of MKK6 prevents the cytokine genes from being switched on.

When the researchers made mutant macrophages with a variant of MKK6 that could not be cleaved by the anthrax toxin, these macrophages responded to lipopolysaccharide by producing cytokines even in the presence of the anthrax toxin. This suggests that developing a drug that could protect MKK6 and prevent anthrax toxin from cleaving it could help to prevent an anthrax infection from getting out of control. The anthrax bacteria would then be unable to evade the normal immune response.

Previous work by other researchers has suggested that anthrax toxin evades the immune system by killing macrophages; however, according to Dr. David, cell death does not fully explain how anthrax bacteria evade the immune system.

"Only some types of macrophages are killed by anthrax toxins, but anthrax toxins do diminish the production of cytokines in all of the macrophages we have tested," he explained. "Also, less toxin is needed to shut off the immune response than is needed to kill the macrophages."

# Activation of Receptor Boosts Development of Precancerous Intestinal Polyps

Vanderbilt-Ingram Cancer Center researchers have provided the first evidence that activation of a particular cellular receptor dramatically increases the development of precancerous polyps in the intestine. The findings suggest a new strategy for preventing colorectal cancer by blocking activation of this receptor. However, they also raise caution about an increased risk of colorectal cancer among people who take drugs that activate this receptor. Such drugs are currently in clinical development to treat obesity and atherosclerosis.

The researchers reported their findings February 2 in the online version of the journal *Nature Medicine* (http://www.nature.com/nm/). The paper was scheduled for publication in the March print edition.

The group found that among mice with a specific genetic mutation, one that is found among 80 percent of human patients with colorectal cancer, the incidence of larger colon polyps increased fivefold with treatment of a compound known to bind very specifically to the peroxisome proliferator-activated receptor delta (PPAR-delta).

"This is extremely significant because it is these larger polyps that are most likely to develop into intestinal cancer," said ASBMB member Dr. Raymond N. DuBois, Hortense B. Ingram Professor of Molecular Oncology.

The team became interested in PPAR-delta's potential role in colorectal cancer development after the observation that the receptor is over-expressed in most colorectal cancer tumors. As part of the lab's ongoing research into the enzyme cyclooxygenase-2 (COX-2) and its role in colorectal cancer, the group noted that PPAR-delta is activated by a COX-2 prostaglandin product.

Evidence for a direct role for PPAR-delta in colorectal cancer has been mixed; however, the Vanderbilt-Ingram scientists noted, those studies did not test agonists (which activate receptors) that strongly bind to PPAR-delta without similar attraction to two other forms of the receptor, named PPAR-alpha and PPAR-gamma.

They selected a molecule for this work with high specificity for the delta version of the receptor, known as GW501516. They tested this ligand in mice with a known mutation in the Apc gene. "APC mutations are found in all individuals with an inherited form of colon cancer called familial adenomatous polyposis (FAP) and is seen in 80 percent of sporadic colorectal cancers, so the mutation is highly relevant to colorectal cancer in humans," Dr. DuBois said.

In line with published data, the untreated mice developed an average of 30 polyps in the small intestine and an average 1.4 polyps in the colon. Treatment with GW501516 led to a twofold increase in small intestine polyps and no change in colon polyps.

The scientists evaluated the data according to polyp size, and found that the mice treated with the PPAR-delta agonist developed five times more polyps larger than 2 mm. They also showed more dysplasia (a precursor of malignancy ) than those from the untreated mice.

Cell culture studies were conducted to eliminate any effects of GW501516 not related to PPAR-delta activation. They treated wild-type cells and cells engineered to remove the PPAR-delta gene, and found no change in cell proliferation. However, treatment with GW501516 significantly suppressed apoptosis in the wild-type cells, but not in the cells lacking PPAR-delta.

"These results argue that PPAR-delta stimulates intestinal adenoma development and size by activating antiapoptotic pathways in intestinal epithelial cells," the researchers wrote. Because the cells avoid cell death, they have a survival advantage, Dr. DuBois explained, suggesting that PPAR-delta may play a role in colorectal cancer not by initiating polyp development but by accelerating their growth.

Additional research is needed, including verifying the results in APC mutant mice which are engineered to eliminate the PPAR-delta receptor. However, the researchers noted, "PPAR-delta may be an attractive target for the development of small molecule antagonists as chemopreventive or chemotherapeutic agents for colorectal cancer."

Because the APC mutation is present in all individuals with FAP, this research suggests that patients with this inherited disorder should not take PPAR-delta agonists for other indications. They also caution that because the mutation occurs in the vast majority of sporadic colorectal tumors, individuals with pre-existing polyps who take PPAR-delta agonists may also be at significantly increased risk for colorectal cancer.

by John D. Thompson, Editor

# Sanofi Launches $60 Billion Hostile Bid for Aventis

French pharmaceuticals maker Sanofi-Synthélabo has launched a hostile bid for its larger French-German rival Aventis, which has rejected at the advance. The bid, worth slightly more than $76 per share or a total of $60 billion, is considered certain to be only the start of a bidding war. Sanofi is likely to be forced to offer a higher price to win shareholder support and avert competitive bids from a possible white knight.

In the last week of January, Aventis officially rejected the Sanofi bid, however a merger was still seen as a possibility. A report by DataMonitor, a London-based provider of business information, showed why. If a the companies merged, the new company would have more than $24 billion in pharmaceutical sales and a cardiovascular franchise projected to be worth $7.1 billion by the end of 2004. The new company would then rank third in the world, behind Pfizer and GlaxoSmithKline. This would be a huge boost for Sanofi, which currently ranks 14th, based on projected 2003 sales of over $7.7 billion, while Aventis was seventh in the world based on its projected 2003 sales.

The increased size from a merger would help the new firm compete with Pfizer and GlaxoSmithKline. In particular, the combination of Sanofi's promising pipeline and Aventis's experience of developing and marketing blockbuster drugs would create a large European-based rival for GlaxoSmithKline.

A merger would reduce the potential impact of Paragraph IV, a concern for both Aventis and Sanofi. Aventis' leading drug Lovenox (enoxaparin) has a Paragraph IV challenge against its 2012 patent, while Sanofi is facing a legal battle over its second highest seller, Plavix. A merger would help lessen the impact of either legal battle being lost, although the new company would still operate with high generic risk, estimated at 32.7 percent of sales in 2008 being potentially at risk to generic competition, based on the expiry of the first US patent.

## Chile Seeks to Boost Biotech Business

"Biotechnology as a tool for development and well-being" is the theme of the Chilean government's plan to boost that nation's economy. Alvaro Diaz, that nation's deputy economic minister used those words in introducing a plan to update legislation affecting biotechnology, creating a biotech regulatory body, expanding the country's scientific and technological base, and encouraging entrepreneurs.

A new law, to be introduced this May in Chile's parliament, is intended to boost the use of biotechnology in fishing and fruit production, as well as forestry and mining. It would also increase oversight of genetically modify products (GMOs) and create and independent Biotechnology Forum to serve as a sounding board for any proposed biotech norms and a forum for public debate.

A prime objective of the proposed legislation, according to *Nature Biotechnology*, is to attract foreign investment and increase exports. As an example, a joint venture of Chile's government-owned mining company, CODELCO, and Japan's Nippon Mining is planning to extract metals with the aid of genetically modified bacteria.

Critics of the government plan range from scientists' concerns about the potential for commercializing research, the possible need for imports to augment Chile's relatively small pool of scientists, and fears that large consortia such as that envisioned for CODELCO and Nippon Mining may overshadow the needs of local companies and researchers.

## India's Glenmark Signs Deal with U.S. Firm

Glenmark Pharmaceuticals Ltd., a mid-sized Indian drug maker, has signed an $80 million deal to license eight of its generic drugs to U.S.-based KV Pharmaceutical Company. KV Pharma will soon file applications with the Food and Drug Administration for permission to market the products in the U.S. The first product is expected to be launched in November-December 2005.

Glenmark will get more than $80 million over the next 10 years, with most of it coming in the year ending in March 2005.

Under the terms of the agreement, Glenmark will manufacture and sell drugs to Lannett, which will then market them in the United States. The Indian company will not transfer proprietary technology.

## Generics Key to Growth of European Pharmaceuticals

The growth of the generics market in Europe should be a key factor in the evolution of the European pharmaceuticals industry, according to London-based DataMonitor. Encouraging the substitution of generics over branded products has been a common cost containment initiative across Europe and is a key factor driving the growth of generic medicines. Currently, 11 of the 15 EU countries have generic substitution policies including the five major European markets: France, Germany, Spain, Italy, and the UK.

A key factor in this development is expected to come from the high number of blockbuster products, at least 32, expected to lose U.S. patent protection by 2008. The consequent growth of the European generics market is expected to reach approximately $6 billion during this period.

The expansion of the generics industry is seen as likely to increase the pressure on companies to develop innovative therapies. At the same time, entry of new states into the European Union will create new opportunities to penetrate new markets. Consequently, predicts DataMonitor, Europe is likely to remain an attractive option for future revenue growth.

# Biotech Crops Grew 15 Percent in 2003

Worldwide cultivation of biotech plants grew 15 percent in 2003, the seventh consecutive year of double-digit growth, according to a new report by the International Service for the Acquisition of Agri-biotech Applications (ISAAA), a group sponsored by various government agencies and industries. More than 67 million hectares (over 615 million acres) of the crops are now planted across the globe.

The report found that 7 million farmers in 18 countries now plant biotech crops, including more than 85 percent of "resource-poor" farmers in the developing world.

The leading growers of biotech crops are the U.S., Argentina, Canada, China, Brazil, and South Africa, which combined account for 99 percent of the global biotech crop area. The greatest increases in 2003 were in China and South Africa, which both planted 33 percent more biotech hectares than in 2002.

***Within the next 5 years, 10 million farmers will plant 100 million hectares of biotech crops.***

ISAAA Chairman and Founder Clive James, speaking of the report, said "Farmers have made up their minds, they continue to rapidly adopt biotech crops because of significant agronomic, economic, environmental, and social advantages." The ISAAA predicts that within the next 5 years, 10 million farmers in 25 or more countries will plant 100 million hectares of biotech crops. It expects the global market value of biotech crops to increase from approximately $4.5 billion this year to $5 billion or more by 2005."

## North Carolina Okays Incentives for Merck

In a one-day special session of the General Assembly, North Carolina legislators approved over $36 million in tax breaks and incentives to bring a new vaccine manufacturing facility to a 246-acre site in the north side of Durham. The lawmakers voted to give Merck up to $24 million for development of the proposed new plant's infrastructure, plus another $12.8 million in incentives, including a $4.8 million rebate on building material and equipment sales taxes. Other pharmaceutical and biotech firms that, at a minimum, invest $100 million and employ 100 new workers would also be eligible for a break on state sales taxes.

Merck has agreed to invest as much as $300 million to build the new facility for the manufacture of vaccines for measles, mumps, and rubella. Construction of the new plant, which would initially employ up to 200 workers, is projected to take two years, and Merck expects that it will take another two years to win FDA approval for the facility to go on stream.

# Medical Schools and Teaching Hospitals Are Major Economic Contributors

U.S. medical schools and teaching hospitals represented by the Association of American Medical Colleges (AAMC) had a combined economic impact of over $326 billion and employed one out of every 54 wage earners in the United States labor force during 2002, according to a new AAMC report. The AAMC represents 126 accredited U.S. medical schools and some 400 major teaching hospitals. The study, "The Economic Impact of Medical College and Teaching Hospital Members of the Association of American Medical Colleges," measures the financial contributions of the association's member institutions in the regions in which they are located and the nation as a whole.

One of the report's important findings is that AAMC medical schools and teaching hospitals are major employers in their home states, accounting for 2.7 million jobs directly or indirectly in 2002. More than half of these - 1.5 million - were full-time positions.

The report also corrects a major misconception that medical schools and teaching hospitals do not generate revenue for respective state governments. Although these institutions are generally not-for-profit, they still helped generate significant revenue in state income taxes. In 2002, AAMC medical schools and teaching hospitals produced a total of $14.7 billion in state government revenues. Within their states, these institutions also generate additional government monies by paying sales taxes, corporate net income taxes and capital stock/franchise taxes.

"This study demonstrates how our institutions play a crucial role in the economic well-being of their communities," said AAMC Division of Health Care Affairs Senior Vice President Robert Dickler. "By serving as major employers and generators of economic activity, the contributions of AAMC medical schools and teaching hospitals extend beyond their traditional missions of education, research, and patient care."

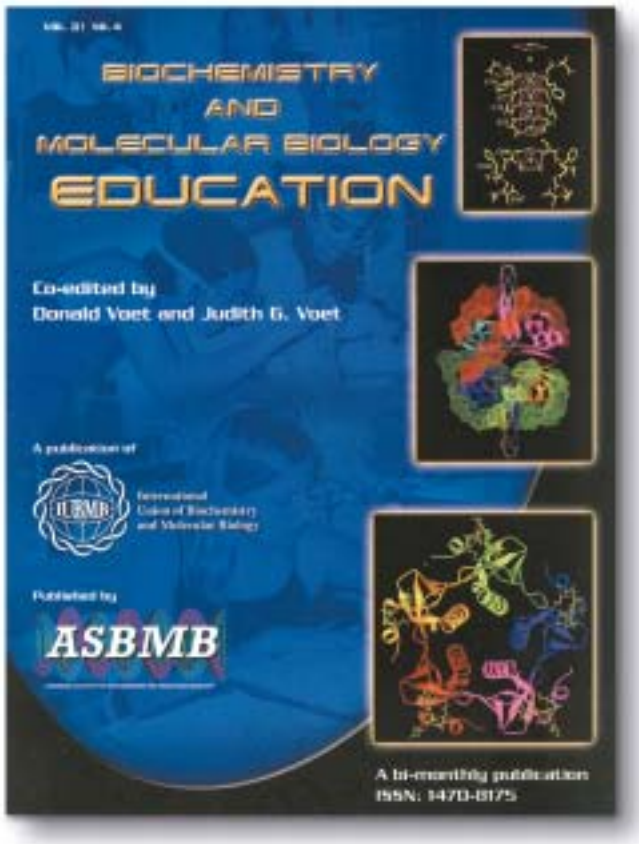
In addition, the study found that AAMC members generate $14 billion in out-of-state medical visitor related revenue. This total includes $1 billion in direct spending, outside of medical schools and teaching hospitals by out-of-state patients, as well as another $1.5 billion spent by the friends and family who visit these patients. These institutions are also major sponsors of meetings, seminars and symposiums in their states. The events draw significant numbers of visitors whose spending provide a major boost to local economies. Spending by this group last year totaled $11 billion.

Tripp Umbach Healthcare Consulting, Inc. prepared the report for the AAMC. For a listing of the key findings of the report for the 24 states (and the District of Columbia) in which AAMC members' economic impact is the highest, contact Retha Sherrod at rsherrod@aamc.org.

# Q: What is the leading education journal in biochemistry and molecular biology?



# A:

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Published by the American Society for Biochemistry and Molecular Biology

"Promoting understanding of the molecular nature of life processes"

# Researchers Unlock Secrets Showing How Tumors Hide From Immune System

Researchers at the University of South Florida's H. Lee Moffitt Cancer Center & Research Institute have unlocked at least part of the mystery of how tumors flourish while keeping their presence a secret from sentries of the body's immune system.

"Flying beneath the radar" is how the February issue of *Nature Reviews Cancer** labeled the mechanism of tumors evading capture, a process described by Dr. Hua Yu, Associate Professor in the USF Department of Medical Microbiology and Immunology and the Immunology Program at Moffitt.

"Cancer is allowed to wreak havoc on the body's immune system because it knows how to fool the body's defensive arsenal," said ASBMB member Jack Pledger, Associate Center Director for Basic Science and Professor of Biochemistry at USF. "The discoveries of Dr. Yu give us vital information about how tumors stay 'invisible.' It opens the way for new treatments to help flush the cancer cells into the open, so the body's armies against disease can destroy them."

The researchers found that blocking Stat3 activation in the B16 mouse tumor cell line by expressing Stat3, dominant-negative Stat3, or using antisense oligonucleotides increased expression of the pro-inflammatory cytokines interferon, tumor-necrosis factor- (Tnf-) and interleukin-6 (Il-6), and the chemokines Rantes and Cxcl10. On the other hand, fibroblasts that were engineered to constitutively express Stat3 failed to express Il-6 or Rantes after stimulation with inflammatory mediators, confirming that Stat3 activation inhibits expression of cytokines and chemokines.

This work demonstrates that constitutive Stat3 activation in tumors, which occurs at very high frequency, inhibits chemokine and cytokine production and induces factors that inhibit the adaptive immune response. Using targeted therapies against Stat3 could relieve this inhibition, allowing the immune system to detect and eliminate tumors.

Other ongoing research at Moffitt related to Stat3 includes using microarray technology to study the characteristic gene expression profiles or "molecular signatures" of certain genes that are regulated by the STAT. Scientists suspect that many genes that are directly or indirectly regulated by Stat3 may contribute to cancer, and they are working to develop new drugs based on inhibiting Stat3 for more effective treatment of breast cancer, prostate cancer, sarcoma, melanoma and other tumors that harbor aberrantly activated Stat3.

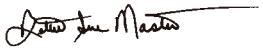
# Ask Not continued ...

*Continued from p. 3*

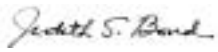
to us (jbond@psu.edu or masters@uthscsa.edu or asbmb@asbmb.faseb.org) expressing your views; let us know if there are activities you would like to participate in. The ASBMB is best served when the Committees have a balance of experienced and new members.

Most biochemists and molecular biologists are busy and do not have the time to do all they would like to do. In addition to our research and teaching activities, who has time to write to Senators, interact with undergraduates to encourage them to see the excitement of our profession, plan or go to meetings that expand our horizons, contemplate how to keep up the standards of our journals, develop strategies to make our publications accessible (back to 1905!) and affordable to scientists and the public? But as a community we can plan and prioritize, and do all of that effectively. Your being a member of the Society helps us represent you. When the current President of ASBMB speaks to a legislator, she can speak for 12,000 members – that speaks louder than an individual. This then is an appeal not only to maintain your membership in ASBMB, but also to challenge you to recruit your trainees and colleagues into the Society, and to let us know your views and what activities you would like to participate in.

Together we can do so much more than we can do as individuals.



**Bettie Sue Masters**
ASBMB President



**Judith S. Bond**
ASBMB President-Elect

# Gene-Disabling Techniques Simplified by Stanford Team

Sometimes the first step to learning a gene's role is to disable it and see what happens. Now researchers at the Stanford University School of Medicine have devised a new way of halting gene expression that is both fast and cheap enough to make the technique practical for widespread use. This work will accelerate efforts to find genes that are involved in cancer and the fate of stem cells, or to find genes that make good targets for therapeutic drugs.

The technique, published in the February issue of *Nature Genetics* (http://www.nature.com/ng/), takes advantage of small molecules called short interfering RNA, or siRNA, which derail the process of translating genes into proteins. Until now, these molecular newcomers in genetics research have been difficult and expensive to produce. Additionally, they could impede the activity of known genes only, leaving a swath of genes in the genetic hinterlands unavailable for study.

"siRNA technology is incredibly useful but it has been limited by expense and labor. A better method for generating siRNA has been needed for the whole field to move forward," said study leader Helen Blau,, Donald E. and Delia B. Baxter Professor of Pharmacology and an ASBMB member. She said some companies are in the process of creating pools, or libraries, of siRNA molecules for all known genes in specific organisms but these libraries aren't yet available.

Pathology graduate students George Sen, Tom Wehrman, and Jason Myers became interested in creating siRNA molecules as a way of screening for genes that alter the fate of stem cells that are capable of self-renewal—the primary interest of Dr. Blau's lab. The students hoped to block protein production for each gene to find out which ones play a critical role in normal stem cell function.

The students came up with a protocol for making an siRNA library to obstruct expression of all genes in a given cell, including genes that were previously uncharacterized. However, they had several hurdles to overcome in developing their protocol. The first was a size limit, an siRNA molecule longer than 29 nucleotides causes wide-ranging problems in the cell. The key to overcoming this barrier was a newly available enzyme that snips potential siRNA molecules into 21-subunit lengths. A further step copied these short snippets into a form that could be inserted into a DNA plasmid. When the researchers put a single plasmid into a cell, it began churning out the gene-blocking siRNA molecule.

The group tested their approach by creating a handful of siRNA molecules to genetically disable three known genes. In each case, their technique generated siRNA that effectively blocked the gene in question. Wehrman said this technique of creating siRNA molecule libraries could be widely used to find genes that, when disabled, cause cells to become cancerous or alter how the cells respond to different drugs. These genes could then become potential targets for drugs to treat disease.

# Calendar of Scientific Meetings

## 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

### Gene Transcription in Yeast EuroConference

**May 29–June 3** • San Feliu de Guixols, Spain
Contact: European Science Foundation, EURESCO Office
Ph: +33(0)3 88 76 71 35; Fx: +33 (0)3 88 36 69 87
Email: euresco@esf.org; Website: http://www.esf.org/euresco

## 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 Phospoproteins

**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

### RELAXIN 2004: Fourth International Conference on Relaxin and Related Peptides

**September 5-10** • Grand Teton National Park, Jackson Hole, WY
This conference will present recent advances on the chemistry, physiology, and pharmacology of relaxin, related peptides, and their receptors.
Email: relaxin-2004@ad.uiuc.edu
Website: http://www.life.uiuc.edu/relaxin2004/

### Stem Cell Biology: Development and Plasticity

**September 16-19** • Scheman Continuing Education Building Iowa State University, Ames, Iowa.
Abstracts due July 16, 2004; Registration deadline: August 16, 2004
Student Travel Grant Applications due July 16, 2004
Contact: Growth Factor and Signal Transduction Conferences Symposium Office
Ph: 515-294-7978; Fx: 515-294-2244; Email: gfst@iastate.edu
Website: http://www.bb.iastate.edu/-gfstlhomepg.htmi

### Cellular and Molecular Basis of Regeneration EuroConference on the Molecular Pathways Leading to Regeneration

**September 18–23** • San Feliu de Guixols, Spain
Contact: European Science Foundation, EURESCO Office
Ph: +33(0)3 88 76 71 35; Fx: +33 (0)3 88 36 69 87
Email: euresco@esf.org; Website: http://www.esf.org/euresco

## 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
Email: autoim04@kenes.com
Website: www.kenes.com/autoim2004

### American Association of Pharmaceutical Scientists AAPS Annual Meeting and Exposition

**November 7-11** • Baltimore, Maryland
Ph: 703 243 2800; Fx: 703 243 9650
Website: www.aapspharmaceutica.com/meetings/futuremeetings/

### Second National Meeting of the American Society for Matrix Biology

**Nov 10–13** • San Diego, California
Contact: ASMB, 2019 Galisteo Street, Building I-1, Santa Fe, NM 87505; Ph: 505 989-4735; email: cindi@sciencemanagers.com
Website: http://www.asmb.net

## DECEMBER 2004

### American Society for Cell Biology, 44th Annual Meeting

**December 4-8** • Washington, DC
Ph: 301-347-9300; Fx: 301-347-9310
Website: http://www.ascb.org/

## 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

## Department Heads Take Note:

# *ASBMB Offers Free Membership to New Ph.D.s*

**ASBMB is now offering a free one-year Associate membership to all students who have, within the past year, earned a Ph.D. degree in the molecular life sciences or related areas.**

**ASBMB implemented this program as a way to recognize the significant accomplishment of earning the Ph.D., and to provide new Ph.D.s with something tangible and of economic value. Membership in ASBMB brings with it a free subscription to the online versions of the *Journal of Biological Chemistry* and *Molecular and Cellular Proteomics,* as well as subscriptions to *The Scientist* and the Society's magazine, *ASBMB Today*, discounts on other publications, and a host of other benefits.**

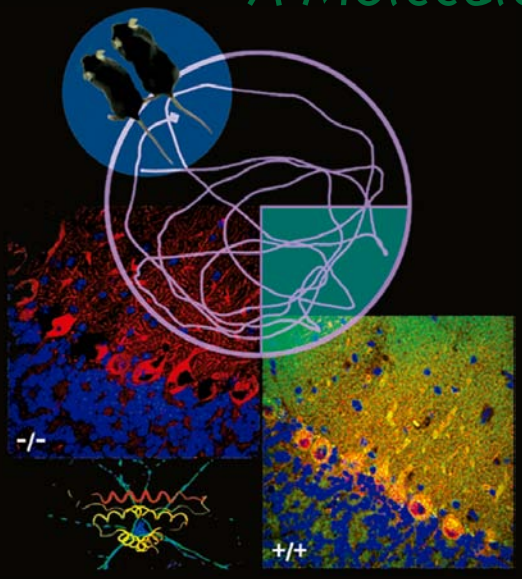
**The Society is asking department chairs to provide ASBMB with the names and addresses of each new Ph.D. recipient from their institutions. Upon receipt of this information, we will write the new Ph.D.s to congratulate them on their accomplishment and offer the free one-year membership in ASBMB. Names and addresses of the new Ph.D.s should be sent to:**

Kathie Cullins
Membership and Subscriptions Manager
American Society for Biochemistry
& Molecular Biology
9650 Rockville Pike
Bethesda, MD 20814
Email: asbmb@asbmb.faseb.org

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.

# IUBMB/ASBMB 2004

## "A Molecular Exploration of the Cell"




**June 12 – 16**

**Boston, MA**

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

Proteomics and Bioinformatics ■ Chemical Biology ■ Molecular Recognition ■ Cellular Biochemistry

### Opening Lecture

*First Annual Herbert Tabor*/Journal of Biological Chemistry *Lectureship*
**Robert J. Lefkowitz**, *HHMI, Duke University Medical Center*

### Organized by:

John D. Scott, HHMI, *Vollum Institute;* Alexandra C. Newton, *UCSD;* Julio Celis, *Danish Cancer Society*, and the 2004 ASBMB Program Planning Committee

**Cellular Organization and Dynamics**
Organizer: Harald A. Stenmark, *Norwegian Rad. Hosp.*

**Genomics, Proteomics and Bioinformatics**
Organizers: Charlie Boone, *Univ. of Toronto* and Michael Snyder, *Yale Univ.*

**Integration of Signaling Mechanisms**
Organizer: Kjetil Tasken, *Univ. of Oslo, Norway*

**Molecular and Cellular Biology of Lipids**
Organizer: Dennis Vance, *Univ. of Alberta*

**Molecular Recognition and Catalysis**
Organizer: Jack E. Dixon, *UCSD*

**Protein Modifications and Turnover**
Organizer: William J. Lennarz, *SUNY at Stony Brook*

**Protein Structure, Catalysis and Dynamics**
Organizer: Susan Taylor, *UCSD*

**Regulation of Gene Expression and Chromosome Transactions**
Organizer: Joan W. Conaway, *Stowers Inst. for Med. Res.*

**Signaling Pathways in Disease**
Organizers: Alexandra Newton, *UCSD* and John D. Scott, *HHMI, Vollum Inst.*

**The Future of Education and Professional Development in the Molecular Life Sciences**
Organizer: J. Ellis Bell, *Univ. of Richmond*

### For further information:

*ASBMB*
*9650 Rockville Pike*
*Bethesda, MD 20814*
*Tel: 301-634-7145*
*Fax: 301-634-7126*
*Email: asbmb@asbmb.faseb.org*
*http://www.asbmb.org*

**www.faseb.org/meetings/asbmb04**

**Late Abstract Deadline: April 21, 2004**

**http://submissions.miracd.com/asbmb2004lb**