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AMERICAN SOCIETY FOR BIOCHEMISTRY AND MOLECULAR BIOLOGY

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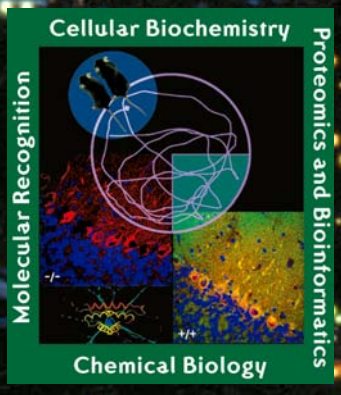
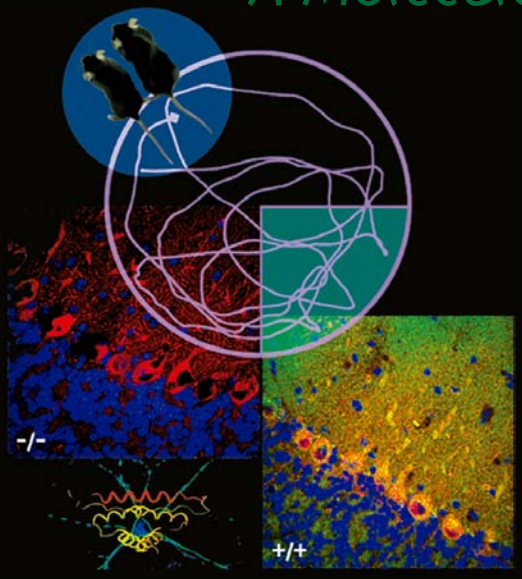


"A Molecular Exploration of the Cell"

ASBMB Annual Meeting
and 8th IUBMB Conference
June 12-16, 2004
Boston, Massachusetts

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*

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ASBMB Today

AMERICAN SOCIETY FOR BIOCHEMISTRY AND MOLECULAR BIOLOGY

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Volume 3, Issue 2

features

ON THE COVER:

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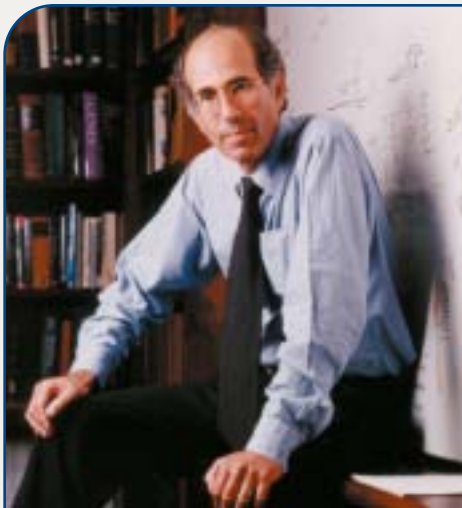
15

departments



10

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ASBMB President Masters

by Peter Farnham, CAE, ASBMB Public Affairs Officer

"We support returning the NSF to its doubling path, authorized in 2002 but not adhered to, by increasing funding this year to approximately $6.39 billion."

This was the message ASBMB President Bettie Sue Masters took to the House Appropriations Committee on March 25 when she delivered oral testimony on the National Science Foundation appropriation for fiscal year 2005. It was the second time in a little over a week that Dr. Masters had represented ASBMB on Capitol Hill. She had also spent March 16 making visits to various Members of Congress with incoming President Judith Bond.

Dr. Masters' comments on NSF came in the context of one of the most difficult budgetary years for science most Washington observers can remember. The National Institutes of Health budget was doubled over a five-year period ending in 2003, and now Congress is strongly interested in spending limited funds on programs other than biomedical research. NSF seems to be among the other programs that can expect some additional money this year, but how much remains very much unsettled.

ASBMB President Dr. Bettie Sue Masters

The President asked for a 3 % increase for NSF this coming year, about $167 million over its 2004 total of $5.57 billion. Dr. Masters characterized this as "clearly inadequate." She made the point that our concern was not related merely to the parsimonious request for NSF-funded biology. She noted:

"…we strongly support increased funding for NSF programs in the chemical, physical, mathematical, social and behavioral, and computational sciences, in addition to the biological sciences. These sciences, as well as being important in their own right, often serve as the underpinning for advances in biomedical research that lead to improvements in the health and well-being of the American people. If research in these areas is allowed to languish, we risk not just world leadership in these specific disciplines, but in biomedical research as well."

As for how the day went, Dr. Masters noted, "I thought it was very useful and educational for me and, I hope, for the members of Congress who listened to us. The two major topics that we discussed—NSF funding and the importance of support for the underpinning sciences in biomedicine—

Tell Us What You Think

We appreciate receiving letters that are suitable for publication from ASBMB members regarding issues of importance or commenting on articles appearing in *ASBMB News*. 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.

Urges House to Support NSF

struck a very good note." Also, she noted, "The testimony was well received by the committee and it appeared to me they were listening and engaged."

Other major points made during her testimony—witnesses were allowed 5 minutes to speak—were:

"ASBMB opposes the transfer of the Math & Science Partnerships program from the NSF to the Department of Education because NSF is an agency that specializes in science education, and the NSF program dispenses funds through a peer-review mechanism, rather than the block-grant approach used at Education;

"NSF needs to spend more of its resources on core science programs, rather than new initiatives that seem to attract most of the additional appropriated dollars;

"The average NSF grant needs to be larger and longer in duration, to an average of approximately $200,000 per year for four years, versus the $140,000 for three years it is now;

"Finally, NSF biological research supports non-medical biology and is thus different from that funded by NIH. The two should not be confused, and just because biomedical research has done well in recent years, other fields of biology have not. This needs to be corrected.

Her thoughts on her Capitol Hill visit?

"It is a vibrant atmosphere," Dr. Masters said. "You walk around the halls of these huge congressional office buildings and see hundreds of other people doing the same thing you are doing, and you realize that when you have an opportunity to speak to Congress in a setting like a congressional hearing, it's very important that you take the opportunity to do so."

The full Society testimony on the NSF budget for fiscal year 2005 can be found on the Society website at http://www.asbmb.org; type the word "testimony" in the search window, and then click on "NSF Testimony."

by Peter Farnham, CAE, ASBMB Public Affairs Officer

Administration Denies it Politicizes Science,

A war of words between the administration and congressional and scientific critics erupted in February over the issue of whether the administration is politicizing science.

This charge has been lurking in the background almost since the Bush Administration took office in 2001. Rep. Henry Waxman (D-CA) maintains a web site called "Politics and Science" (www.politicsandscience.org) where he claims that in dozens of cases, the Bush administration has distorted scientific research to serve its policy goals, manipulated public information in a wide variety of areas from the environment to public health and safety, and stacked scientific committees with ideologues who support the administration rather than scientific truth.

However, the skirmishing escalated to full-scale warfare in February, when the Union of Concerned Scientists (UCS) issued a report denouncing the Bush administration for politicizing science. The report, "Scientific Integrity in Policymaking: An Investigation into the Bush Administration's Misuse of Science," claimed that in at least 27 cases, the administration tailored or modified scientific information to support its policy positions on a host of issues from climate change and global warming to abortion, condom use, lead poisoning, and appointments to advisory committees. A letter signed by 60 prominent scientists, including 20 Nobel laureates, strongly endorsed the UCS report.

At the end of February, two members of the President's Council on Bioethics known for being supportive of somatic cell nuclear transfer (SCNT) research were removed from the Council and replaced with persons thought to be more in tune with the White House view that such research is not in keeping with its prolife stance. On March 1, ASBMB President Bettie Sue Masters wrote a letter to the President criticizing the administration over the firings.

Things got worse for the White House on March 22, when a letter signed by 27 Democratic senators, including Presidential candidate John Kerry, went to President Bush criticizing him for politicizing science and for the bioethics council firings. The letter called on him to "respect and restore the integrity of the scientific research conducted by the federal government, end this misuse of the scientific process, and ensure that members of scientific advisory panels are selected on the basis of merit—not ideology."

White House allies began to return fire in March, when the Marshall Institute, a conservative policy think tank, held a press conference to refute the UCS report. Various newspaper columnists began to write articles criticizing the UCS and other White House critics.

Gregg Easterbrook, senior editor of the New Republic, called the UCS report "a mix of serious charges and trivia." He characterizes most of the major allegations as attempts to politicize policy disputes. He says, "…it's common in Washington for each side to consider its own views as science and the other side's as a misuse of science. Bush, the Democrats and the Union of Concerned Scientists disagree on subjects like forestry management or allowable parts-per-billion of dioxin, where science can only give guidance, not perfect answers. And such disagreements should be called what they are: legitimate policy disputes, not malfeasance."

The administration began to fire back in its own right on April 2, when the White House Office of Science and Technology Policy released a glossy, full-color report called "Bush Administration Science & Technology Accomplishments: Promoting Innovation for a Stronger, Safer America." Among the accomplishments claimed: a 44% growth in R&D funding between 2001 and the President's budget proposal for 2005; the highest level of discretionary outlays committed to R&D in 37 years; the doubling of the NIH budget and a 30% increase in NSF funding since 2001; an internet tax moratorium and support for the Research & Experimentation tax credit, and other, more dubious claims.

Also on April 2, Marburger weighed in with a 20-page report to Congress strongly rebutting the UCS document, even to the point of referring to one of the UCS charges as "highly offensive." He wrote in the preface:

in Election Year War of Words

"I believe the UCS accusations are wrong and misleading. The accusations in the document are inaccurate, and certainly do not justify the sweeping conclusions of either the document or the accompanying statement. I believe the document has methodological flaws that undermine its own conclusions, not the least of which is the failure to consider publicly available information or to seek and reflect responses or explanations from responsible government officials. Unfortunately, these flaws are not necessarily obvious to those who are unfamiliar with the issues, and the misleading, incomplete, and even personal accusations made in the document concern me deeply."

What are we to make of all this? First, it is important to remember that there is an election being held this year, and it is shaping up to be a quite bitterly fought one in the bargain. Thus, every statement takes on political overtones, and both Republican and Democrat charges and countercharges fly back and forth.

Politics in an election year? One is reminded of Captain Louis Renault, Claude Rains' charmingly amoral character in the film Casablanca, who, when forced under Nazi pressure to shut down Rick's Café, announced loudly, "I am shocked, shocked, to find that gambling is going on in here!" (just before the roulette croupier hands him his night's winnings).

But, while one may be "shocked, shocked" that politics is going on in an election year, there is at least some truth to the charges both sides are leveling. For example, the UCS has backed off some of its claims, Science magazine reports, and has quietly issued a revised critique of the administration's actions "correcting and clarifying some points."

Perhaps the area where the administration is most vulnerable to accusations of manipulation of science is in the area of appointments to advisory committees. While the UCS report made some errors in this regard, there are a number of recent cases that can only be characterized as disquieting, including the removal of Dr. Elizabeth Blackburn and William May from the President's Council on Bioethics in February (after the report was released). Another example: the UCS report claims that the State Department's Arms Control and Non-proliferation Advisory Group was disbanded. Marburger replied that the group's charter had merely expired and it was being reconstituted. However, Marburger did not note that the charter expired 32 months ago and the group has still not been reconstituted.

In addition, the White House and OSTP are apparently not above padding their resumes in their rebuttal of the UCS accusations. It is fair to say that the Bush administration completed doubling of the NIH budget over five years, as it promised to do during the 2000 campaign. The NSF budget has also increased 30% since 2001 (although Congress has stepped in on several occasions to boost poor administration budget requests). A variety of other defensible claims are made.

However, the OSTP also claims among the administration's science and technology accomplishments the creation of the "do not call" registry, and the fact that the president signed into law an anti-spam and pornography law last year. Various free trade agreements and the "president's economic growth package" are touted as spurring R&D and technological innovation. One must ask, is it reasonable to characterize these as "scientific and technological accomplishments?"

Thus, as in most disputes of this type, there is ample ammunition for partisans on both sides to continue the open warfare. One can only hope that it can be conducted with a measure of civility that has been lacking in the discussion up to now. One hopes that Marburger's planned attendance at the April 16-20 National Academy of Sciences meeting and meet with some of the scientists who support the UCS report will help clear the air.

If not, expect everyone concerned to be "shocked, shocked" by continued partisan warfare, including highly personal recriminations and even name-calling, over a subject that ought to be above it—the nature of scientific truth and its role in policy-making.

WHI Study Finds No Heart Disease Benefit, Increased Risk With Estrogen Alone

A large, multi-center heart disease prevention study, part of the Women's Health Initiative (WHI), has found that estrogen-alone hormone therapy had no effect on coronary heart disease risk but increased the risk of stroke for postmenopausal women. The study also found that estrogen-alone therapy significantly increased the risk of deep vein thrombosis, had no significant effect on the risk of breast or colorectal cancer, and reduced the risk of hip and other fractures. The WHI is sponsored by NIH's National Heart, Lung, and Blood Institute (NHLBI).

The estrogen-alone study was stopped at the end of February 2004 because the hormone increased the risk of stroke and did not reduce the risk of coronary heart disease, a key question of the trial. Initial findings appeared in the April 14 issue of The Journal of the American Medical Association (http://jama.ama-assn.org/). The article includes data collected through February 2004

"These findings confirm that estrogen-alone therapy should not be used to prevent chronic disease," said NHLBI Acting Director Dr. Barbara Alving. "We believe the findings support current FDA recommendations that hormone therapy only be used to treat menopausal symptoms and that it be used at the smallest effective dose for the shortest possible time."

"The results make clear that hormone therapy does not protect women against coronary heart disease and increases their risk for stroke," said Dr. Jacques Rossouw, WHI Project Officer. "This may be especially true for older women, those aged 60 and older."

As of July 2003, about 10 million American women were taking some form of hormone therapy. It is estimated that about 6.7 million of those take estrogen alone and 3.3 million take estrogen plus progestin. The drugs tested in the WHI are those most commonly used in the United States.

The estrogen-alone study involved 40 clinical centers and 10,739 generally healthy postmenopausal women ages 50-79 who did not have a uterus. Their average age at enrollment was nearly 64 and about 70 when the study stopped. They enrolled in the study between 1993 and 1998.

About 75% of the women were white, 15% black, and 6% Hispanic. Most were overweight and some 8% had diabetes. About 35% used hormone therapy in the past, and 13% were current users.

The women were randomized to two groups-one received 0.625 mg/day of conjugated equine estrogens (Premarin) and the other a placebo. The women were followed for an average of 6.8 years, visited their clinic at least once a year, and had annual mammograms and clinical breast exams.

NIH, FDA Launch Information System on Human Gene Transfer Research

The National Institutes of Health and the Food and Drug Administration (FDA) have launched a new Web-accessible database and information system on human gene transfer research that will help expedite institutions reporting of adverse events. The goal of the Genetic Modification Clinical Research Information System (GeMCRIS) is to improve the government's ability to monitor this research, while providing valuable information to the public on the characteristics of ongoing trials.

GeMCRIS will now provide investigators and sponsors conducting humangene transfer research with a secure, electronic interface for reportingadverse events immediately to NIH, and generates a paper record to besubmitted to FDA in accordance with federal regulation. Both agencies emphasized that GeMCRIS will enable patients and the public to become better informed about human gene transfer research through its easy-to-use report format, available on its public Web site http://www.gemcris.od.nih.gov.

Investigators and sponsors who wish to use the system to report adverse events must first contact the GeMCRIS Systems Administrator at (gemcris@od.nih.gov).

Biomedical Informatics for Clinical Decision Support: A Vision for the 21st Century!

Registration is now open for the NIH symposium, Biomedical Informatics for Clinical Decision Support: A Vision for the 21st Century, June 21 and 22, 2004, at the Natcher Conference Center on the NIH campus in Bethesda.

The symposium focuses on software tools and approaches to deliver biomedical information technologies to clinicians and patients at the time and place where decisions are made regarding risk, diagnosis, treatment, and followup.

The symposium will identify major challenges and opportunities that should be addressed by NIH policies and funding programs, including partnerships with the private sector. Those attending are invited to submit scientific abstracts for a poster presentation.

Satellite sessions will include: Using Semantic Standards to Integrate Biomedical Imaging into Clinical Decision-Making will explore the potential of integrating biomedical imaging into the clinical decision-making process.

Public Private Partnerships: Potential means to support Biomedical Informatics Resources, will explore how public-private partnerships can support the development of web assessable public resources, such as databases for validation of software tools and the development and dissemination of open source software.

A third session will be dedicated to current funding opportunities across the NIH. For more information visit www.becon.nih.gov/symposium2004.htm.

Continuing Medical Education

The National Institutes of Health/Foundation for Advanced Education in the Sciences designates this educational activity for a maximum of 10.75 category 1 credits toward the AMA Physician's Recognition Award.

New RNA Libraries Termed Major Step Forward

Researchers have produced vast libraries of short segments of ribonucleic acid (RNA) that can be used to turn off individual human and mouse genes to study their function. Commenting on the significance of the studies, Andrew Fraser at the Wellcome Trust Sanger Institute wrote: "As no single laboratory can specialize in every aspect of gene function, the general availability of these [short hairpin RNA] libraries as a communal resource is a major step forward, harnessing the screening expertise of the entire mammalian-cell research community."

RNA interference is a technique used with much success by researchers to switch off genes in lower organisms, including the fruit fly *Drosophila* and the roundworm *C. elegans*. Researchers stumbled upon this powerful tool for gene analysis when they discovered that introduced sequences of double-stranded RNA identical to a target messenger RNA actually triggered degradation of the messenger RNA.

The libraries will be made widely available to laboratories studying human biology and disease. The researchers are optimistic that the libraries will become a powerful research tool for gene analysis and discovery.

Two independent research groups reported on their respective RNA interference (RNAi) libraries in the March 25, 2004, issue of the journal *Nature*. Gregory Hannon of the Cold Spring Harbor Laboratory and Howard Hughes Medical Institute Investigator and ASBMB member Stephen J. Elledge at Harvard Medical School and Brigham and Women's Hospital led the first group. ASBMB member René Bernards of The Netherlands Cancer Institute led a second group.

Messenger RNA molecules are the genetic templates for proteins. In constructing proteins, the mRNA template is transcribed from DNA genes and transported to the ribosomes. RNA interference is a technique that essentially shuts down the activity of the gene under study.

"But RNAi didn't work in the vast majority of human or mouse cells because there are additional antiviral responses that recognize double-stranded RNA," said Dr. Elledge. "While the machinery to do RNAi is in mammalian cells, the antiviral machinery makes the introduced RNA toxic, and the cells die."

Researchers subsequently discovered that short segments of interfering RNA could be introduced into mammalian cells and remain unnoticed by the antiviral machinery, said Elledge. Furthermore, they discovered that the cell itself could be engineered to make interfering RNAs by introducing the gene for short hairpin RNA molecules that fold back on themselves to create a small RNA.

To construct a library of mammalian genes for short hairpin RNA molecules, Hannon and his colleagues first had to settle on an optimal design for a short-hairpin-RNA molecule. "We tested a lot of different things — for example, the length of the hairpin, the loop structure, the structure of the transcript and what promoters to use," said Dr. Hannon. "And we arrived at an optimal structure for this phase of the science."

Hannon emphasized, however, "that set of parameters is something that is going to evolve continuously. There have been many advances over the last year in understanding of the biochemistry of RNAi. So, we are now constructing even more effective structures and even more effective delivery vehicles which will be built into future generations of this library."

Once an optimized basic design of the short hairpin RNA molecule was finished, the researchers then produced a library of genes for short hairpin RNAs that could target 9,610 human genes and 5,563 mouse genes. The genes chosen were those that were likely to be involved in human disease, or to be key molecular switches in the cell.

The library of genes was integrated into a retroviral vector that was capable of shuttling the genes into other cell types. The researchers also incorporated a DNA "bar-coding" system, by which each RNA molecule can be tagged with a unique DNA sequence.

By determining the sequence of a given bar code for a short hairpin RNA, researchers using the library to screen for genes affecting a specific cellular process can identify which RNA molecule among the thousands in the library is switching off the activity of a particular gene.

But the retroviral vectors used for shuttling the short hairpin RNAs into cells only went so far. They were not

Continued on next page

Experimental Smallpox Vaccine Tested Against Monkeypox

An experimental smallpox vaccine, modified vaccinia Ankara (MVA), was found nearly as effective as the standard smallpox vaccine in protecting monkeys against monkeypox, in a study by researchers of the National Institute of Allergy and Infectious Diseases (NIAID) found. The study appeared in the March 11, 2004, issue of *Nature*.

Currently, Dryvax is the only commercially available smallpox vaccine in the U.A., and NIAID Director Anthony Fauci explained,"Because an initial MVA injection may help lessen side effects experienced from Dryvax, MVA may serve as an important pre-vaccine for large-scale vaccination efforts in the event of a bioterror threat involving smallpox."

NIAID's Bernard Moss, an ASBMB member and senior author on the paper, added, "This study shows that the MVA vaccine holds great promise as an alternative to the current vaccine. Although MVA may not quite equal Dryvax in its effectiveness, it did extraordinarily well, with all of the monkeys who were vaccinated with MVA surviving a potentially lethal monkeypox infection and, aside from a few minor lesions, showing no clinical signs of disease."

In a separate study published in the March 11, 2004, online edition of the *Proceedings of the National Academy of Sciences*, the researchers found that, in addition to protecting healthy mice against a lethal form of the vaccinia virus, MVA protects mice with certain immune deficiencies.

They found that mice survived a deadly dose of vaccinia virus if they'd been immunized with MVA, even if they were lacking antibody-producing immune cells or special proteins that help alert killer T cells to an infection. This indicated that MVA could be an alternative to Dryvax in humans.

To compare MVA with Dryvax, 24 cynomologus monkeys were divided into four groups of six. Group one received two MVA injections—one at the start of the study and the second two months later. Group two received the MVA vaccine at the start of the study and the Dryvax vaccine two months later. Group three received no injection at the start but received a Dryvax injection after two months. Group four, the control, received no vaccines.

Two months after the second vaccination, all 24 monkeys were exposed to monkeypox. All were healthy with no signs of disease, except for a small number of lesions seen on several monkeys from the MVA-only group. Those unvaccinated, however, had had over 500 lesions each and became seriously ill or died.

Continued from previous page

efficient for getting genetic short hairpin RNAs into all cell types. That's where an innovative technique developed by Elledge and his colleagues came in handy. This technique, called "mating-assisted genetically integrated cloning" (MAGIC), greatly assisted the transfer of the short hairpin RNA library into all cell types via bacterial mating.

In order to validate that the library worked in human cells, the researchers tested it in a genetic screen designed to report defects in human proteasome function. The proteasome is a key component of the machinery by which the cell breaks down unwanted proteins. "This was a thorough test of the system because there are a great number of different genes whose loss could interfere with proteasome function," said Elledge. "We found quite a few genes, and concluded that the library had worked quite efficiently as a screening tool."

Current efforts are aimed at increasing the number of human genes targeted by the library, said the researchers. They emphasized that the current and future libraries will be made available to the research community at a nominal cost through Open Biosystems, Inc., in Huntsville, Alabama.

"For the first time this gives us the opportunity to do a version of forward genetics in mammalian cells where we can look at hypomorphic mutations, ranging from mild to severe, and their consequences on phenotypes, on what will eventually evolve to a genome-wide scale," said Hannon. "Thus, these libraries will evolve into an important resource for the research community."

Mouse Cloned Successfully With Mature Olfactory Neurons

Researchers have successfully cloned a mouse using mature olfactory neurons as the genetic donor. The scientists credit the idea for the experiments to Woody Allen whose classic comedy *Sleeper* depicted scientists who try to clone a dead dictator from his nose.

The current study aims to answer longstanding questions about the developmental potential of mature cells. In doing their experiments, the researchers were seeking to determine whether the nucleus of a single mature olfactory neuron, when introduced into an egg, or oocyte, depleted of its nucleus, could revert to an undifferentiated state in which it could give rise to an adult mouse possessing the full range of olfactory receptors.

Indeed, the resulting mice exhibited an array of well organized odorant receptors that were indistinguishable from those of normal mice, the researchers reported in the March 4 issue of the journal *Nature*. The research was performed in the laboratories of Dr. Rudolf Jaenisch at the Whitehead Institute for Biomedical Research at MIT, and ASBMB member Richard Axel, a Howard Hughes Medical Institute Investigator and Professor at Columbia University.

"Our study demonstrates for the first time that animals can be derived from the nucleus of mature neurons following transfer into the oocyte. Because the cloned animals are normal, our experiment also shows that some brain functions do not involve genetic alterations of the neuron's genome," said Dr. Jaenisch.

According to the researchers, previous cloning efforts had failed to clone animals from the nuclei of any mature "post-mitotic" cells such as neurons—that is, those that had ceased dividing to produce new cells.

Dr. Richard Axel

A central question, said the scientists, was whether mature cells had undergone certain irreversible genetic processes, such as gene rearrangements, that would prevent them from reprogramming their nuclei to allow totipotent development. These processes might interfere with the cell's ability to become totipotent, a property of certain stem cells that permits them to differentiate into any cell type.

The researchers chose olfactory neurons as the source of genetic material because previous research had suggested that these cells might undergo gene rearrangements during development. Whatever the underlying process involved in generating their spectacular diversity, olfactory neurons are distinguished by their ability to randomly express any one of some 1,500 diverse odor receptor genes. Such genes give rise to the protein receptors on the surface of the neurons that detect specific chemical odorants.

In their efforts, the researchers in Dr. Axel's laboratory generated mice with olfactory sensory neurons tagged using genetic marker molecules. Using standard cloning techniques, the researchers in Jaenisch's laboratory then isolated individual neurons, removed nuclei from the tagged cells and introduced the nuclei into mouse eggs from which the nuclei had been removed. When these eggs were introduced into surrogate mother mice, the resulting offspring proved viable and fertile. Furthermore, they exhibited the normal pattern of odorant-receptor gene expression and organization of odorant receptor genes.

According to Dr. Axel, the cloning achievement eliminates one potential mechanism and narrows the possible ways in which a cell chooses one of thousands of receptor genes. The findings also demonstrate that the developmental changes are reversible.

Dr. Axel said that the cloning technique should be broadly applicable. "From a mechanistic point of view, it's very important to be able to investigate whether irreversible changes in the DNA accompany development, differentiation and maturation," he said. "This approach, although technologically demanding, affords an opportunity to detect those changes that are irreversible in virtually all cell types."

FASEB Summer Research Conference

FASEB Summer Research Conference on Trace Element Metabolism: Integrating Basic and Applied Research. June 26-July 1, 2004 in Snowmass Village, Colorado. Organizers: David Eide and Richard Eisenstein. Eleven sessions and 47 speakers covering trace element metabolism from microbes to humans. Topics covered: trace element transport and acquisition; trace elements and disease; nutritional aspects of trace element metabolism; metalloprotein biogenesis and others. The preliminary program can be found at http://src.faseb.org. The meeting application isalso on this website. For additional information, contact jlevin@faseb.org.

Redox Signaling in Biology and Disease

Kiawah Island, South Carolina, October 21-24, 2004

An ASBMB Sponsored Symposia

Organizers

Larry Marnett, **Vanderbilt University**; Roy J. Soberman, **Harvard Medical School**

Plenary Lecture

Regulation of Mammalian Clock Genes

Professor Steven L. McKnight, **University of Texas, Southwestern Medical Center**

Interpreting Redox and Oxygen Changes in the Cell Nucleus

William G. Kaelin Jr., ***Chair***
Susan L. Ackerman

Signaling by Nitric Oxide

Bettie Sue Masters, ***Chair***
Michael Marletta, Linda Roman

Signaling by H_2O_2 and Sulfhydryl Bonds

Roy J. Soberman, ***Chair***
Sue Goo Rhee, David A. Hildeman, Peter Cresswell, M. Amin Arnaout

The Cellular Consequences of Redox Signaling

Larry Marnett, ***Chair***
Dan Liebler,
Frank Fitzpatrick, Robert C. Murphy

Additional Speakers will be selected from abstracts.
Abstract deadline July 15.

For More Information and to Register Email:

asbmb@asbmb.org

Cutting Edge Research at the Interface

The world's two leading organizations for biochemistry and molecular biology will come together at the Hynes Convention Center in Boston June 12-16 for the combined annual meeting of the American Society for Biochemistry and Molecular Biology (ASBMB) and the 8th Annual Conference of the International Union for Biochemistry and Molecular Biology (IUBMB).

John D. Scott

For five days in June, scientists from across the United States and the world will present the latest research on how cells work at the molecular level, and how scientists are using this new knowledge to create diagnostic profiles for diseases; intervene in disease processes; and develop new therapies and therapeutic approaches. The meeting theme, the "Molecular Exploration of the Cell," integrates some of the major research approaches in this rapidly expanding arena, including cellular biochemistry, molecular recognition, chemical biology, proteomics, and bioinformatics.

ASBMB President Bettie Sue Masters says the 2004 meeting represents a rare opportunity for scientists from throughout the world to provide this in-depth focus. ASBMB has met intermittently with FASEB since 1923, and since 2001 has joined other societies to meet in the multidisciplinary Experimental Biology meetings, sharing information across specialties. The Society will do so again next year and through 2008, says Dr. Masters, but "this year, many members wanted an opportunity to meet with foreign colleagues in our disciplines, through a joint meeting with IUBMB, to explore new areas, including molecular and cellular proteomics, as well as to gain state-of-the-art information in the many areas to which our members contribute."

The June program was organized by **John D. Scott**, Howard Hughes Medical Institute, Vollum Institute, Oregon Health Science University, Portland; **Alexandra C. Newton**, University of California at San Diego; and **Julio Celis**, Danish Cancer Society, and members of the program planning committee.

The program includes more than 100 individual presentations of new research findings; seven distinguished award lectures by scientists internationally honored for discoveries such as the molecular basis of the therapeutic action of aspirin, the mechanisms that modulate T-cell response, and the targeting of membrane-spanning receptors by new therapeutic drugs. In addition, an intertwined series of symposia along 10 major themes, which cover the major areas of cellular biochemistry.

Alexandra C. Newton

The meeting also includes Society business meetings, receptions (including special receptions for minorities and women scientists), and an exhibit of the complex new technology required for much biochemistry/molecular biology research.

The opening lecture, 6:00 p.m. Saturday, June 12, will delivered by **Robert J. Lefkowitz**, Howard Hughes Medical Institute, Duke University Medical Center, and winner of the first annual Herbert Tabor/Journal of Biological Chemistry Lectureship. The award honors Dr. Lefkowitz for his groundbreaking research on the most common family of receptors, including the beta-adrenergic receptors that mediate the body's fight or flight response as well as virtually all sensory receptors. Since the beta adrenergic receptors respond to the hormone adrenaline, continuing research on these receptors in the Lefkowitz laboratory is contributing to the development of a wide range of drugs to treat disorders including heart disease, high blood pressure, asthma and pain. His lecture topic will be Seven Membrane Spanning Receptors.

Robert J. Lefkowitz

Awards Lectures

The Schering-Plough Research Institute Young Investigator Award will be presented at 4:45 p.m. Sunday, June 13, to Pehr A. B. Harbury, Stanford University School of Medicine. His lecture topic will be DNA Display in vitro Evolution of Combinatorial Chemistry Libraries.

The ASBMB-Avanti Award in Lipids will be received by William L. Smith, University of Michigan Medical School. The topic of his lecture at 8:30 a.m. Monday, June 14, will be

# of Biochemistry and Human Health

Prostaglandin Endoperoxide H Synathses/Cyclogenases.

Steven C. Almo, Albert Einstein College of Medicine, will receive the ASBMB-Amgen Award and deliver his lecture, Munday, June 14, at 4:45 p.m. His topic will be Structural Basis for T-cell Costimulation.

Cytochrome c Oxidase and the Particulate Methane Monooxygenase will be the topic for William C. Rose Award recipient Sunney I. Chan, California Institute of Technology. His lecture will be at 4:45 p.m. Monday, June 14.

Jack L. Strominger of Harvard University, will receive the ASBMB-Merck Award and deliver his lesture at 8:30 a.m. Tuesday, June 15. His topic will be The Structure of MHC Proteins and the Therapy of Multiple Sclerosis.

The Herbert A. Sober Lectureship awardee, Ronald W. Davis, Stanford University School of Medicine, will deliver his lecture, New Genomic Technology for Yeast and Human, at 4:45 p.m. Tuesday, June 15.

Symposia

The symposia series is organized on the basis of 10 themes.

Cellular Organization and Dynamics, organized by Harald A. Stenmark, Norwegian Rad. Hospital, with individual symposia on topics such as biosensors and apoptosis.

Genomics, Proteomics and Bioinformatics, organized by Charlie Boone, University of Toronto and Michael Snyder, Yale University, with symposia on topics such as macromolecular machines and proteomics and medicine.

Integration of Signaling Mechanisms, organized by Kjetil Tasken, University of Oslo, Norway, with symposia on topics such as informatics and modeling of signaling pathways and genetic and molecular resolutions of signaling.

Molecular and Cellular Biology of Lipids, organized by Dennis Vance, University of Alberta, with symposia on topics such as lipids and obesity, obesity and minority populations, regulation of lipid biosynthesis, and how changes in fat cells influence energy metabolism of the organism.

Molecular Recognition and Catalysis, organized by Jack E. Dixon, University of California at San Diego, with symposia on topics such as catalysis in health and disease and pathogens which intercept mammalian signal transduction pathways.

Protein Modifications and Turnover, organized by William J. Lennarz, SUNY at Stony Brook, with symposia on topics such as folding in the ER and degradation of proteins.

Protein Structures, Catalysis and Dynamics, organized by Susan Taylor, University of California at San Diego, with symposia on topics such as site-directed drug discovery and tethering and targeting of proteins.

Regulation of Gene Expression and Chromosome Transactions, organized by Joan W. Conaway, Stowers Institute for Medical Research, with symposia on topics such as how checkpoints respond to replication perturbations, DNA replication, and chromatin dynamics.

Signaling Pathways in Disease, organized by Alexandra Newton, University of California at San Diego and John D. Scott, Vollum Institute, with symposia on topics including stress signaling pathways, cancer and the cell cycle, diagnostic profiling in disease, and molecular basis of aging.

The Future of Education and Professional Development in the Molecular Life Sciences Meeting, organized by J. Ellis Bell, University of Richmond, with symposia on topics including using the Internet; outreach activities in the undergraduate, graduate and postdoctoral education; and BioMolecules Alive, The ASBMB Digital Library.

University of Michigan
Department of
Biological Chemistry
Social Hour
Sunday, June 13th
at ASBMB Annual Meeting
in Boston

The University of Michigan, Department of Biological Chemistry, is hosting a social hour at the annual ASBMB meeting in June 2004. The Department's friends and all present and past members are invited. It will be held on Sunday, June 13, 2004 from 5:30 - 8:00 p.m. in the Boston Marriot Hotel. The social hour reception will consist of a hosted bar serrrvice and hors d'oeuvres. Information on this reception will be listted in the ASBMB program book and on the hotel bulletin board; or please contact June Bialecki at jbialeck@umich.edu for more information.

An ASBMB Sponsored Symposia

Transcriptional Regulation by Chromatin And RNA Polymerase II

Granlibakken, Lake Tahoe, October 29-November 1, 2004

Abstracts Due: August 1, 2004

Organized by: Ali Shilatifard, **Saint Louis University School of Medicine**

Keynote Speakers:
Joan Conaway and Ronald Conaway, **Stowers Institute**

Invited Speakers include:

Shelly Berger, Jaques Cote, Dale Dorsett,
Barbara Graves, Tony Kouzarides, Robert Roeder,
Ramin Shiekhattar, Kevin Struhl, Jerry Workman
and many more...

Topics include:

Transcriptional initiation and promoter clearance
Transcriptional elongation and termination
Transcriptional repression and activation
Histone modifications
ATP-dependent chromatin remodeling
Chromosomal structure and transcription
Signaling in transcriptional regulation and development
Genomic/Proteomic approaches in transcription.

A large portion of the oral presentations will be selected from the submitted abstracts.

Please note that all registrations and abstracts MUST be submitted by the abstract deadline, August 1. Due to space limitation (about 200 participants) we encourage you to submit your abstract and register early. Late registration may be accepted after the abstract deadline should the meeting not be over-subscribed. In the event of over-subscription, we will make every effort to make sure that as many as possible of the research groups who wish to participate are represented.

For More Information and to Register
Email: **asbmb@asbmb.org**

Drug Addiction and Learning Share Common Brain Protein

Howard Hughes Medical Institute investigators at Duke University Medical Center have linked a gene previously shown to play a role in learning and memory to the early manifestations of drug addiction in the brain. Although scientists had previously speculated that similar brain processes underlie aspects of learning and addiction, the current study in mice is the first to identify a direct molecular link between the two.

The findings suggest new genetic approaches for assessing an individual's susceptibility to drug addiction. They also illuminate the complex series of molecular events that underlie addiction, the researchers said, and ultimately may lead to new therapeutic methods to interfere with that process, thereby curbing the cravings common to addiction.

The study, which examined genes involved in the brain's response to cocaine, appeared in the February 19, 2004, issue of *Neuron*.

"There has been the idea that brain changes in response to psychostimulants may be similar to those critical for learning and memory," said ASBMB member Marc G. Caron, an HHMI investigator at Duke. "Now, for the first time, we have found a molecule that links drug-induced plasticity in one part of the brain to a mechanism that underlies learning and memory in another brain region."

Previous work by other researchers revealed that exposure to cocaine triggers changes in a brain region called the striatum — a reward center that also plays a fundamental role in movement and emotional responses. Cocaine leads to a sharp increase in communication among nerve cells in the striatum that use dopamine as their chemical messenger. This brain chemical surge is responsible for the feeling of pleasure, or high, that leads drug users to crave more.

Dr. Marc Caron

"Drugs essentially hijack the brain's natural reward system," thereby leading to addiction, explained Dr. Wei-Dong Yao, an HHMI Fellow at Duke and first author of the new study.

The study sought to identify genes involved in the brain's heightened response after drug use. The researchers compared the activity of more than 36,000 genes in the striatum of mice that had "super-sensitivity" to cocaine due to a genetic defect or prior cocaine exposure, with the gene activity in the same brain region of normal mice. The genetic screen revealed six genes with consistently increased or decreased activity in super-sensitive versus normal mice, the team reported.

The protein encoded by one of the genes, postsynaptic density-95 or PSD-95, dropped by half in the brains of super-sensitive mice, the researchers found. The protein had never before been linked to addiction, Dr. Caron said, but had been shown by Seth Grant, a member of the research team at the Wellcome Trust Sanger Institute, to play a role in learning. Mice lacking PSD-95 take longer than normal mice to learn their way around a maze, while mice with normal amounts of PSD-95 appear less likely to become addicted and more likely to learn.

Two of the other five genes had earlier been suggested to play a role in addiction. The function of the remaining three genes is not known, Dr. Caron said, and will be the focus of further investigation.

Among the mice that were more responsive to the effects of cocaine, the decline in PSD-95 occurred only in the striatum, while levels of the protein in other brain regions remained unaffected. In normal mice, the protein shift occurred after three injections of cocaine and lasted for more than two months.

The researchers also measured the activity of nerve cells in brain slices from the different groups of mice. Neurons in the brains of super-sensitive mice exhibited a greater response to electrical stimulation than did the nerve cells of control mice. Neurons from mice lacking a functional copy of PSD-95 showed a similar increase in activity, the team reported.

Mice deficient in PSD-95 also became more hyperactive than normal mice following cocaine injection, further linking the protein to the drug's brain effects. However, the deficient mice failed to gain further sensitivity upon repeated cocaine exposure, as mice typically do.

"Drug abuse is a complex disorder and will therefore be influenced by multiple genes," Dr. Caron noted. "PSD-95 represents one cog in the wheel."

Continued on follwong page

Marine Sponges Provide Model for Nanoscale Materials Production

"Nature was nano before nano was cool," stated Henry Fountain in a recent *New York Times* article on the proliferation of nanotechnology research projects. No one is more aware of this fact of nature than Dan Morse, Chair of the Department of Biomolecular Science and Engineering, and Professor of Molecular Genetics and Biochemistry at the University of California, Santa Barbara. His research groups have been studying the ways that nature builds ocean organisms at the nanoscale for over 10 years. For example, they have studied the abalone shell for its high-performance, super-resistant, composite mineral structure.

Now they are now looking to learn new biotechnological routes to make high performance electronic and optical materials.

"We are now learning how to harness the biomolecular mechanism that directs the nanofabrication of silica in living organisms," says Dr. Morse an ASBMB member. "This is to learn to direct the synthesis of photovoltaic and semiconductor nanocrystals of titanium dioxide, gallium oxide and other semiconductors—materials with which nature has never built structures before."

Most recently, Morse and his students have made advances in copying the way marine sponges construct skeletal glass needles at the nanoscale. The research group is using nature's example to produce semiconductors and photovoltaic materials in an environmentally benign way—as they report in a recent issue of the journal Chemistry of Materials.

"Sponges are abundant right here off-shore and they provide a uniquely tractable model system that opens the paths to the discovery of the molecular mechanism that governs biological synthesis from silicon," says Morse. "This sponge produces copious quantities of fiberglass needles made from silicon and oxygen."

The work is particularly exciting, according to Morse, because silicon has been called the most important element on the planet technologically—silicon chips are fundamental components of computers, telecommunications devices, and in combination with oxygen forms fiber optics and drives other high-tech applications.

He explains that his research group discovered that the center of the sponge's fine glass needles contains a filament of protein that controls the synthesis of the needles. By cloning and sequencing the DNA of the gene that codes for this protein, they discovered that the protein is an enzyme that acts as a catalyst, a surprising discovery. Never before had a protein been found to serve as a catalyst to promote chemical reactions to form the glass or a rock-like material of a biomineral. From that discovery, the research group learned that this enzyme actively promotes the formation of the glass while simultaneously serving as a template to guide the shape of the growing mineral (glass) that it produces.

Drug Addiction ... continued

Continued from previous page

The brain protein likely plays a role in addiction to other drugs–including nicotine, alcohol, morphine and heroine–because they all exert effects through dopamine, he added. Natural variation in brain levels of PSD-95 might lead to differences in individual susceptibility to drugs of abuse, he suggested. The gene might therefore represent a useful marker for measuring such differences.

The researchers will next examine the effects of PSD-95 on the addictive behavior of mice, by testing whether PSD-95-deficient mice self-administer greater amounts of cocaine than do normal mice.

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.

Ion Gutiezzez Aguirre
University of Ljubljana

Michael L. Cartron
University of Oxford

Jong-Min Lee*
University of Wisconsin School of Pharmacy

Mara-Eliza Robu*
University of Wisconsin - Madison

Shine S. Tu
Cornell University

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

Obesity Drug Inhibits Prostate Tumor Growth;

Proteomics Screen Identifies Novel Prostate Cancer Target

The Burnham Institute's Jeffrey Smith, an ASBMB member, has discovered that orlistat, commonly prescribed as an anti-obesity drug, has a positive side-effect: it inhibits cancer growth. Dr. Smith, Associate Scientific Director for Technology at The Burnham Institute, made this discovery using an activity-based proteomics screening technique that makes it possible to identify active targets and simultaneously screen for their inhibitors. The results were published in the journal Cancer Research on March 15.

The metabolism of a tumor cell is different from its normal counterpart. Scientists have long suspected that this metabolism is connected to tumor progression. Dr. Smith and co-workers designed a proteomics screen based on monitoring the activity of a family of enzymes-serine hydrolyases-involved in metabolism. They used their screen to compare normal prostate cells with prostate cancer cells and discovered that the prostate cancer cells are affected by an increased activity of fatty acid synthase. The screen also identified orlistat, marketed by Roche as XenicalTM, as an inhibitor of fatty acid synthase.

These discoveries held true when tested in mice. When they administered orlistat bearing prostate tumors, the Smith group discovered that the drug was able to inhibit tumor growth. Further experiments confirmed that orlistat has no effect on normal prostate cells and no apparent side effects in the mice; it appears to act specifically on fatty acid synthase.

Additional screening of breast cancer and colon cancer cells revealed that fatty acid synthase activity is upregulated in these tumors, as well, presenting the possibility of designing new treatments for these cancers based on inhibiting the enzyme's activity with orlistat or a new drug based on orlistat's inhibitory activity.

Orlistat was originally developed as an inhibitor of pancreatic lipase. Pancreatic lipase is a member of the same enzyme family-the serine hyrdolases-used in Dr. Smith's screening. It is involved in processing of fats in the digestive tract, which is how the drug prevents adsorption of dietary fat.

Proteomics screening appears to be an efficient way to determine proof of concept needed before a potential treatment can be refined for clinical trials. In a matter of weeks, Dr. Smith was able to glean the initial discovery that linked excessive fatty acid synthase activity with flawed metabolism in cancer cells, and identified orlistat as its inhibitor.

"This discovery with orlistat has given us a very nice wedge with which we can go in and perturb tumor cells and ask the question, 'What are the active targets, what are the other changes that take place when you inhibit fatty acid synthase?'" says Dr. Smith, "and that will give us really good insights into the mechanism, and we anticipate that's going to reveal a whole swath of additional drug targets along this pathway. This is a big advance in the sense that we have an approved drug—approved for one indication—that has another target and another potential disease indication, prostate cancer."

FDA Seeks to Accelerate Drug

A Food and Drug Administration (FDA) report issued in March spotlighted problems and potential solutions to the task of ensuring that breakthroughs in medical science are safe, effective and get to patients as quickly and inexpensively as possible. The report, Innovation or Stagnation? — Challenge and Opportunity on the Critical Path to New Medical Products, the report examines the development path for all types of medical products—drugs, biologics and medical devices—the problems that exist and steps that need to be taken to meet the needs of the twenty-first century. It focuses, in particular, on opportunities to make the path from research to patient faster, predictable, and less costly.

The report was prepared under the direction of Janet Woodcock, Director of the FDA's Cross Center Initiatives Taskforce, who explained, "We're not seeing the increases in new products that we expected based on all the advances in science."

"Today, as never before, we face a tremendous potential for new medicines to prevent and cure diseases, but fewer new products are actually reaching the FDA," said FDA Commissioner Mark B. McClellan. "With so much promising technology in development in the clinical labs, ranging from engineered tissues to new kinds of biological and genomics-based treatments, we need to turn the process of bringing these technologies to patients from a costly and time-consuming art form to a well-understood science. FDA intends to launch a new effort with our public and private partners in improving the public health to turn the critical path of product development into a fast, certain, and more affordable process, to improve access to better treatments for all Americans. Our researchers have a unique vantage point on scientific challenges that cause delays and failures in product testing and manufacture. This thoughtful report outlines how critically important it is that the agency work with academics and industry to identify ways the medical product development process can be improved to keep pace with basic science innovation."

The report states that despite notable advances in such innovative fields of biomedical research as genomics, proteomics, and nanotechnology, there has been a downward trend in recent years in the number of innovative medical product applications worldwide. The FDA estimates that a new drug costs from $800,000 to $1.7 billion to bring to market, and despite a growth in government and private investment, the number of new drugs with novel chemical structures has fallen from roughly 70 in 1993 to less than 30 in 2003. New biologics applications have fallen from just under 30 to just under 20 during the same time period. Although these problems can be attributed to a variety of factors, the FDA report singles out one—science is not being adequately harnessed to guide the technology development process in the same way that it is accelerating the discovery process.

To meet this challenge, the report calls for the FDA, together with academia, patient groups, industry, and other government agencies, to embark on an aggressive, collaborative research effort to create a new generation of performance standards and predictive tools that will provide better answers

ASBMB Members Elected to National Academy of Sciences

Five ASBMB members were among 72 new members elected to the National Academy of Sciences at its 141st annual meeting last month.

Newly elected to the Academy were the following ASBMB members:

Susan G. Amara, Thomas Detre Professor and Chair, Department of Neurobiology, University of Pittsburgh School of Medicine.

Kevin P. Campbel, Howard Hughes Medical Institute Investigator and Roy J. Carver Professor and Chair, Department of Physiology and Biophysics, and Professor, Department of Neurology, Roy J. and Lucille A. Carver College of Medicine, University of Iowa, Iowa City

Barry H. Honig, Howard Hughes Medical Institute Investigator and Professor, Department of Biochemistry and Molecular Biophysics, Columbia University

Xiaodong Wang, Investigator, Howard Hughes Medical Institute and George L. MacGregor Distinguished Chair in Biomedical Science, University of Texas Southwestern Medical Center, Dallas

Sue Hengren Wickner, Chief, DNA Molecular Biology Section, Laboratory of Molecular Biology, National Cancer Institute, National Institutes of Health, Bethesda, Md.

Election to membership in the Academy is considered one of the highest honors that can be accorded a U.S. scientist or engineer. Those elected in April bring the total number of active members to 1,949. There also 351 foreign associates.

Development Process

about the safety and effectiveness of investigational products, faster and with more certainty. Key to this effort is to be the collaborative development of a Critical Path Opportunities List, which will identify those areas of product development that could most benefit from innovative approaches and emerging technological advances.

The report said that the FDA intends to make internal changes and implement new collaborations to medical breakthroughs to patients more quickly, and in ways that ensure greater understanding about how to maximize patient benefits and minimize their risks. The efficiencies gained through such innovations, it stated, could bring significant economies that could provide both more affordable medical products and a much greater payoff from greater predictability and speed for investment in medical research and development.

Stress Hormones and Heart Failure; Receptors Could Lead to New Treatments

A hormone that helps the body adapt to stress may provide a key to designing treatments for congestive heart failure, according to a study by researchers at the Salk Institute for Biological Studies and the University of California, San Diego (UCSD) School of Medicine.

Published in the March 9 issue of Proceedings of the National Academy of Sciences, the study establishes a firm link between a family of stress hormones called urocortins and heart disease, and may lead to new treatments for heart failure. Congestive heart failure is an increasingly common condition among Americans, currently contributing to the deaths of more than 250,000 people annually. The ailment is marked by an impairment of heart muscle function, which eventually leads to a loss in the ability of the heart to pump blood. The known causes of congestive heart failure are multiple, and can be either acquired or inherited. In some individuals, the cause is unknown.

Wylie W. Vale, Helene MacLoraine Professor of Molecular Neurobiology at the Salk, Dr. Kirk L. Peterson, UCSD Edith and William Perlman Professor of Clinical Cardiology, and their colleagues found that a specific member of the urocortin family of proteins, called urocortin II, administered intravenously in a small dose, significantly enhanced heart muscle cell contractions in mice. The hormone bound to a receptor molecule called CRF2 on muscle cells. Mice bred specifically to lack the CRF2 receptor showed no response to urocortin II and higher than normal blood pressure

In addition, mice that were bred to exhibit a form of congestive heart failure were found to have a dramatic improvement in their cardiovascular function when treated with urocortin II.

"We hope that this study expands our understanding of the potent actions of urocortin II in cardiovascular physiology and points to a precise targeting of the CRF2 receptor for improved treatment of heart diseases," Vale said.

"We believe urocortin II represents a new class of cardiovascular-active agents that may prove to have a beneficial role in the treatment of congestive heart failure," said Peterson. "However, human urocortin is somewhat different from mouse urocortin, and further experimentation will be needed before we have a usable treatment for people."

The researchers are continuing to work on pinpointing all of the mechanisms by which urocortin II triggers its beneficial cardiovascular effects. Further studies will take place in animals. Following their completion, human clinical trials will begin.

Additional authors of the paper were first author Tracy L. Bale, previously with the Salk Institute and currently with the University of Pennsylvania; and Mashahiko Hoshijima, Yusu Gu, Nancy Dalton and Kenneth Chien, UCSD; and Keith R. Anderson, Kuo-Fen Lee and Jean Rivier, the Salk Institute.

The study was funded by the Foundation for Research, the San Diego Foundation for Cardiovascular Research and Education, National Institute of Diabetes and Digestive and Kidney Diseases, and the Kleberg Foundation.

by John D. Thompson, Editor

Aventis Accepts $65.5 Billion Takeover Offer

The French-German drug company Aventis announced, just before this magazine went to press, that it had reversed course and accepted an offer from a once-hostile bidder, Sanofi-Synthélabo, of 55.3 billion euros ($65.5 billion). The purchase price is 14% higher than Sanofi's original bid in January.

The new company will be called Sanofi-Aventis, even though Aventis is about twice as large as Sanofi, and the Sanofi Chairman and CEO, Jean-François Dehecq, will chair the management committee. The committee will be split between Aventis and Sanofi.

The action came four days after the Swiss drug company Novartis said it would begin formal talks with Aventis about a merger, and then—the night before Aventis accepted Sanofi's offer—Novartis withdrew its offer claiming that none of its conditions for a deal had been met. A more likely reason for Novartis' change of heart came in a subsequent statement, which stated, "Following Aventis' decision to engage in discussions with Sanofi, at the strong intervention of the French government, Novartis decided not to proceed."

The agreement with Sanofi, based in Paris, came in response to the French government's pressure to ensure that France remained home to Aventis. The combined Aventis and Sanofi will be the world's third-largest pharmaceutical company, with combined sales of $30 billion in 2003.

The higher offer represented a shift for both Sanofi, which had steadfastly refused to alter its original $60 billion bid for Aventis, and for Aventis, which had insisted that it would be a stronger company if it did not combine with Sanofi.

Firm with Vatican Ties Buys Drug Lab

The *Congregazione dei Figli dell'Immacolata Concezione* (CFIC), a nonprofit group with close links to the Vatican, is to be the new owner of one of Italy's leading drug research labs. The lab in Nerviano, close to Milan, is currently owned by drug giant Pfizer, which is shutting down its Italian outfit. A binding contract on the deal is to be signed by the two companies on May 15, and Umberto Rosa, previously chief of *Sorin Biomedica*, will be the director of the new entity.

The pharmaceutical center in Nerviano has 800 employees and international fame in oncology drug research. Pfizer's research there focused on kinase inhibitors targeting specific oncogenesis cascades, five of which are in clinical trials at the moment.

"It is still premature to foresee the future," Giulio Draetta, scientific director in Nerviano, told *The Scientist*. "However, it would be a pity to stop our research line, since Italy, and in particular the Milan area, is a leader in oncology research after the United Kingdom."

According to the agreement, Pfizer will transfer to CFIC technologies associated with the lab, including the access to the kinase platform and a number of research and development projects. CFIC, founded in 1857, is already engaged in healthcare and plans to invest 300 million ($363 million) in the new enterprise.

Extracting Metal from the Sea; The Environmentally Friendly Way

A novel method that uses bacteria to mine valuable minerals from the ocean has been developed. Nodules collected from the Indian Ocean seabed can be treated to extract scarce land-based minerals in an environmentally sound way.

Using the marine species *Bacillus M1*, cobalt, copper and nickel can be extracted from the nodules at a near neutral pH and room temperature. In a single four-hour process, 45% cobalt and 25% of both copper and nickel can be extracted and dissolved in solution. Unlike traditional methods, the new process uses no acids or harmful chemicals. By using a multiple stage process, the metal dissolution can be further enhanced to leach nearly 85% Cobalt and 60% Nickel solution from the nodules.

Ashok Raichur, a researcher on the project at the Indian Institute of Science, Bangalore, told *Newswise,* "We are looking into the application of this process for recycling of various metallic waste."

South Africa Sees its Future in Generics

This month, Africa's biggest pharmaceutical company, Aspen Pharmacare, will open a new 150 million rand ($23 million) drug-manufacturing plant in Port Elizabeth, South Africa. The new facility, which will double Aspen's annual output to more than 5 billion pills, most of them generics, follows on the heels of Aspen's 20 billion rand purchase in March of Fine Chemicals, which produces medicines in tablet form.

Another South African pharmaceutical, Adcock Ingram, recently announced a joint venture with Ranbaxy Laboratories, the largest drug manufacturer in India. Once approved by the nation's Medicines Control Council Thembalami, the firm born of this merger, will be on the road to producing 13 different generic medicines.

The two South African firms are riding on the growth of generics. The government is pressing to reduce the prices of branded medicines by as much as 50% and urging wider use of generics, At the same time, South Africa, whose 5 million patients make it the home of the world's largest AIDS epidemic, is considering the dissemination of free antiretroviral drugs in state-run clinics and hospitals.

Astrazeneca CEO Calls for Integrated Biomedical Research Strategy

Sir Tom McKillop, AstraZeneca CEO, called for an integrated biomedical research strategy and a European Market Place as to reverse Europe's decline in biomedical research, in an address to Britain's Academy of Medical Sciences.

"In the last 20 years," he said, "total research expenditure in the U.S. has grown to 2.8% of GDP whilst in Europe it has fallen from 2.4% to 1.9% of GDP. The success of the pharmaceuticals industry is linked to research. In 1980, eight of the ten top drugs in the world were invented in European laboratories. Today, eight of the top ten top were invented in the U.S. This mirrors the progressive decline in the relative size of the European Pharmaceutical Market caused by the slow adoption of new medicines and an unwillingness to reward innovative products. European citizens are being denied access to the best new treatments."

Killop called for the establishment of a European biomedical research strategy with clear priorities and proper funding to increase investment in science education and training, encourage more entrepreneurship and industrial collaborations in universities, strengthen European research capabilities, and improve the regulatory and legal framework.

Eli Lilly Investigated

The office of the U.S. Attorney for the Eastern District of Pennsylvania has advised Eli Lilly and Company that it has commenced a civil investigation relating to the company's marketing and promotional practices. Based on the information provided by the U.S. Attorney's office, Lilly believes that the company products likely to be involved include Evista, Prozac, and Zyprexa. The company said it intends to cooperate with the U.S. Attorney in this investigation.

GE Completes Acquisition of Amersham

General Electric Company has acquired all the outstanding shares of Amersham plc, a leader in diagnostic imaging agents and life sciences. Together with GE Medical Systems, a provider of medical imaging, healthcare services, and information technology, the combined $14 billion business, now known as GE Healthcare, is expected to generate $16 billion in revenues in 2005.

GE Healthcare will have its global headquarters based in Chalfont St. Giles, United Kingdom. GE Healthcare Technologies will be headquartered in Waukesha, Wisconsin, and GE Healthcare Bio-Sciences will be headquartered in Little Chalfont, UK.

GE's management believes the acquisition will create a group of technology and service driven healthcare businesses that will have combined 2004 revenues in excess of $14 billion, and accelerate the development of molecular imaging and personalized medicine.

Department of Defense Funds Swedish Stem Cell Research

Although embryonic stem (ES) cell research may be a controversial issue in the U.S., the Department of Defense (DoD) has awarded $240,000 to a research group at Lund University, in Sweden, to study the therapeutic use of human embryonic stem cells in rats.

Patrik Brundin, Professor and leader of the Neuronal Survival Research Group at Lund, was quoted as explaining, "We are studying if the ES cells can differentiate into dopamine neurons, and if such dopamine neurons can survive grafting to the brains of Parkinson rats, and actually function too."

The Michael J. Fox Foundation for Parkinson's Research had encouraged Brundin to apply for the grant program. "My understanding is that the DoD wants to develop therapies against brain damage that can occur in response to toxins," he told *The Scientist*. "Parkinson's disease can be viewed as a model disease in this respect."

Despite earlier reports to the contrary, he said his group has not created new stem cell lines for its study. "The cell lines we use are among the Bush-approved cell lines," Brundin said. "We do not intend to develop new cell lines."

NETRP is currently funding 80 projects, including researchers from Canada, France, Germany, Israel, Italy, and Sweden.

Canada's Auditor General Says NRC Outgrowing Budget

The Canadian federal government's Auditor General, Sheila Fraser, told Parliament last month that the National Research Council of Canada (NRC)—a CAN $800-million-a-year (U.S. $611 million) agency—is at risk of outgrowing its financial resources. Fraser said the NRC needs "stronger governance and improved priority setting" and expressed concern that its research activities are grower faster than its ability to finance them.

The auditor general was quoted by *The Scientist* as telling reporters, "NRC's Governing Council… provides no effective challenge to management plans and decisions to ensure that the council's research activities continue to be sustainable."

The council's biggest challenge, the auditor general's report stated, is for the NRC to "review its corporate mechanisms for setting priorities to avoid an imbalance between its research activities and available funding. Although it has had no core budget increase, it is currently launching several long-term initiatives that include major increases in infrastructure and staff."

Fraser acknowledged that the NRC generally followed good practices for developing its vision, which is closely aligned with the federal government's 1996 science and technology strategy and its 2002 innovation strategy, but continues to expand the scope of its research activities and infrastructure, despite a lack of core budget increase.

Fraser recommended, among other things, that NRC's Governing Council should define its role and put in place necessary governance mechanisms and review the its corporate senior management structure. The NRC "has accepted and agreed with all our recommendations," Fraser noted, with responses to her recommendations included in the report.

NRC Secretary General Pat Mortimer was reported to have said in a broadcast interview that the council has known all along it would have to make a good case for continued funding. "This is not new for us, we're not concerned … When the time comes to make a decision for the government to renew that funding, we'll be in a good position to make a case."

An NRC spokesperson quoted NRC President Arthur J. Carty as saying, "We do recognize… that the NRC over the last 10 years has undergone some quite dramatic changes, and we accept the challenge that it might be time to update, for example, our corporate governance and management systems to match the exciting and dynamic environment we've created here. So, we find the auditor general's comments useful, and we'll work to implement the key recommendations."

David Thomas, Director of the Royal Society of Canada's Life Sciences Executive Committee, told *The Scientist* that the NRC has to find a new role. "It's trying to do too much with too few resources," said Thomas, who chairs McGill University's Biochemistry Department. "Unlike the National Research Council in the US, the NRC continues to do in-house research."

Functional Genomics Lab To Open in Germany

A research center for functional genomics is to be opened at Greifswald University in northern Germany at the end of this year as a focus for the development and coordination of research integrating the computational and biological sciences.

"The center is unique in Germany because faculty and participants drawn from the departments of mathematics, science, and medicine will be working closely together for the first time," according to Uwe Volker, Principal Investigator at Greifswald's Functional Genomics Lab.

Dr. Volker said that the center's research on the biomathematical analysis of proteins and their subcellular localization would be of central importance to a major research program at the university on the molecular mechanisms behind infectious diseases.

"With the help of functional genomics, we want to find out how bacterial pathogens interact with the host cell. If we can identify the key proteins that allow pathogenic bacteria to communicate with the host cells, then we will be able to target those proteins with antibiotics," he explained.

Broader research on the molecular causes of infectious diseases at Greifswald is being spearheaded by the Microbiological Institute, which employs 60 research staff drawn from diverse faculties.

The center expects to provide research training opportunities at the interfaces of computational and biomedical sciences for 12 postdoctoral and doctoral positions. "This center will cater for the needs of young scientists. We hope to recruit two leading young internationally known researchers to lead the teams there," said Dr. Volker..

The German Federal Ministry for Education and Research will fund the teams. It has already pledged 9 million ($10.7 million).

"We hope that the establishment of the functional genomics center will help Greifswald build on its reputation as one of the leaders for functional genomics in Germany and even in the world," said Greifswald University Rector Rainer Westermann.

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
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9650 Rockville Pike
Bethesda, MD 20814
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This is an ongoing project; please advise us whenever a student in your department earns the Ph.D., so that we can make this free membership offer to him or her.

Calendar of Scientific Meetings

JUNE 2004

Third International Congress on Plant Metabolomics

June 3–6 • Iowa State University, Ames, Iowa.
For more information: Ph: 515-294-7978
Email: pbmb@iastate.edu
Website: http://www.bb.iastate.edu/~gfst/phomepg.html

Pacific Northwest National Laboratory 2nd Annual Northwest Symposium for Systems Biology, Regulation of Cells in Time and Space.

June 7–8 • Richland, Washington
Poster deadline: May 14, 2004
Register at: www.pnl.gov/northwestsymposium
For more information go to www.sysbio.org

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

June 12–16 • Boston, Massachusetts
Contact: Joan Geiling; Ph: 301-634-7145; Fx: 301-634-7126
Email: jgeiling@asbmb.org;
Website: www.asbmb.org/meetings

Society of Toxicologic Pathology Annual Meeting

June 13–17 • Salt Lake City
Hepatotoxicigy is the theme of this year's meeting. In addition, the Society is hosting two continuing education sessions, Toxicologic Ocular Pathology and Imunotoxicology for Toxicologic Pathologists. For more and to register visit: http://eshow2000.com/STP/index.cfm

Mathematical Models in Signaling Systems

June 16–8 • VanderbiltUniversity, Nashville
Ph.: 615-322-0672; Email: cme@vanderbilt.edu
Website: http://medschool.mc.vanderbilt.edu/vusc

Kingsbrook Jewish Medical Center Conference on Nutritional and Metabolic Aspects of Low Carbohydrate Diets.

June 18-19 • Brooklyn (New York) Marriott
Contact: Richard Feinman; Ph: 718-270-2252
Email: rfeinman@downstate.edu
Website: http://downstate.edu/kingsbrook

4th International Symposium on Hormonal Carcinogenesis

June 21-25 • Palau de la Musica, Valencia, Spain
Contact: Tandria Price/Dr. Jonathan J. Li
Dept. of Pharmacology, Toxicology and Therapeutics
University of Kansas Medical Center
Ph: 913-588-4744; Fx: 913-588-4740; Email: tprice@kumc.edu
Website: http://www.kumc.edu/hormonecancers

JULY 2004

International Conference on Genomics, Proteomics and Bioinformatics for Medicine

July 14-19 • 2004 Moscow, Russia
Fx: +7 (095) 245-0857
http://www.ibmh.msk.su/gpbm2004/english.htm

4th ANNUAL CONFERENCE OF FOCIS (Federation of Clinical Immunology Societies)

July 18-23 • Montréal, Canada
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

FASEB Conference: Transcriptional Regulation During Cell Growth, Differentiation, and Development

August 14–19 • Saxtons River, Vermont
Co-organizers: Barbara Graves and John Tamkun
Go to http://src.faseb.org to fill out online application.
Student travel awards available.

Macromolecular Organization & Cell Function

August 15–20 • Queen's College, Oxford, UK
Ph: 401-783-4011; Email: grc@grc.org
Website: http://www.grc.uri.edu/programs/2004/macromol.htm

EuroScience Open Forum 2004: Highlighting Science, Technology & Innovation in Europe

August 25–28 • Stockholm
Contact: Gabriella Norlin, Project Leader
Phone: +46 8 546 44 154; Fax: +46 8 546 44 155
Email: gabriella.norlin@esof2004.org
Postal address: Swedish Research Council
SE-103 78 Stockholm, Sweden

International Congress on Biocatalysis 2004

August 29–September 1 • University of Technology, Hamburg, Germany
Contact: Gerlinde Loebkens; FON +49-40-76618012
FAX +49-40-76618018; e-mail: loebkens@tutech.de
Website: www.biocat2004.de

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

5th Meeting on Methods in Protein Structure Analysis

August 29-September 2 • University of Washington, Seattle
Ph: 206-706-8118; Email: mpsa2004@u.washington.edu
Website: http://depts.washington.edu/biowww/mpsa2004/

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

OCTOBER 2004

Redox Signaling in Biology and Medicine

October 22–24 • Kiawah Island, South Carolina
Contact: Joan Geiling; Ph: 301-634-7145
Fx: 301-634-7392
email: jgeiling@asbmb.org

The American Society of Biochemistry and Molecular Biology Sponsored Symposia on: Transcriptional Regulation by Chromatin and RNA Polymerase II

October 29–November 1 • Granlibakken, Lake Tahoe
Abstracts Due: August 1, 2004; Contact: Joan Geiling
Ph: 301-634-7145; Fx: 301-634-7392
email: jgeiling@asbmb.org

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

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