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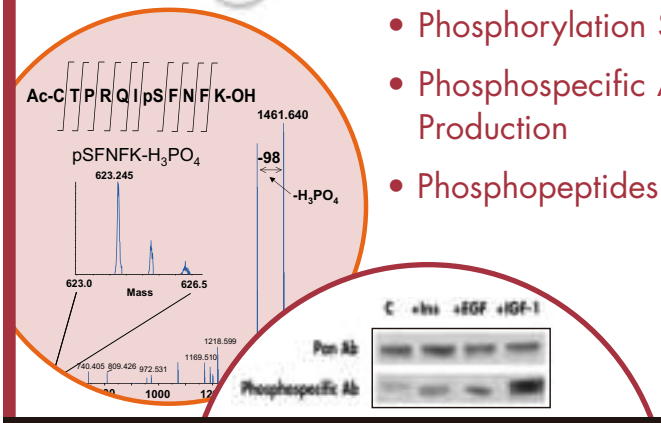

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AMERICAN SOCIETY FOR BIOCHEMISTRY AND MOLECULAR BIOLOGY

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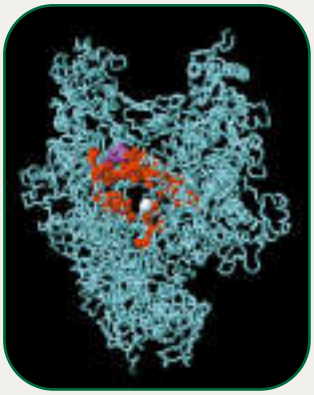

ON THE COVER:

8 Peptide's 'Cork in a Bottle' Mechanism May Lead to New Generation of Antibiotics.

Image courtesy Richard H. Ebright, Rutgers University.

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Problem With Shortage of Scientists Is the Teaching

Dear Editor:

I wish to congratulate you on the excellent translational reports in your last issue; non-science friends of mine understood these reports and said they were not condescending like many such reports. More important I want to discuss the problem of the decreasing number of scientists.

In general the introduction of students to science is hardly captivating; those not interested are not converted and those already interested are frequently turned aside. There is no pulse of the vibrant forefront of life sciences and little evidence of the tight relation to new technology; none of the mystery of discovery; nor do the presentations effectively connect theory with practice or dollars with effort. In many cases science is taught as a necessary evil like evolution, a burden to the student and imposition on the teacher who is generally not prepared well in science and rarely up to date on modern biological experimentation such as sequencing and robotics, things which would appeal to a computer minded generation. Clearly, the training of science teachers is critical!

Alongside this, the absence of hands-on lab experience even at the college level makes science courses dreary and unexciting. Also at the college level the general tendency to have junior faculty present introductory courses rather than senior professors denies students inspirational teaching and feelings of wonderment. There is no general correction for all of this. However, without drastic improvement of science teaching beginning in the grades and flowing thru to introductory college courses there can be no real hope of progress. Perhaps legislation as to standards is necessary here. In non research institutions, ways of exposing students to research scientists is essential, and this exposure should

There can be no hope for the future without drastically increasing the participation of minorities in science.

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 Today*. Letters should be sent to the editor, John Thompson, at the address found at left. Letters must be signed and must contain the writer's address and telephone number. The editor reserves the right to edit all letters. Letter published do not necessarily reflect the opinions of ASBMB.

include industry representatives not just job fairs. Students have to get a convincing description of where things really are and where they are going, particularly in the life sciences for the next generation to produce more candidates.

Alongside this, there can be no hope for the future without drastically increasing the participation of minorities in science. African-Americans and Latinos are woefully absent from all of science with the deficiencies increasing from the lowest educational and occupational levels to the highest. Our specific efforts to reach and inspire minority students must begin with major improvement in the science programs and facilites in minority and inner-city schools which goes beyond installation of a science school here and there. Particular attention needs to be paid to historic Black colleges, schools in Latino communities, two year and community colleges. Visits to these schools of scientists and representatives of life science industry can play a major role in interesting and retaining students, including many gifted ones who would otherwise drop out of science for economic reasons. A considerable expansion of subsidized summer programs carrying stipends for students who would otherwise have summer jobs is essential. Perhaps ASBMB can seize the leadership in initiating projects. Science industries simply have to play a very much larger role in sponsoring, financing and paricipating in seconday and college programs. Here again ASBMB and also FASEB can take the lead in organizing, national, regional and local educational and planning conferences.

The problem will not go away by itself. We must demonstrate that all students are really welcome in science. Scientists must actively intervene in science education for all groups at all education levels as a regular part of their scientific activity .

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by Peter Farnham, CAE, ASBMB Public Affairs Officer

NIH Plans Open Access

NIH intends to move in the near future—perhaps as soon as the end of this year—toward some kind of open access for the scientific literature its research dollars paid for. While the details are negotiable, the principle will be implemented because of public demand for freer access to NIH-funded research.

This was the principal message of NIH Director Elias Zerhouni at an invitation-only meeting of publishers and society representatives on July 28. The meeting came less than two weeks after the House Appropriations Subcommittee on Labor/HHS (which funds NIH) published a report calling on NIH to move to open access. However, Zerhouni assured the attendees that the agency has been considering various approaches to increase public access to NIH-funded research results for some time, and that NIH did not write the language in the House panel's report (although it was apparently aware that it was in the works).

The House subcommittee report on NIH funding for FY 2005 expressed concern about "insufficient public access to reports and data resulting from NIH-funded research," and said the situation was made worse by large increases in subscription prices. The panel recommended that "NIH develop a policy … requiring that a complete electronic copy of any manuscript reporting work supported by NIH grants or contracts be provided to PubMed Central (PMC) upon acceptance of the manuscript for publication in any scientific journal listed in the PMC directory." PMC would begin making these reports publicly available six months after publication, "or immediately in cases in which some or all of the publication costs are paid with NIH grants funds." NIH was instructed to report to Congress by December 1 on how it intends to implement this policy.

Many Concerns Expressed

About 50 people attended the meeting, including ASBMB President Judith Bond, representatives from other scientific societies, publishing houses and publishers' associations, and the Public Library of Science.

Zerhouni made it clear that NIH intends to move forward with some kind of open access initiative. He repeatedly made the point that the taxpaying public deserves access to the results of research they have funded.

Slogans Confuse Issues over

By Judith Bond, ASBMB President

Elias Zerhouni is quoted by *The Scientist* (29 July 04) as asserting that "The public needs to have access to what they've paid for." By "public" Zerhouni appears to mean the individual and corporate tax-payers of the United States. The rank-and-file of the individual American tax-payer is not seeking access to the technical literature, but rather is looking for synthesis and interpretation of a body of research results. A number of disease-related associations span the breadth of the needs of their constituencies by disseminating information targeted on the one hand to the informed lay population, and on the other hand, to physicians and clinical investigators. The disease-related associations, such as the American Cancer Society or the American Diabetes Association, produce technical journals, distribute a range of non-technical print material, sponsor technical and non-technical meetings, and maintain web sites serving readers with quite disparate backgrounds. Posting full-text materials in a searchable database such as PubMed Central, will not make all NIH-financed research freely available to the public in a useful context.

Dr. Judith Bond

Zerhouni also commented that "The status quo just can't stand." Every publisher of science and health information is acutely aware of the rapid changes in the art and technology of communicating to their constituency. Both technical and non-technical distributors of science and health information are exploring strategies and delivery tools to sustain the interest and loyalty of their readership. Compact disks are often included with print publications to provide supplemental graphics and information. Videotapes, Digital Video Disks, and Web Sites supplement meetings and print material as a means of communicating to the

to Research Publications

He said a draft proposal was being developed, and would appear in the *Federal Register* or the *NIH Guide to Grants and Contracts*. He did not specify a date, but NIH staff subsequently indicated that the proposal would appear by December.

The NIH Director apparently does not plan any further meetings with publishers, although he supposedly will be meeting with patient advocacy groups. Zerhouni said these groups were clamoring for open access. He did not specify which groups are doing the clamoring. Most of the big patient advocacy groups are publicly neutral on the issue of open access, with some indicating privately that they do not support it. An alliance of groups advocating for rare, genetics-based diseases apparently has Zerhouni's ear.

The Internet has Changed Everything

Zerhouni began the meeting by saying that NIH has given a great deal of thought to the issue of improving access to NIH-funded research. He noted that widespread use of the Internet has fundamentally changed the way information is distributed, and consequently there has been an exponential growth in demand for information. While NIH has not endorsed any particular model for improving access, he could see value in the open access model. However, he also noted that "there are other values besides open access," such as what societies provide—communities of interest, job information, and basic information about disciplines and fields. He also noted that NIH already pays a lot of money to distribute information, through pages charges and other means involving both direct and indirect costs.

Nevertheless, Zerhouni noted, there were important public interests at stake in the debate. First, NIH invests in public-funded research. The public is requesting better access, and technology has made it easier to satisfy that demand. In addition to increased public demand for open access, NIH has also been asked to account for the productivity of the enterprise, and to provide a full compendium of research results to demonstrate productivity.

He reiterated that "we will work with you" (the societies and publishers) and that any draft policy would be open for public comment. He said "we want balance" in the policy, and that his

Continued on next pagre

Communicating Science

target population. Distributors of technical information have continuously explored alternative means to communicate with their constituency. Scientific societies offer a variety of meeting formats ranging from large meetings with multiple themes to small conferences addressing a single topic to videoconferences supplemented with websites and telephone call-ins. Similarly scientific societies offer a variety of redacted formats, ranging from monographs to traditional journals to online distribution. The relative use of this potpourri of communication styles is in a dynamic state of flux. Certainly no one believes that the status quo can be sustained.

The American Society for Biochemistry and Molecular Biology (ASBMB) has an overriding commitment to distributing scientific information worldwide. The stated purpose of the Society is to advance the science of biochemistry and molecular biology through publication of scientific and educational journals, organization of scientific meetings, advocacy for funding of basic research and education, support of science education at all levels, and promoting the diversity of individuals entering the scientific workforce. The ASBMB has been a leader in the biomedical sciences of making its technical literature freely available online to the world scientific community. ASBMB makes all of its contents available immediately upon acceptance to the international scientific community regardless of sponsorship of the research. ASBMB not only communicates science to the research worker, but through its education journal and meetings, provides updates, syntheses and interpretation of biochemistry and molecular biology to teachers and students. It has been disappointing that the leaders of the NIH, Members of Congress and the Public Library of Science have not recognized the accessibility and innovations in publishing instituted by the Not-For-Profit Society publishers.

Continued from previous pagre
sole interest in the matter was NIH and the taxpayers who support it. He then opened the meeting up to questions, and particularly requested information on what he called the "pressure points" that were driving the high level of concern.

Among the major points:

Many societies already support a variety of models to bring about open access, and societies bring much added value to the literature through peer review and editing. Societies also play many other roles such as nurturing the next generation of scientists.

The "mandatory compliance" inherent in the House report language was a matter of considerable concern. ASBMB President Bond noted that ASBMB has 10 years experience in providing open access, and mentioned the *Journal of Biological Chemistry's* approach, including the "Papers in Press" feature which makes manuscripts available to the public free within days of acceptance. She also noted that half of *JBC*'s authors are foreign, which would greatly affect how many papers got deposited in the archive.

Dr. Bond further recommended an approach using multiple institutions as repositories of articles; she is worried about PMC being the only allowable repository. In response, Zerhouni noted that some private repositories don't last very long; he said 20 percent of them disappear after 5 years, and that a government repository would be permanent and funded adequately. Dr. Bond said that the government could support other repositories, not just PMC. Dr. Bond also noted political risks in having all research deposited at one government-controlled and funded repository. Zerhouni noted that only NIH-funded research would be located at PMC.

AAAS President Alan Leshner expressed concern that the House language required that if any amount of NIH money was involved in the publication process (i.e., as little as a couple of dollars for a color charge) the entire document has to be "immediately" deposited in PMC.

Association of American Publishers President Pat Schroeder, expressed concern that there had been no hearings, and that the federal government appeared to be "putting its thumb on the scale" in favor of open access, thereby disrupting the system. She said the publishing system already provided plenty of public access, and that publishers and the societies needed to do a better job of explaining how citizens could get detailed scientific information through libraries, contact with authors, and other means.

Concerns were also expressed about the lack of definition of many terms in the House language. For example, does the language require deposit of a manuscript or an article? In addition, the policy was of great concern to "non-biomedical societies," many of which are small and would not be able to survive on an author-pays model. Although Zerhouni noted that the draft policy would only apply to NIH-funded research, the fear expressed was that the NIH policy would be adopted as a model by other federal agencies, and would soon spread to publications outside the biomedical arena.

Zerhouni said at one point, "The status quo must change," to which a questioner responded, "What is the status quo that must change? More people have more access, more frequently at less cost, than ever before in history—is this the status quo we're trying to change?" While open access has tremendous promise, mandating a particular system is "foolish."

One publisher noted that the time an article is restricted varies from journal to journal, some are six months, some are two months, some are a year, but any mandated time limit could be a problem for some society. Zerhouni said, "The public needs to have access to research it paid for in a way that is not onerous to you (the publishers) or to them."

Not all attendees were opposed to open access. Nick Cozzarelli, with the Proceedings of the National Academy of Sciences, indicated that PNAS welcomed the new policy. Elizabeth Marincola, Executive Officer of the American Society for Cell Biology, concurred with this view, and praised NIH for demanding the public get access to NIH-funded research.

After the meeting, Dr. Bond told *ASBMB Today* that "One approach we should consider working towards, is linking from our journal sites to PubMed Central. This linking, rather than transferring all our content, would allow us to retain our system and provide PubMed Central with NIH funded publications in whatever timeframe they like." She expressed the hope that Dr. Zerhouni would support this approach.

NAS Report Says GMOs 'Not Inherently Hazardous'

Genetically modified foods are safe to eat and genetic engineering is "not an inherently hazardous process," states a report released in late July by the National Academy of Sciences (NAS). Regardless of whether genetically modified foods were created by manipulating DNA in a laboratory or by traditional breeding, safety assessments should focus on the changes in a particular crop, not on the method used to create them, according to the report from NAS's National Research Council and Institute of Medicine (NRCIM).

The report suggests widespread "premarket" safety assessments of any new genetically modified food based on presence of abnormal levels of compounds. It also calls for epidemiological surveillance to track any unexplained and unexpected clusters of adverse health effects that might arise only after a large population has been exposed to a particular food. But such assessments and surveillance would occur for all kinds of foods, not just GM foods, according to a framework for decision making presented in the report.

"All evidence, to date, indicates that any breeding technique that alters a plant or animal, whether by genetic engineering or other genetic modification methods, has the potential to create unintended changes in the quality or amounts of food components that could harm health," explained ASBMB Past-President Bettie Sue Masters who chaired the panel that prepared the report. "The possible impact of such compositional changes should be examined on a case-by-case basis to determine whether and how much further evaluation is needed."

Dr. Bettie Sue Masters, NAS Panel Chair

Masters told *The Scientist* that she envisions a comprehensive "feedback loop" in which industry and regulators assess food safety for consumers while, at the same time, health effects in the marketplace are efficiently communicated back to those regulating and developing the technology—only if such post-market surveillance is deemed warranted for a particular food.

Michael Philips, Vice President of Agricultural Science and Regulatory Policy at the Biotechnology Industry Organization (BIO), praised the report, stating: "Critics of the technology always want to point to the method. Just because you use the method, you've got to go through all of these hoops of regulatory policy, and that's not the founding principle on which we base regulations. We base regulation on the end product and how it is potentially changed though genetic modification."

The report acknowledged that genetic engineering is "more likely to cause unintended changes than some techniques, such as simple selection," but it pointed out that this process is "less likely to do so than other currently used methods, such as those that use radiation or chemicals."

The report also calls for new research and methodologies to discover and track the potential ill effects of modified foods by, for example, profiling techniques in animal models that would link altered gene expression with metabolic components, and extensive databases of the biological composition of many different species. The compounds in a novel genetically modified plant could then be compared with a large control group of its safe, "conventional" cousins.

Peptide's 'Cork in a Bottle' Mechanism May Lead to New Generation of Antibiotics

By Nicole Kresge, Staff Science Writer

The rapid emergence of antibiotic-resistant strains of bacteria is of growing concern to physicians and scientists alike. The Center for Disease Control estimates that every year nearly 2 million Americans acquire bacterial infections while in hospitals, and that 45% of them die from their infections. More than 70 percent of these bacteria are resistant to one or more of the antibiotics in common use. These unsettling statistics are driving investigations into the development of new antimicrobial therapies.

Recent research by Richard H. Ebright*, a Howard Hughes Medical Institute investigator and Professor of Chemistry and member of the Waksman Institute at Rutgers, may open up the doors for the design of a new family of antibacterial drugs. In a paper published in the June 18 issue of *Molecular Cell*, Dr. Ebright and his colleagues report on their work with the antimicrobial peptide microcin J25 (MccJ25).

MccJ25 is a naturally-occurring peptide antibiotic that is produced by certain strains of *Escherichia coli*. It exhibits antibacterial activity against several gram-negative bacterial species by targeting RNA polymerase (the enzyme responsible for RNA synthesis) to inhibit transcription. MccJ25 specifically binds to a channel in RNA polymerase that connects the exterior surface of the polymerase to its active center. This channel, known as the "secondary channel" or "NTP uptake channel," is used by RNA polymerase to draw in raw materials for RNA synthesis and to expel the byproducts of transcription.

Dr. Ebright's interest in MccJ25 stems from his laboratory's focus on RNA polymerase. "In 2000, after the three-dimensional structure of RNA polymerase was reported, we noted that the secondary channel would be a 'choke point' for RNA polymerase and proposed to use combinatorial-chemistry approaches to identify small molecules that would bind within, and obstruct, the RNA polymerase secondary channel. In 2001, Delgado *et al.* reported that MccJ25 inhibits RNA polymerase and reported the isolation and sequencing of a MccJ25-resistant mutant of RNA polymerase. On reading the Delgado *et al.* report, we mapped the sequence of their mutant onto the structure of RNA polymerase, noted that the mutant was located within the secondary channel, hypothesized that MccJ25 might be an example of the class of small molecules we were seeking, and immediately sought to obtain MccJ25 for analysis," explained Dr. Ebright.

To determine how MccJ25 blocks transcription, the researchers randomly mutated the entire gene encoding the β' subunit of RNA polymerase and looked for MccJ25-resistant strains. They then sequenced these mutants and mapped the mutated amino acids onto the three-dimensional structure of RNA polymerase to construct a 'genetic footprint' of the MccJ25 binding site. The team found that all the substituted amino acids clustered around the interior lining and the rim of the secondary channel.

To verify that MccJ25 does indeed bind at the head of the channel, the researchers attached fluorescent tags to MccJ25 and to different points on RNA polymerase. By monitoring the interactions between the MccJ25 tag and RNA polymerase tags, the group was able to confirm that MccJ25 does

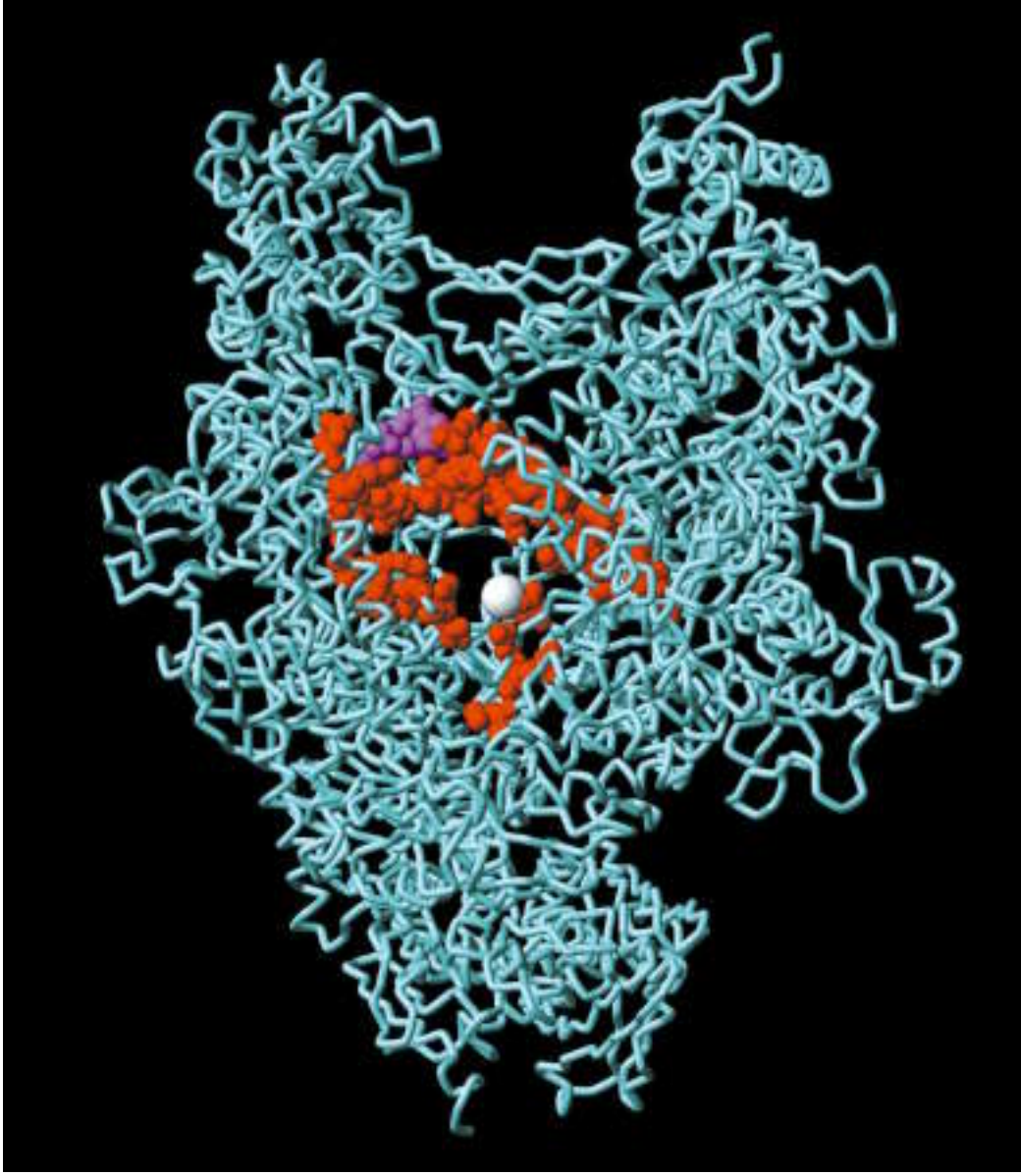
indeed bind within or immediately adjacent to the secondary channel.

The group also docked the structure of MccJ25 into the structure of RNA polymerase. They found MccJ25 can fit perfectly in the secondary channel and seal it up like a "cork in a bottle." This seal prevents substrates from moving into the active center, effectively putting a halt to transcription.

A second research team, led by Dr. Konstantin Severinov, also at Rutgers, derived a similar model using different experimental methods. Dr. Severinov's group used biochemical and biophysical methods to come up with a model of transcription inhibition by MccJ25. This research is also published in the June 18 issue of *Molecular Cell*.

Other antibiotics targeting RNA polymerase either interfere with its active center or sterically prevent the synthesis of RNA products. Dr. Ebright believes that this novel 'cork in a bottle' mechanism of action represents an attractive target for the design of future antibiotics for a variety of reasons. For example, the secondary channel has a large surface that is complementary to a wide variety of molecules. Bacterial and eukaryotic RNA polymerase secondary channels also have different patterns of sequence conservation, allowing for the design of agents that only target bacteria.

MccJ25 itself is a great model for antibiotic design for three main reasons, said Dr. Ebright. "First, MccJ25 inhibits the same enzyme as rifampicin (an antibiotic with wide clinical use, especially in treatment of tuberculosis), but exhibits no cross-resistance with rifampicin. Second, MccJ25 has an unusual lariat-protoknot structure that confers exceptionally stability—including stability to autoclaving. Thus, MccJ25 can be used for surface decontamination under extreme conditions. Third, MccJ25 is a gene product. Thus, new derivatives of MccJ25, and libraries of new derivatives of MccJ25, can be generated using simple molecular-biology procedures rather than complex organic-chemistry procedures."



Microcin J25 (MccJ25) inhibits bacterial transcription by binding within, and obstructing, the bacterial RNA polymerase secondary channel—acting essentially as a "cork in a bottle." Sites of single-residue substitutions in RNA polymerase that confer MccJ25-resistance are shown in red (β' subunit) and pink (β subunit). The RNA polymerase active-center Mg++ is shown in white. Image courtesy Richard H. Ebright, Rutgers University.

However this potential new family of antibiotics is not without its problems. "Because MccJ25 interacts with more than fifty residues of RNA polymerase, including some residues not conserved in RNA polymerase from all bacterial species, MccJ25 exhibits a narrow species spectrum," explained Dr. Ebright. This interaction also contributes to a broad resistance spectrum for MccJ25. Dr. Ebright noted another problem with MccJ25 is that it only interacts with RNA polymerase with moderate affinity (Kd ~ 1 uM), meaning that a relatively high concentration of MccJ25 is required for effective inhibition.

"In current work, we are addressing each of these points," said Dr. Ebright. "We have identified a MccJ25 derivative with a narrower resistance spectrum and believe we have identified an approach to generate MccJ25 derivatives with higher affinity." Hopefully these new derivatives will be the beginnings of a new class of antibiotics ℵ.

** ASBMB member*

Nobel Laureates to Open ASBMB Annual Meeting in 2005

In a first for ASBMB, two Nobel Laureates will share the Herbert Tabor/Journal of Biological Chemistry Lectureship which will open the ASBMB Annual Meeting. Both Dr. Michael S. Brown and Dr. Joseph L. Goldstein, who were awarded the 1985 Nobel Prize in Physiology or Medicine for their discoveries concerning the regulation of cholesterol metabolism, will be on stage next year to open the Society's April 2-6, 2005 Meeting in San Diego.

The Herbert Tabor/*Journal of Biological Chemistry* Lecture will be the opening lecture of every ASBMB Annual Meeting. The award honors Dr. Tabor for his long service to the Society and to the *JBC*. Recipients are selected from among those whose names represent outstanding research in addition to service to the Society, including its publication efforts. The Award was instituted in 2004 and the first recipient was Dr. Robert Lefkowitz, James B. Duke Professor and Howard Hughes Medical Institute Investigator at Duke University Medical Center.

In announcing their 1985 award, the Nobel Assembly stated, "Michael S. Brown and Joseph L. Goldstein have through their discoveries revolutionized our knowledge about the regulation of cholesterol metabolism and the treatment of diseases caused by abnormally elevated cholesterol levels in the blood. They found that cells on their surfaces have receptors which mediate the uptake of the cholesterol-containing particles called low-density lipoprotein (LDL) that circulate in the blood stream. Brown and Goldstein have discovered that the underlying mechanism to the severe hereditary familial hypercholesterolemia is a complete, or partial, lack of functional LDL-receptors. In normal individuals the uptake of dietary cholesterol inhibits the cells own synthesis of cholesterol. As a consequence the number of LDL-receptors on the cell surface is reduced. This leads to increased levels of cholesterol in the blood which subsequently may accumulate in the wall of arteries causing atherosclerosis and eventually a heart attack or a stroke. Brown and Goldstein's discoveries have lead to new principles for treatment, and prevention, of atherosclerosis."

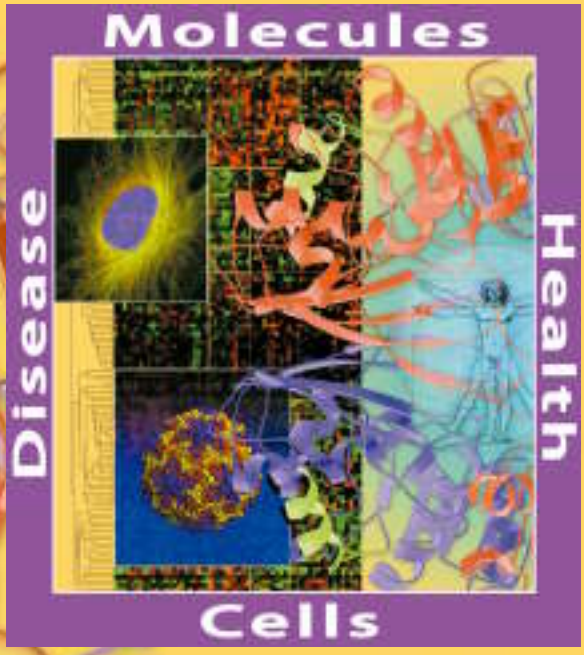
Nobel Laureates Joseph L. Goldstein, left, and Michael S. Brown in the Brown Goldstein Laboratory at the University of Texas Southwestern Medical Center, Dallas.

Goldstein, Professor and Chair, Department of Molecular Genetics, University of Texas Southwestern Medical Center at Dallas, and his colleague Brown, Professor, Department of Molecular Genetics at UT Southwestern Medical Center, have worked together for the last 30 years on the genetics and regulation of cholesterol metabolism. Their discovery of the LDL receptor as the major molecule regulating cholesterol metabolism and its genetic disruption in the human disease familial hypercholesterolemia have been recognized by their receipt of numerous awards, including the Albert D. Lasker Award in Basic Medical Research (1985), Nobel Prize in Physiology or Medicine (1985), and the U.S. National Medal of Science (1988). More recently, their discovery of the SREBP family of membrane-bound transcription factors and the elucidation of the proteolytic pathway by which the SREBPs become activated to regulate lipid metabolism were recognized by the receipt of the Albany Medical Prize in Biomedical Sciences in 2003.

The Brown Goldstein Laboratory is at the heart of UT Southwestern's approach to research. Their findings led to the development of statin drugs, the cholesterol-lowering compounds that today are used by 16 million Americans and are the most widely prescribed medications in the United States. And their discovery is improving more lives every year. New federal cholesterol guidelines will triple the number of Americans taking statin drugs to lower their cholesterol, reduc-

Continued on page 12

See You Next Year in San Diego!



2005 ASBMB Annual Meeting

Held in conjunction with EB 2005

April 2-6, 2005

San Diego, CA

Meeting Organizers

Dennis R. Voelker, National Jewish Medical Research Center

Cecile Rochette-Egly, IGBMC, Strasbourg

and the 2005 ASBMB Program Planning Committee

Symposia Themes

Dynamics of Protein—Protein Interactions (Bumping in the Night)
Chair: Ben Margolis, HHMI, University of Michigan

DNA Replication and Interactive Repair and Recombinational Processes
Chair: Charles S. McHenry, University of Colorado Health Sciences Center

Coordinate Regulation of Transcription
Chair: Cecile Rochette-Egly, IGBMC, Strasbourg

Interactions and Functions of Glycoconjugates
Chair: Mark A. Lehrman, University of Texas Southwestern Medical Center

Integration and Organization of Signaling Pathways
Chair: Alex Toker, Beth Israel Deaconess Medical Center

Minority Affairs Committee Symposia
Chair: Phillip A. Ortiz, Empire State College

Biochemistry and Molecular Biology of Lipids
Chair: Charles O. Rock, St. Jude Children's Research Hospital

Organelle Biogenesis and Dynamics
Co-Chairs: Carla Koehler, UCLA and Danny Schnell, University of Massachusetts, Amherst

Proteolysis and Disease
Chair: Charles Craik, University of California, San Francisco

Catalysis: Structure, Function, and Evolution
Chair: John A. Gerlt, University of Illinois, Urbana-Champaign

Metabolic Regulatory Circuits
Chair: M. Daniel Lane, Johns Hopkins University School of Medicine

Genomes and Proteomes
Chair: Andrew J. Link, Vanderbilt University

Education in the Biomolecular Sciences: The Next Generation
Co-Chairs: Judith G. Voet, Swarthmore College and Marion O'Leary, California State University at Sacramento

Experimental Biology 2005

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ASBMB American Society for Biochemistry and Molecular Biology

Continued from page 10
ing the risk of heart disease and stroke for countless people.

Their research is directed at unraveling the mechanism by which the SREBP pathway regulates cholesterol metabolism at the molecular, cellular, and whole body levels.

Sterol Regulatory Element Binding Proteins (SREBPs) are membrane-bound bHLH-Zip transcription factors that regulate the synthesis and uptake of cholesterol and fatty acids in animal cells. Two SREBPs, designated SREBP-1a and SREBP-2, predominate in cultured cells. The activities of both SREBPs are regulated by the sterol content of the cells. When cells are replete with sterols, the SREBPS remain bound to membranes of the endoplasmic reticulum and nuclear envelope and are therefore inactive. When cells are depleted of sterols, a two-step proteolytic process releases the active portions of the SREBPs, which enter the nucleus and stimulate transcription of genes in three pathways of lipid metabolism: 1) cholesterol biosynthesis (HMG CoA synthase, HMG CoA reductase, farnesyl diphosphate synthase, squalene synthase); 2) uptake of cholesterol and fatty acids from plasma (LDL receptor and lipoprotein lipase); and 3) fatty acid biosynthesis (acetyl CoA carboxylase, fatty acid synthase, stearoyl CoA desaturase-1).

This feedback mechanism assures a steady supply of cholesterol and unsaturated fatty acids, and it prevents over accumulation. Mutant cells with blocks in SREBP processing fail to grow in the absence of added cholesterol and unsaturated fatty acids. Making use of these mutant cells lines, they recently cloned two membrane-bound proteases and a membrane-bound sterol-sensing regulatory molecule that together mediate the regulated release of SREBPs from membranes. These proteins appear to be the key players in the pathway that controls the lipid composition of cell membranes.

The Brown Goldstein Laboratory's research interests focus on the regulation of cholesterol metabolism and membrane composition, the genetics of human disease, and the mechanism of vesicular transport in animal cells.

Hiroshi Nikaido Selected to Receive Bristol-Myers Squibb Research Award

Hiroshi Nikaido,* Professor of Biochemistry and Molecular Biology at the University of California, Berkeley, has been selected to receive the 14th annual Bristol-Myers Squibb Freedom to Discover Award for Distinguished Achievement in Infectious Diseases Research. He was recognized for his groundbreaking contributions to better understanding the mechanisms of resistance by bacterial cells to antibiotics.

Dr. Nikaido was selected to receive the Award by an independent panel of his peers in a process in which Bristol-Myers Squibb takes no active role. The Award, a $50,000 cash prize and a silver commemorative medallion, will be presented at a dinner in New York City on October 14.

Beginning in 1959, even before he completed his doctorate, Dr. Nikaido began to develop a series of studies to answer questions about why some bacteria, particularly Gram negative bacteria, are so resistant to many popular antibiotics. His initial findings led to the discovery of the role of double membranes that surround these bacterial cells and a particular constituent of these membranes, called LPS, which essentially acts to create a barrier to certain large molecules and various inhibitors, including many antibiotics. By 1976, he discovered a totally new class of proteins, called porins, which produced channels within these cells through which smaller molecules, including necessary nutrients, could enter—even as the outer membrane inhibited entry by antibiotics.

Over the years, Dr. Nikaido and his colleagues extended their research, defining a variety of factors that affect drug penetration of the cell wall. In so doing, his insights helped other scientists pursue new approaches to antibiotic design, including fourth generation cephalosporins that could overcome or circumvent some of these factors. He also refined his discoveries, including finding a new class of proteins, slow porins, which seemed to play an even greater role in most antibiotic resistance. In addition, in looking at another class of bacteria, mycobacteria, implicated in tuberculosis, for example, his group discovered how the lipids in the cell walls of these bacteria are tightly organized in bilayers. If those layers are pierced, a wide range of antimicrobial drugs can in fact work. His laboratory also has focused on an additional factor that is implicated in antibiotic resistance. In the 1990s he discovered that Gram negative bacteria have multidrug efflux pumps, essentially intracellular mechanisms that actively transport antibiotics back out of the cell, thus avoiding harm to the bacteria.

Dr. Hiroshi Nikaido

"Dr. Hiroshi Nikaido's laboratory has applied both biochemistry and genetics, as well as a great deal of scientific rigor, to the question of what causes antibiotic resistance and what science can do to overcome that resistance and create more effective antibiotics," said Richard Colonno, Vice President, Infectious Diseases Drug Discovery, Bristol-Myers Squibb. "From his initial pioneering work on the role of outer membranes, to his more recent efforts on the transport systems inside the cell that can actually pump antibiotics out again, Dr. Nikaido has demonstrated that there is no single answer to the many complex questions we face in this area of infectious disease research."

Born in Tokyo, Dr. Nikaido received his medical degree in 1955 and his doctorate in medical science in 1961, both from Keio University School of Medicine in Tokyo. He did post-doctoral work at Osaka University and at Harvard Medical School. In 1963, he joined Harvard Medical School as a faculty member, first as an associate and then as an assistant professor of bacteriology, while also serving as an assistant biochemist at Massachusetts General Hospital. He became an associate professor in the Department of Bacteriology and Immunology at the University of California, Berkeley, in 1969, and was named to his current position as professor of biochemistry and molecular biology in the Department of Molecular and Cell Biology in 1989.

The Bristol-Myers Squibb Freedom to Discover Unrestricted Biomedical Research Grants and Awards Program, under which the Distinguished Achievement Award is presented, was initiated in 1977. It has provided $100 million in no-strings-attached funding in six biomedical research areas: cancer, cardiovascular disease, infectious disease, metabolic disease, neuroscience, and nutrition.

**ASBMB member*

Thomas Südhof of UT Southwestern at Dallas Wins Bristol-Myers Squibb Neuroscience Research Award

Thomas C. Südhof,* Professor of Molecular Genetics and Director, Center for Basic Neuroscience at the University of Texas Southwestern Medical Center at Dallas, and a Howard Hughes Medical Institute Investigator, has been selected to receive the 17th annual Bristol-Myers Squibb Freedom to Discover Award for Distinguished Achievement in Neuroscience Research.

Dr. Südhof was recognized for his pioneering work elucidating the molecular mechanisms by which neurons transmit information across synapses. Synaptic transmission starts when a presynaptic neuron releases a chemical messenger, i.e., a neurotransmitter. It had been known that neurotransmitter release is triggered very rapidly—within a few hundred microseconds—by the inflow of calcium ions into presynaptic terminals, but it was unknown how exactly calcium ions trigger release. Dr. Südhof solved this mystery in the 1990s when he identified a synaptic protein named synaptotagmin that functions as a calcium sensor in triggering release. Dr. Südhof and his colleagues have built upon this discovery by exploring the structure, function and genetic makeup of synaptic proteins that collaborate with synaptotagmin to mediate release. This work elucidated a cascade of protein-protein interactions that prepare the release mechanisms for synaptotagmin action, and regulate the amount of release triggered by synaptotagmin. In an extension of these studies, he is currently exploring how the normal functions of a synapse relate to pathological changes observed in neurodegenerative disorders like Alzheimer's and Parkinson's disease.

At a synapse, neurotransmitter release is mediated by the fusion with the presynaptic plasma membrane, of secretory organelles filled with neurotransmitters and called synaptic vesicles. Dr. Südhof's work not only revealed how synaptotagmin acts as a calcium sensor in release, but also uncovered a cascade of protein-protein interactions in the presynaptic terminal that are required for release. He identified sequential protein complexes that prime release upstream of synaptotagmin action. These proteins are themselves regulated, and thereby also control the extent of release triggered by synaptotagmin action. Overall, his work has contributed to a comprehensive molecular description of nerve terminals that forms the basis of our current understanding of neuronal secretion, and has had profound implications for other secretory processes, e.g., insulin secretion.

"Dr. Südhof's work over more than a decade has given us extraordinary and critical insights into synaptic transmission, when information is transferred from one neuron to another. In neurodegenerative diseases such as Parkinson's and Alzheimer's these tightly regulated processes seem to become abnormal. While his remarkable discoveries at the molecular level have aided us in gaining a better understanding of a process that is central to all neural functions, his laboratory is now working on understanding how these key findings play a role in the pathology of these diseases. Such insights will be crucial in developing new therapies that may eventually help treat these disorders," said Frank Yocca, Executive Director, Neuroscience Clinical Design and Evaluation at the Bristol-Myers Squibb Pharmaceutical Research Institute.

Dr. Thomas Südhof

The Bristol-Myers Squibb Freedom to Discover Unrestricted Biomedical Research Grants and Awards Program, under which the Distinguished Achievement Award is presented, was initiated in 1977. It marked its 25th anniversary in 2002, reaching a $100 million milestone in no-strings-attached funding in six biomedical research areas: cancer, cardiovascular diseases, infectious diseases, metabolic diseases, neuroscience and nutrition. Dr. Südhof was selected by an independent panel of his peers, in a process in which Bristol-Myers Squibb takes no active role. The Award, a $50,000 cash prize and a silver commemorative medallion, is awarded annually in each of the six therapeutic areas. Dr. Südhof will receive his award at a dinner to be held in New York City on October 14, 2004.

** ASBMB member*

Gene Alteration Points to Longevity, Thinness

Researchers You-Jun Fei and Vadivel Ganapathy* have found the Indy gene is critical in providing cells with energy, producing a transporter that helps deliver key ingredients of the fuel that drives cells. Indy delivers metabolic substrates such as citrate and succinate to cells where they enter the mitochondria and are used to produce ATP, the fuel for cells, says Dr. Fei, a molecular biologist.

Unfortunate byproducts of this oxygen metabolism are reactive oxygen species, which damage cells and may contribute to diseases from Parkinson's to Alzheimer's. "This is why people think we age; these byproducts of oxygen metabolism cause cells to degenerate," says Dr. Ganapathy, who became Chair of the Medical College of Georgia Department of Biochemistry and Molecular Biology on July 1. The MCG researchers have identified this longevity gene in humans, mice, rats, zebrafish, and *C. elegans*.

Armed with a new $605,000, three-year grant from the NIH Institute on Aging, the researchers want to know the activity level that optimizes longevity and find compounds to control that level.

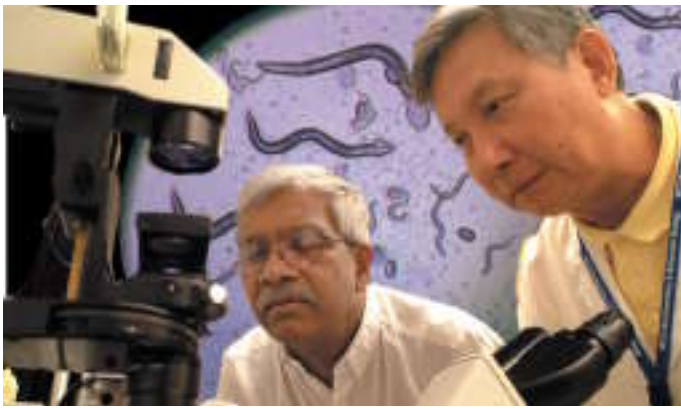
"The human lifespan is a phenotype determined by multiple genes," says Dr. Fei, principal investigator on the grant. "Our Indy gene is only one of the life-determinant genes. But I can say that when the function of this single gene is knocked down, the animal can extend its lifespan."

University of Connecticut researchers were the first to recognize the relationship between Indy–short for 'I'm not dead yet'–and longevity when they found spontaneous mutations of the gene in the adult fruit fly that nearly doubled its lifespan. Their research, published in the journal *Science* in December 2000, says the mutations may create a metabolic state that mimics caloric restriction, which has been shown to extend lifespan. They were uncertain of the gene's function, but suspected it was a transporter.

"When you look at the protein coded by this gene you can guess what the gene does because transporters have certain structural features and the protein made by this gene has the same kind of structural features of the transport system," Dr. Ganapathy says. The structure looked a lot like two dicarboxylate transporters Drs. Fei and Ganapathy had been studying for years. So they cloned the Indy gene from the fruit fly but found it didn't quite match either transporter. "We knew there had to be something else," said Dr. Ganapathy.

That something else turned out to be a third transporter of dicarboxylates and tricarboxylates, which include citrate, succinate and other components of the citric acid cycle, the primary pathway for energy production in cells. "Now there are three transporters with a similar function. How do we prove that the third one is actually Indy? We need an animal model that enables us to study the effect on lifespan," he says.

The researchers chose *C. elegans* as their animal model. Dr. Fei cloned all three of the acid transporters in the *C. elegans*, knocked down the activity of each and found that the newest transporter Indy increased the lifespan of the worm and decreased body size and fat content without apparent ill effects. They published their initial cloning work in the *Journal of Biochemistry* in 2003 and the work on the biological function of Indy in the *Biochemical Journal* this year.



Medical College of Georgia researchers Dr. Vadivel Ganapathy, at left, and Dr. You-Jun Fei were able to mimic the spontaneous genetic mutation that Connecticut researchers found in the fruit fly by feeding C. elegans specially engineered bacteria that knock down the activity of Indy.

They were able to mimic the spontaneous genetic mutation that Connecticut researchers found in the fruit fly by feeding *C. elegans* specially engineered bacteria that knock down the activity of Indy. Their model netted a 15-20 percent increase in lifespan in addition to the other benefits. Unlike true genetic knockouts, with scientists completely removing both copies of a gene so 100 percent of function is gone or taking out one copy so the gene functions at half capacity, the MCG scientists cannot determine the exact gene activity level in their animal model. "These worms reflect what happens with reduced activity in the transporter," Dr. Ganapathy says. "But we don't yet have a stable mutant line. That is one of the aims for the NIH grant."

**ASBMB member*

DNA Repair Machinery Is 'Two-Way Street'

Biochemists at Duke University Medical Center have discovered key components that enable the cell's DNA repair machinery to adeptly launch its action in either direction along a DNA strand to strip out faulty DNA. Such flexibility exemplifies the power of the repair machinery, which guards cells against mutations by editing out errors that occur during the process of chromosome replication. Malfunction of the "mismatch repair" machinery is the cause of several types of cancer, including relatively common forms of colon cancer.

The researchers, led by Howard Hughes Medical Institute Investigator and Professor Paul Modrich,* at Duke University Medical Center, reported their findings in the July 2, 2004, issue of the journal *Molecular Cell*. Joint first authors on the paper were Leonid Dzantiev and Nicoleta Constantin, and the other co-authors were Jochen Genschel, Ravi Iyer, and Peter Burgers. The research was supported by NIH.

Dr. Modrich and his colleagues have long studied the mismatch repair machinery of the cell. This machinery detects and corrects errors in DNA replication in which the wrong DNA unit is stitched into place in a newly forming DNA strand. Normally such units, nucleotides, on one strand of the double-stranded DNA molecule bond with complementary nucleotides on the other strand, like complementary pieces of a puzzle. Thus, an adenine on one strand is normally paired with a thymine on the other, and a guanine on one strand with a cytosine on another.

The process of mismatch repair involves first recognizing the mismatch, for example an adenine with a cytosine. The machinery then recognizes a break in the newly synthesized DNA strand, which triggers the machinery to excise the section including the mismatch, starting at the strand break and working toward the mismatch and slightly beyond. The system then replaces the mismatched strand with one containing the correct complementary nucleotide.

The central mystery is how the mismatch repair system is flexible enough to recognize such a triggering strand break on either side of the mismatch along the DNA strand, said Dr. Modrich. In the *Molecular Cell* paper, he and his colleagues have defined the protein components of the machinery that allows such bidirectionality and figured out how those components assemble at the strand break to direct the excision.

Importantly, the researchers' biochemical experiments and analyses of mutations in the repair proteins revealed how the machinery for excising the faulty DNA strand "knows" which way to go from the strand break to the mismatch.

Basically, they found that a protein, PCNA, is clamped onto the DNA at the strand break. PCNA, together with the protein that clamps PCNA onto the DNA double helix, regulate the enzyme whose job it is to snip out the segment containing the mismatch, by "aiming" the enzyme, exonuclease I, in the right direction to work itself along the strand, stripping out the segment containing the mismatch.

Dr. Paul Modrich

"A surprising feature of the repair system is that it can evaluate the placement of the strand signal to one side or the other of the mismatch and work from there," said Dr. Modrich. According to him, placement of the strand break that directs repair to one side or the other of the mismatch is likely a consequence of the mechanism by

UT Southwestern Researchers Identify Gene as Essential for Vascular Smooth Muscle Development

Researchers at the University of Texas Southwestern Medical Center, Dallas, have discovered a major mechanism to explain normal and abnormal smooth muscle growth, a finding that could help in the development of novel therapeutics for disorders like hypertension and asthma. Their work appeared in the March 11, 2004, issue of *Nature*.

Smooth muscle cells are essential for the formation and function of the cardiovascular system, as well as many internal organs such as the stomach, intestine, bladder and uterus. Abnormalities in their growth can cause a wide range of human disorders, including atherosclerosis, hypertension, asthma and leiomyosarcoma (a fatal smooth-muscle cancer). The molecular mechanisms that control smooth muscle cell growth and differentiation, however, have been poorly understood.

"It has long been known that many diseases result from abnormal growth of smooth muscle cells," said Eric Olson,* Chairman of Molecular Biology and senior author of the study. "The new findings are quite exciting because they reveal a previously unknown mechanism that controls the growth and differentiation of smooth muscle cells. Knowing this mechanism, we can think about ways of regulating it to control smooth muscle growth during disease."

Dr. Olson recently discovered a master regulator of smooth muscle development, a protein called myocardin. This regulator turns on smooth muscle genes by interacting with serum response factor (SRF), a widely expressed protein that binds DNA.

In the *Nature* study, he and his colleagues showed that the ability of myocardin to turn on smooth muscle genes is counteracted by another protein, Elk-1, which prevents myocardin from binding to SRF. When Elk-1 displaces the myocardin from SRF, it triggers smooth muscle cell proliferation, an effect associated with cardiovascular disease.

With these findings, scientists now have important new insights into the cellular mechanisms that control the growth and differentiation of smooth muscle cells. The findings also offer many interesting opportunities for therapeutic intervention, according to Dr. Olson.

** ASBMB member*

Continued from previous page
which DNA is copied by the replication machinery.

He and his colleagues are continuing their studies by seeking to identify other components of the repair system, which could have implications for understanding how cancers become resistant to chemotherapy.

"This system does more than just repair DNA biosynthetic errors," he said. "Many cancer chemotherapeutic drugs work by damaging DNA, which selectively kills cancer cells because they are proliferating more than resting cells. The mismatch repair machinery senses certain types of DNA damage, which leads to activation of the cell's suicide machinery, called apoptosis, resulting in cell death. Inactivation of the mismatch repair system not only predisposes cells to tumor development, but also renders them resistant to certain anti-tumor drugs.

"Such findings as the ones we are reporting build on the basic understanding of mismatch repair and may allow us to explore such possibilities," explained Dr. Modrich.

** ASBMB member*

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.

Gil Ben-Menachem
Hebrew University, Jerusalem, Israel

Yali Friedman
State University of New York, Buffalo

Jing Zhao
Weizmann Institute of Science, Rehovot, Israel

Top 25 of All Institutions Receiving NIH Awards in FY 2003

In the July issue we published a list of the top 25 medical schools receiving NIH grants in fiscal 2003. Following is the top 25 of all institutions that received NIH grants in FY 2003. The complete chart can be found at http://www.grants.nih.gov/grants/award/awardtr.htm#c.

	Organization	All Awards Number	All Awards Amount	Research Grants Number	Research Grants Amount	R&D Contracts Number	R&D Contracts Amount
1	Johns Hopkins University	1,306	$555,875,515	1,117	$495,118,653	26	$ 27,177,529
2	University of Washington	1,002	$440,877,371	877	$397,267,118	11	$ 13,692,703
3	University of Pennsylvania	1,166	$434,456,754	998	$396,370,046	7	$ 2,783,250
4	University of California, San Francisco	926	$420,731,695	793	$358,100,498	11	$ 43,766,678
5	Science Applications International Corp.	3	$417,351,396	0	$ 0	3	$417,351,396
6	Washington University	834	$383,225,085	740	$354,317,063	6	$ 11,330,595
7	University of Michigan	920	$362,149,790	793	$325,609,616	10	$ 8,037,680
8	University of Pittsburgh	864	$348,225,811	780	$310,310,080	13	$ 10,041,235
9	University of California, Los Angeles	885	$347,022,527	765	$320,604,076	11	$ 8,855,859
10	Duke University	769	$345,801,850	677	$308,371,676	9	$ 11,266,708
11	Yale University	812	$303,459,245	696	$275,537,603	1	$ 3,347,436
12	Harvard University	707	$301,641,145	531	$274,023,603	1	$ 419,082
13	Boston University, Charles River	399	$292,519,118	353	$140,519,567	3	$ 16,487,551
14	Columbia University	738	$291,304,116	644	$265,526,751	6	$ 5,541,163
15	University of California, San Diego	625	$288,497,646	538	$261,891,721	8	$ 9,900,030
16	Stanford University	713	$271,769,664	592	$246,500,102	3	$ 4,812,344
17	Massachusetts General Hospital	645	$271,691,371	583	$248,925,540	7	$ 15,596,706
18	University of North Carolina, Chapel Hill	722	$270,978,554	607	$236,637,784	8	$ 17,339,964
19	Baylor College of Medicine	563	$249,559,238	488	$222,205,006	10	$ 18,150,248
20	University of Alabama at Birmingham	557	$248,932,918	496	$196,337,663	23	$ 25,053,330
21	University of Wisconsin, Madison	643	$247,466,299	540	$217,100,338	6	$ 6,652,500
22	University of Minnesota	595	$230,606,234	522	$206,988,279	17	$ 14,946,918
23	Vanderbilt University	613	$228,391,370	535	$209,413,141	2	$ 1,027,999
24	Case Western Reserve University	598	$225,260,595	551	$202,633,478	7	$ 14,347,126
25	Brigham and Women's Hospital	528	$220,315,712	480	$207,657,951	4	$ 5,978,027

Soybeans May Reduce Risk of Colon Cancer

A substance found in soybeans may reduce the risk of colon cancer, the third most common form of cancer in the world according to the World Health Organization. Georgia Tech researcher Al Merrill,* along with colleagues from Emory University and the Karmanos Cancer Institute, found that soy glucosylceramide (soy GlcCer) was effective in reducing the formation and growth of tumor cells in the gastrointestinal (GI) tract in mice. The results were published in the May 2004 issue of the *Journal of Nutrition*.

"Soy is known to have a number of health benefits, including the suppression of cancer. Based on our results, some of this benefit may be due to a group of molecules known as sphingolipids," said Dr. Merrill.

Soy GlcCer is just one of the many types of sphingolipids found in plants and animals, and Dr. Merrill and colleagues had already shown that milk sphingolipids can suppress tumor formation. This, however, he said is the first study that has established that the sphingolipids of plants can also inhibit colon cancer.

In his latest study, he found that soy GlcCer was able to reduce the number of tumors in both mice with an inherited defect that leads to GI cancer and in mice exposed to a chemical that causes colon cancer.

One finding that he termed especially promising is that it didn't take massive doses of soy GlcCer to show an anti-cancer effect. The amounts used in the study were similar to those naturally found in soybeans. Another result was that unlike many substances that are digested, soy GlcCer survives the journey through the stomach and intestine with enough power to affect cancerous cells in the colon.

It is not known exactly how sphingolipids suppress cancer; there are probably many mechanisms involved according to Dr. Merrill. Targeting beta-catenin, a protein involved in cell growth, seems to be one method. Too much of this protein, and the cells grow unchecked. Soy GlcCer reduces the amount of beta-catenin in the cells, helping the body regain control. "In essence, sphingolipids are bypassing the genetic defect," says Dr. Merrill.

With funding from the National Cancer Institute, Dr. Merrill and colleagues are developing new compounds based on sphingolipids that might be useful as anti-cancer drugs. "We are looking for even more potent forms of these molecules that might be effective for cancer treatment," he said.

Dr. Merrill hopes to begin studies to see if sphingolipids have similar effects on humans as they have for mice. "If naturally occurring sphingolipids like soy GlcCer suppress cancer in humans, this has the potential to allow the public to select their diets in a more rational way," he said. However, because sphingolipids haven't been classified as a nutrient, they don't appear in food composition tables, so epidemiologists cannot evaluate their importance to public health.

"Foods contain many substances that are beneficial to health that haven't yet been categorized as nutrients. The new challenge for the field of diet and health is to find out the entire spectrum of molecules that are important to health," commented Dr. Merrill.

**ASBMB member*

ASBMB GRADUATION SURVEY

The 2003-2004 ASBMB Graduation survey has been sent to all program coordinators for programs that we know offer degrees in Biochemistry, Molecular Biology, Chemistry with a Biochemistry track or the newly added category of Biotechnology. To see if your program is on the list please visit http://www.asbmb.org/asbmb/site.nsf/Sub/ListofSchools?Opendocument and click on the appropriate List of Schools. If your program is not there, please contact the ASBMB office (education@asbmb.org).

If your program is listed, please make sure your program coordinator has returned the form before the September 30 deadline. Note that when replying there is an option to have a link to your program from the ASBMB web site.

Your help is vital in obtaining the best information possible.

Top Institutions Receiving NIH Awards in FY 2003

Item 21 in the table on page 8 of the June issue of *ASBMB Today*, identified the institution as University of Texas at Dallas. It should have specified University of Texas Southwestern Medical Center at Dallas.

by John D. Thompson, Editor

Project Bioshield No Help Say Drug Companies

When President Bush signed Project Bioshield into law, it might have seemed that companies such as Rockville, Maryland-based Human Genome Sciences Inc., would have been leading the applause. After all, that company has spent over $10 million to develop a drug to protect against anthrax infections. However, Project Bioshield, which the Bush administration had ballyhooed as a key step in creating a biodefense industry in the U.S., has received little applause from the companies it was supposedly going to help.

Anthrax infections are rare, so there is little market for the Rockville company's drug, and that is the problem Project Bioshield was intended to solve. The bill authorizes $5.6 billion for the government to stockpile a medical arsenal against biological weapons, thus providing Human Genome Sciences just what it needs: a buyer with deep pockets. The company's response, however, has been rather muted. A government purchase, when and if it comes, will probably be rather small and therefore contribute little to profit.

Yet executives at Human Genome Sciences are hardly cheering. The drug has cleared several tests, but the government has not ordered a single dose. And even if it does, it may buy only a small amount, making it hard for the company to earn much of a profit.

Industry executives and observers say that developing medicines to protect against a biological attack is a highly risky enterprise, with lengthy development times, slim profits, and the threat of devastating lawsuits if a drug fails. As Frank M. Rapoport, who represents Aventis Pasteur SA, told *The Washington Post*, "Until the liability question is solved, we're not going to see big drug companies come to the table. They have too much to lose."

Industry lobbyists had pressed for the inclusion in the legislation setting up Project Bioshield bill stronger incentives such as research and development tax credits, extension of existing patents, and stronger liability protection. Such efforts were, however, rejected by Congress.

Generic Drug Manufacturer to Buy Rival for $4 Billion

Mylan Laboratories, the nation's largest maker of generic drugs, agreed in late July to acquire a rival, King Pharmaceuticals, for about $4 billion in stock.

The transaction is the latest move among generic drug makers to bulk up and diversify their business as they face escalating pressure from the big pharmaceutical companies, which are scrambling to extend patent protection for their branded drugs. Mylan, for example, seeks a foothold in the branded drug market where King has built an extensive sales and marketing infrastructure aimed at acquiring branded products and companies. In particular, Mylan seeks to take advantage of King's experience in selling Altace, an inhibitor for hypertension and cardiovascular protection. Mylan is planning to market its own branded version of the hypertension product nebivolol, which is working its way through the FDA approval process and expected to be available in 2006.

The deal comes as a further example of how generic makers are switching their focus toward branded drugs to bolster their margins. Teva Pharmaceutical, Barr Laboratories, Forest Laboratories, Watson Pharmaceuticals, and others, which account for some 40 percent of all prescriptions, are building their sales and marketing forces to better market branded drugs. The pressure for strategic change strategy is intensifying as fewer and fewer patents for name brand drugs are due to expire in this decade. This leaves generic makers, who typically make the most money during the first two years after a patent expires, with little opportunity to expand their business.

Under the terms of the agreement, King shareholders will receive 0.9 Mylan common share—or about $16.659 for each outstanding King common share. Upon completion of Mylan's acquisition of King, Mylan shareholders will own approximately 56 percent of the outstanding common shares of Mylan, and King shareholders will own approximately 44 percent. For the 12 months ended March 31, the combined company would have had approximately $3 billion in revenue, approximately $650 million in operating cash flow and nearly 6,000 employees, with a combined sales force of almost 1,400.

Others See Ample Opportunities for Life Science Suppliers

Biodefense research is one of the fastest growing markets for suppliers of life science products and instrumentation according to a recently released study by BioInformatics, LLC, a market research firm located in Arlington, Virginia. The report says that government spending on biodefense research is likely to continue to increase at a rate exceeding investment in other areas of biological research and development, and is attracting both scientists and the companies who support them.

Although biodefense researchers represent a wide range of scientific disciplines that have always been served by the life science industry, their newly increased purchasing power and urgency of their work distinguish them from other customer groups in the market. The report, "Market Opportunities in Biodefense Research," reveals that currently funded biodefense researchers are using the products of their existing suppliers, and when necessary, easily adapting them to their applications—indicating that suppliers should have little difficulty in leveraging their existing product line in this market. In fact, products from well-known companies such as Invitrogen, Sigma-Aldrich, Bio-Rad, and Qiagen are widely used in biodefense laboratories despite the fact that few of their products are specifically designed for biodefense research.

"The widespread recognition and awareness of these brands—particularly in the cell biology and microbiology communities—most likely contributed to their high market share. Researchers already in the field are adapting existing products to their biodefense applications which is likely to further reinforce the dominant position of the market's leading companies because customers tend to prefer suppliers and products with which they are familiar over new market entrants," said Bill Kelly, President of BioInformatics, LLC.

Biotech Firms Want to Overturn SBA Funding Ban

Washington, DC area biotech entrepreneurs are backing legislation to overturn a Small Business Administration ruling that prohibits companies backed by venture capital from receiving federal grants for early-stage research. Their target is an SBA ruling that restricts such grants to companies that are 51 percent owned by "individuals," a term defined as excluding venture capitalists according to agency spokeswoman Tiffani Clements.

The SBA claims that the rule merely restores the program to its original mission of helping startup companies develop innovative technologies. However, biotechnology entrepreneurs and investors say the new ruling has exacerbated a shortage of capital for biotech companies, and that agencies have applied the policy unevenly, and locked them out of both grants of about $75,000 that are allocated for six months to test the feasibility of an idea and others of $750,000 over two years to evaluate a product's commercial potential.

A bill that would reverse the Small Business Administration's action has been cosponsored by Senators Olympia J. Snowe (R-Maine), Edward M. Kennedy (D-Mass.) and Christopher S. Bond (R-Mo.).

The focus of the lobbying effort is the Small Business Administration's 21-year-old Small Business Innovation Research (SBIR) Program. The program requires certain federal agencies to set aside about 2 percent of their research and development budgets for competitive grants to U.S. companies with 500 or fewer employees that are owned by individuals, not institutions or companies. Federal agencies award peer-reviewed

The Biotechnology Industry Alliance in Washington, DC, and the National Venture Capital Association in Arlington, Virginia are leading the lobbying effort.

Congressman Greenwood Named Next BIO President

Congressman James C. Greenwood (R-PA) has been named the next President of the Biotechnology Industry Organization (BIO). Greenwood will retire from Congress and take over as President of BIO on January 5, 2005. He will be replacing Carl B. Feldbaum who has headed BIO since its establishment in July of 1993. During his tenure BIO has grown from 16 employees and a $2.1 million budget to almost a 100 member staff with a $40 million budget. BIO members are involved in the research and development of healthcare, agricultural, industrial and environmental biotechnology products. The industry group represents more than 1,000 small and large companies, as well as academic and research centers which use biotechnology to develop medical, agricultural, industrial and environmental products. BIO has members in all 50 U.S. states and 33 other nations.

Gordon Appointed To Direct Center for Genome Sciences

Jeffrey I. Gordon,* the Dr. Robert J. Glaser Distinguished University Professor, has been appointed Director of the new Center for Genome Sciences at Washington University in St. Louis.

The center is an interdepartmental, interdisciplinary and University-wide program strategically located adjacent to the Genome Sequencing Center at the School of Medicine, which played a major role in the success of the Human Genome Project.

The new Center for Genome Sciences is the first of three major components to be implemented for BioMed 21, the University's visionary initiative dedicated to using the latest knowledge of the human genetic blueprint to develop new ways to diagnose, treat and ultimately prevent a variety of common human diseases.

"Not only is Jeff one of the University's most valued and esteemed leaders, he also is internationally respected as one of the foremost scientists in his field," said Larry J. Shapiro, Executive Vice Chancellor for Medical Affairs and Dean of the School of Medicine. "He has been extremely influential in the exciting new field of translating basic genetic data into clinically relevant research, which embodies the goals of our BioMed 21 initiative."

The new center will provide space for faculty and students from throughout the University and bind together research and educational programs in comparative genomics and systems biology. These emerging fields combine computational science with quantitative experimental biology to examine the origin, structure and function of the complex networks of genes and gene products that regulate cellular behavior. Information gained through this research promises to lead to key insights about the basis of human health and disease.

Gordon joined the Washington University faculty in 1981 after completing his clinical training in internal medicine and gastroenterology and serving as a research associate at the National Institutes of Health. He served as head of the Department of Molecular Biology and Pharmacology at the School of Medicine from 1991 to 2004. From 1994 to 2003, he was Director of the Division of Biology and Biomedical Sciences, which oversees graduate student education in those sciences. He also served as a member, then chairperson, of a Burroughs Wellcome Fund advisory committee that directs a nationwide program to promote institutional transformations that allow talented young individuals to conduct innovative work at the interface between the biological and physical/computational sciences and mathematics.

**ASBMB member*

DNA Scientist Francis Crick Dies at 88

Nobel Prize-winning scientist Francis Crick who with James Watson discovered the "double-helix" structure of DNA, paving the way for everything from DNA blood tests to genetically engineered tomatoes, died July 28 at age 88.

Dr. Crick, an honorary member of ASBMB, died Wednesday at the University of California, San Diego's Thornton Hospital. Crick had been battling colon cancer.

It was in 1953, while working in Cavendish Laboratory in Cambridge, England, that the British-born Crick, 36 at the time, and the American-born Watson, just 24, struck upon the famous double-helix structure of deoxyribonucleic acid, or DNA.

Not until years after the discovery were the pairs' conclusions about the molecular structure of DNA firmly established. At the time, Dr. Crick later said, only a small number of people "even thought it was interesting."

A half-century later, the biotechnology industry is based largely upon Crick's and Watson's discovery. So, too, are genetically engineered foods like bigger tomatoes and innovative medical technologies like gene therapy.

The two were awarded the Nobel Prize in physiology or medicine in 1962. In a statement Thursday, Dr. Watson hailed Dr. Crick "for his extraordinarily focused intelligence and for the many ways he showed me kindness and developed my self-confidence. He treated me as though I were a member of his family. Being with him for two years in a small room in Cambridge was truly a privilege. I always looked forward to being with him and speaking to him, up until the moment of his death."

Dr. Francis Crick

Career Opportunities

POSTDOCTORAL RESEARCH ASSOCIATE

Positions are available on an ongoing basis within different research groups in the Institute of Molecular Biology and the Institute of Neuroscience at the University of Oregon. The purpose of this notice is to establish and maintain a pool of qualified applicants for future consideration. Ph.D. in Molecular Biology, Neuroscience, or related field is required. Please see our websites: www.molbio.uoregon.edu and www.neuro.uoregon.edu for information about the type of research being done. Women and minorities are encouraged to apply. Salary dependent upon experience. For application materials, please call 541/346-5151, or email: rita@prospero.uoregon.edu and mention posting number 060405. *The University of Oregon is an Equal Opportunity/Affirmative Action Institution committed to cultural diversity and compliance with the Americans with Disabilities Act.*

TENURE-TRACK POSITION

Myocardial ischemia/cardiac regeneration

Tenure-track position at the Assistant or Associate Professor level available at the Institute of Molecular Cardiology. The successful candidate will join a multidisciplinary team (fourteen Ph.D. or M.D. Faculty members) to do research on stem cell biology/cardiac regeneration, gene therapy, and/or the molecular basis of myocardial ischemia. Applicants must hold M.D. or Ph.D., have three years post-doctoral training, and be capable of establishing a strong independent research program. Send CV, statement of interest, and three references to Roberto Bolli, M.D., Division of Cardiology, University of Louisville, Louisville, KY 40292. EEOC/AA

FASEB MARC VISITING SCIENTIST AND PEER MENTOR REFERRAL NETWORK PROGRAM

Visiting Scientist Responsibilities

- Visit minority institutions for periods of one or more days to present lectures and seminars of general and practical interests.
- Provide advice on research, curriculum, and graduate opportunities.
- Discuss career trends and opportunities in the biomedical/behavioral sciences.
- Assist in the preparation and development of grant proposals.

Peer Mentor Responsibilities

- Attend selected scientific meetings to mentor and serve as a guide for undergraduate students attending the meetings. Activities to include but not limited to: giving advice, visiting poster and oral presentations, guided tours through the exhibit halls that will help enhance the experience of the attending student.
- Give presentations on topics such as:
  - ° Graduate school and/or postdoctoral experiences.
  - ° Selecting the correct mentors and advisors.
  - ° Staying motivated and committed to pursuing a career in life sciences.
- Network with students to foster collaborative communications.

Visits may be initiated by the Visiting Scientist, Peer Mentor or Host Institution. Follow-up visits by the scientists and peer mentors are encouraged. Visiting Scientist/Peer Mentor travel expenses and funds for necessary supplies, slides reproduction, etc. are provided by the FASEB MARC Program.

*The visiting scientist or peer mentor **must** be an active member of one of FASEB's Constituent Societies.*

Visit:
http://www.faseb.org/faseb/societies.html (For Society List)
Visit:
http://ns2.faseb.org/vsp/vsmain.asp (For Complete Roster of Members)
Visit:
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FOR MORE INFORMATION PLEASE CONTACT…
Cheryl Wright, Program Coordinator
Email: cwright@faseb.org
Phone: 301-634-7109

Calendar of Scientific Meetings

OCTOBER 2004

American Society For Bone And Mineral Research (ASBMR) Annual Meeting 2004

October 1–5 • Washington State Convention and Trade Center, Seattle
Contact: Conference Registrar; Ph: 202-367-1161
Fax: 202-367-2161; Email: asbmr@dc.sba.com

Brain Uptake and Utilization of Fatty Acids, Lipids & Lipoproteins: Applications to Neurological Disorders

Sponsored by the Kennedy Krieger Institute and Department of Neurology, Johns Hopkins University School of Medicine
October 7–9 • Holiday Inn Select, Bethesda, Maryland
Organizers: Paul Watkins, Kennedy Krieger Institute; James Hamilton, Boston University; Cecilia Hillard, Medical College of Wisconsin; and Arthur Spector, University of Iowa
Email: watkins@kennedykrieger.org
Website: http://fattyacid.kennedykrieger.org

Cytokines in Cancer and Immunity: Joint Conference of ICS and ISICR

October 21–25 • San Juan, Puerto Rico
An exceptional meeting bringing together leading investigators in cytokine biology, cancer and immunology.
Keynote speakers: Michael Karin and Tak Mak.
Abstract deadline: June 11, 2004
Email: info@cytokines2004.org; Fax: 706 228-4685
Website: www.cytokines2004.org

An ASBMB Sponsored Symposium: Redox Signaling in Biology and Disease

October 21–24 • Kiawah Island, South Carolina
Organized by Larry Marnett, Vanderbilt U. and Roy J. Soberman, Harvard Med. School
Plenary Lecture: Regulation of Mammalian Clock Genes
Steven L. McKnight, U. of Texas, Southwestern Medical Center
Contact: Joan Geiling, Ph: 301-634-7145; Fax: 301-634-7126
Email: asbmb@asbmb.org; Website: www.asbmb.org

Inhibition of Matrix Metalloproteinases: Expanding the Horizons

October 23–25 • Crowne Plaza LaGuardia Hotel, New York City
This meeting will focus on new ideas in development of inhibitors of MMPs to treat disease (done in collaboration with NYAS). Abstracts welcomed.
Sponsored by Northshore LIJ Medical Center
Contact: Robert Greenwald; Ph: 516-465-5410
Fax: 516-465-5454 ; Email: rgreenwald@lij.edu or
Stanley Zucker: s_zucker@yahoo.com

An ASBMB Sponsored Symposium: Transcriptional Regulation by Chromatin and RNA Polymerase II

October 29–November 1 • Granlibakken, Lake Tahoe, California
Organized by Ali Shilatifard, St. Louis U. School of Med.
Keynote Speakers: Joan Conaway and Ronald Conaway
Contact: Joan Geiling, Ph: 301-634-7145; Fax: 301-634-7126
Email: asbmb@asbmb.org; Website: www.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/

First Latin-American Protein Society Meeting

November 8–12 • Hotel do Frade, Rio de Janeiro, Brazil
Sponsored by The Protein Society, The Wellcome Trust, and Brazilian research funding agencies.
For more information: Dr. Alberto Spisni
Brazilian Synchrotron Light Laboratory, Campinas, Brazil, and Dept. Experimental Medicine, University of Parma, Italy
Caixa Postal 6192 - CEP 13084-971, Campinas, SP, Brazil
Ph: +55 19 3287-4520; Fx: +55 19 3287-4632
Email: alberto@lnls.br; Website: www.lnls.br/lapsm

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/

APRIL 2005

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

April 2 – 6 • San Diego
Contact: Experimental Biology 2005, 9650 Rockville Pike
Bethesda, MD 20814-3008; Ph: 301-634-7010
Fax: 301-634-7014; www.faseb.org/meeting

The 46th ENC Experimental Nuclear Magnetic Resonance

April 10–15 • Rhode Island Convention Center, Providence, Rhode Island
Contact: ENC, 2019 Galisteo Street, Building I
Santa Fe, New Mexico 87505 (USA); Phone: 505-989-4573
Fax:(505-989-1073; E-mail: enc@enc-conference.org
Web page: http://www.enc-conference.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

SEPTEMBER 2005

Strategies for Engineered Negligible Senescence (SENS), 2nd Conference

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

Department Heads Take Note:

ASBMB Offers Free Membership to New Ph.D.s

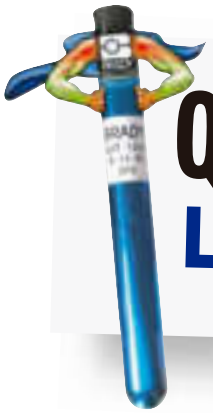
ASBMB is now offering a free one-year Associate membership to all students who have, within the past year, earned a Ph.D. degree in the molecular life sciences or related areas.

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:

Membership at ASBMB
American Society for Biochemistry
& Molecular Biology
9650 Rockville Pike
Bethesda, MD 20814
Email: membership@asbmb.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.



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