JANUARY 2005

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AMERICAN SOCIETY FOR BIOCHEMISTRY AND MOLECULAR BIOLOGY

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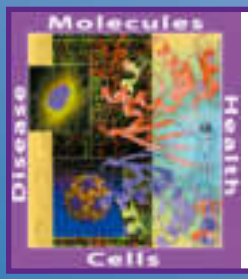

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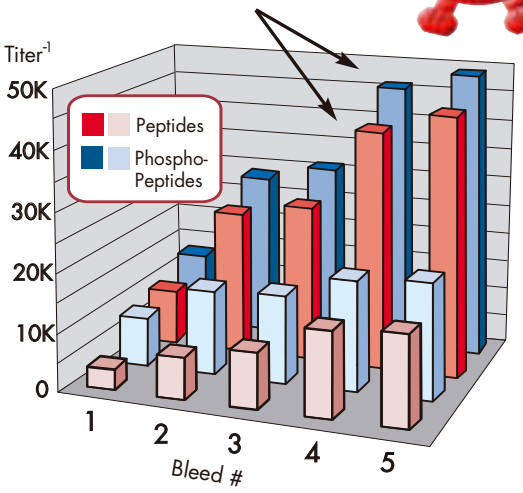

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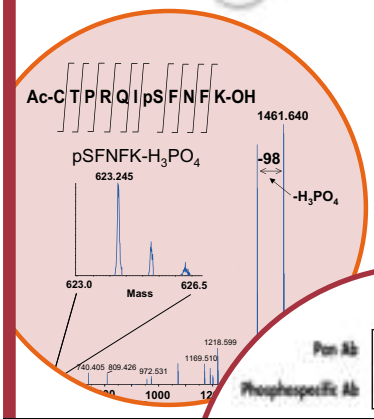

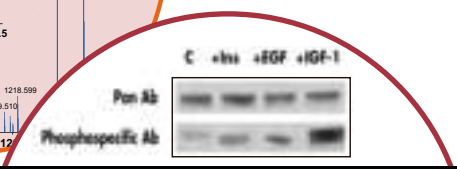

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ASBMB Today

AMERICAN SOCIETY FOR BIOCHEMISTRY AND MOLECULAR BIOLOGY

JANUARY 2005,
Volume 3, Issue 10

features

ON THE COVER:

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Comments

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New Protein Structure May Aid in Design of Therapeutics for Autoimmune Disease

A *Journal of Biological Chemistry* Paper of the Week

By Nicole Kresge, Staff Science Writer

Scientists have determined the crystal structure of a protein kinase C (PKC) isozyme, in this case the novel PKC family member PKC theta (PKCθ). This structure should prove extremely useful in the rational design of small molecule inhibitors of PKCθ, which has been implicated in T-cell mediated disease processes including inflammation and autoimmunity.

The research appears as a "Paper of the Week" in the November 26 issue of *The Journal of Biological Chemistry*, an American Society for Biochemistry and Molecular Biology journal.

PKCθ is a key signaling molecule in a class of immune cells called T lymphocytes, or T cells. These cells recognize short amino acid chains, or antigens, that are displayed on the surface of antigen-presenting cells and initiate immune responses when activated by the antigens.

"PKCθ is selectively recruited to the contact region between T cells and antigen-presenting cells where it interacts with several signaling molecules to induce activation signals essential for productive T cell activation," explains Dr. Will Somers, of Wyeth Research. "Inhibiting PKCθ signal transduction results in defects in T cell activation and cytokine production."

Dr. Somers and his colleagues at Wyeth determined the three-dimensional structure of the catalytic domain of PKCθ using x-ray crystallography. "This is the first structure of a PKC at atomic resolution," notes Dr. Somers. "Moreover, the structure reported here was solved in the presence of the high potency protein kinase inhibitor, staurosporine, revealing the structural basis of inhibitor binding."

Dr. Somers believes his results have the potential to aid in identifying selective inhibitors of kinase function that can act as therapeutics for diseases in which T cells are targeting native rather than foreign antigens. Inhibiting PKC in these cases would disable the T cells and halt the autoimmune reaction. Currently, several PKC inhibitors are being used in clinical trials for various types of cancer and diabetes-related retinopathy.

"This structure provides a starting point for the rational drug design of high potency inhibitors of the catalytic activity of PKCθ for use as potential therapeutics," says Dr. Somers. "Modulation of PKCθ kinase activity presents an ideal therapeutic target in T cell mediated disease processes, including T cell leukemias and T cell mediated autoimmune and respiratory diseases such as asthma."

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.

From the Desk of the President:

Dr. Judith Bond

As we enter the year 2005, it is time to report to you about activities of the Society and the 'state of the union'. During my first six months as President of ASBMB, I have made it a priority to meet our staff at the Beaumont House on the Bethesda campus of FASEB, and to attend several of our Society Committee Meetings to observe them at work. I have also participated in conferences and meetings with organizations that our Society interacts with such as FASEB, the American Chemical Society and the Association of American Medical Colleges. It has been a busy time, eventful and rewarding. I can report to you with confidence that our Society of approximately 12,000 members and 21 staff is indeed healthy! The staff and volunteer members are committed to our mission of "promoting understanding of the molecular nature of life processes", and are proud to be associated with a Society that has had a leadership role in online publications and public access to scientific journals, that is reaching out to the next generation of scientists, and is about to celebrate a century of achievements of its members and the discipline.

I am impressed with the spirit and energy of the volunteers and staff who lead the society (See our web site – www.asbmb.org - for the names of individuals on Council, Committees and staff.) The Finance committee takes responsibility for overseeing our $20 million annual budget, and $25 million reserves. This Committee needs to use a crystal ball to make recommendations to the Council that will keep our Society sustainable in a time of changing economics and revenues (especially with changes in print to online journals and subscriptions for journals). The Education and Professional Development Committee and the Minority Affairs Committee are working to serve the current and next generation of scientists by forming networks in undergraduate colleges, making recommendations on curricula and providing resources such as digital libraries of structures and articles in BAMBED, helping with career choices for graduate and postdoctoral trainees, and welcoming a diverse population into our society. The Public Affairs Advisory Committee is working to inform public decision-makers and to communicate the impact of governmental decisions on science to our members. This year a group of enthusiastic undergraduate students helped us to communicate our message to staff of congressmen in a "Student Hill Day". Our new Director of Publications (Nancy Rodnan), Editors, Associate Editors, Editorial Boards members, and the Publication Committee are constantly working to keep up the high quality of our journals and serve authors, scientists and the public. There are many behind the scene activities, and we could not do without focused committees (e.g., Nominating, Audit, Awards, Meetings/Program Committees) and individuals who represent us at various other organizations.

One of the issues that took center stage in the last six months on the national scene was that of accessibility of scientific publications. You are aware of the issues surrounding the NIH proposed policy for enhanced public access to NIH research information, and the call for comments on the policy. Space constraints do not allow me to summarize the issues here, but suffice it to say that there was a wide range of strong feelings about this proposed policy, from great support to total rejection – even among members of our Society. The proposed policy as written will not affect our Society because author's versions of our accepted manuscripts are already available to the public free of charge upon acceptance. However, there are matters of concern as articulated by many not-for-profit societies, including our own (see the ASBMB comment on our web page).

ASBMB has been a leader in online publications (since 1995), immediate access to our articles upon acceptance (since 1999), and free access to all our publications back to 1905 (since 2003). These are among the things we have to celebrate!! This brings me to final thoughts for this message. The 100th anniversary of the JBC and the ASBMB will be celebrated in San Francisco in April 2006. Mark your calendars, and plan to be with us! Several groups of our members are working towards pulling together material on the History of the Society, the JBC, instrumentation, and achievements of individuals in the discipline over the last 100 years. There will be special compendium, exhibits, informal interactions, and entertainment as we celebrate the progress of the past, the excitement of present science, and the potential for future discovery and advances in the understanding of the molecular nature of life processes. We would love to see you in April 2005 in San Diego at our annual meeting, as well as in April 2006 in San Francisco. Be there! Celebrate with us at our Birthday to launch the second century of biochemical and molecular biology achievements.

Judith Bond
President, ASBMB

by Peter Farnham, CAE, ASBMB Public Affairs Officer

Appropriations Roundup

During its lame duck session Congress passed an omnibus spending bill totaling over $388 billion. The bill, approved overwhelmingly in both House and Senate on November 20, rolled into one package the nine appropriations bills that still had not passed when Congress adjourned in early October. President Bush was expected to sign the bill.

The bill includes funding for NIH, NSF, and other science agencies. The overall amount of funding in the bill freezes total spending for domestic programs compared to last year (in total—some agencies got increases while others were cut or remained static). In addition, a 0.83% across-the-board cut is also mandated.

NIH's Bottom Line: <2%

Congress provided NIH with an appropriation of $28.6 billion, $800 million over FY 2004. Once the 0.83% across-the-board cut is factored in, the final figure is $28.4 billion, just $563 million (about 2%) over FY 2004. However, numerous taps must be subtracted from that $28.4 billion, including a $100 million transfer of funds to help combat Global HIV/AIDS, and a 0.24% tap for "program evaluation." In sum, the actual amount of money available to NIH for research, education, training, and its many other programs is far below the 4% increase the Senate called for last summer, and does not even keep up with the 3.5% projected level of biomedical research inflation this year. It is difficult to see how NIH will be able to fund very many (if any) new grants this coming year, given the parsimonious funding the agency has received.

Report Language on Open Access

In September, NIH proposed a policy on "enhanced public access to NIH-funded research." Congress weighed in on the proposal in language accompanying the NIH bill, stating: "NIH is directed to give full and fair consideration to all comments before publishing its final policy. The conferees request NIH to provide the estimated costs of implementing this policy each year in its annual Justification of Estimates to the House and Senate Appropriations Committees. In addition, the conferees direct NIH to continue to work with the publishers of scientific journals to maintain the integrity of the peer review system."

NSF Cut 2%

While NIH received a disappointing increase, at least there was some movement above zero. Unfortunately, NSF received an actual cut of about 2% in the omnibus bill—over $100 million below last year's funding level.

The cuts at NSF are across-the-board—although Research and Related Activities, the core research program at NSF, was relatively unscathed, going down a mere $30 million to $4.22 billion. Education and Human Resources was the big loser, suffering almost $100 million in cuts to about $840 million. Also, the Math and Science Partnerships program to fund cooperative research and education efforts between universities and high schools was zeroed out.

Rep. Vern Ehlers (R-MI), a senior member of the House Science Committee, released a statement saying he was "concerned and astonished" at the outcome of congressional deliberations on NSF. He said he voted in favor of the bill "under protest."

Ehlers continued, "While I understand the need to make hard choices in the face of fiscal constraint, I do not see the wisdom in putting science funding far behind other priorities. We have cut NSF despite the fact that this omnibus bill increases spending for the 2005 fiscal year, so clearly we could find room to grow basic research while maintaining fiscal constraint. But not only are we not keeping pace with inflationary growth, we are actually cutting the portion basic research receives in the overall budget."

Where the Money Went

Commenting on the slashing of the NSF budget, Robert Pear pointed out in the *New York Times* on November 30, "While cutting the budget of the [NSF], Congress found money for the Rock and Roll Hall of Fame, the Alabama Sports Hall of Fame in Birmingham, the Country Music Hall of Fame in Nashville, bathhouses in Hot Springs, Arkansas, and hundreds of similar projects."

David Stonner, head of congressional relations for NSF, told *ASBMB Today* that congressional staff have assured him that the cuts do not indicate congressional displeasure with NSF. "Rather, we're a victim of budgetary circumstances. They have to fund veter-

Continued bottom of next column

Stem Cell Conference Focuses on Engaging Public

A blue-ribbon gathering of international scientists, advocates, patients, politicians, and ethicists gathered in late November at Rice University to consider the latest science, and thinking on ethics, associated with human embryonic stem cell (hESC) research.

The conference brought together business and community leaders, policymakers, ethicists, science journalists, and scientists to explore new ways to engage the general public in a dialogue on such issues as: Should the United States be involved in hESC research? What are the medical, political, and economic consequences of letting other nations take over the leadership role? How would the U.S. regulate hESC research if it were allowed?

The conference, Stem Cells: Saving Lives or Crossing Lines, held at Rice University's Baker Institute for Public Policy was sponsored by the University of Texas M.D. Anderson Cancer Center, University of Texas Health Science Center at Houston, and Baylor College of Medicine.

Baylor's William Brinkley (Chairman of ASBMB's Public Affairs Advisory Committee), commented that today, "Human embryonic stem cell research and its remarkable potential for medical science stands at a pivotal, but uncertain threshold." He described the current debate as between two groups: those who believe life begins with conception and that to use hESC is tantamount to destruction of human life, and those who believe "that it is less an ethical risk to use these cells for the advancement of medical science than to sanction their ultimate demise in a freezer" in an IVF clinic. Brinkley noted, "If there is hope for effective leadership in stem cell research, we must find a way around this impasse, as we have done previously in other controversial areas of science and medicine."

Recent surveys indicate that much of the public has begun to appreciate the potential of stem cell research for medicine As reported by Mary Woolley, President of Research!America, reported that over 80% of the responders in a recent poll indicated that stem cell research should be allowed, and over 60% supported therapeutic cloning.

Still, opposition to hESC continues to be strong, and a major subject of discussion was how to move to some sort of consensus. The idea was raised of a meeting similar to the Asilomar conference in the early 1970s which addressed the possible dangers associated with recombinant DNA research, then a new and very unknown field.

However, some prominent scientists believe an Asilomar conference would not be appropriate. They noted that Asilomar dealt with scientific issues, while the debate involving hESC involves social and ethical issues that do not lend themselves to scientific study or consensus.

Nevertheless, Brinkley noted, "If America is to establish leadership in this arena, we must strive to create a more effective dialog with those who oppose, and in some cases, misunderstand the biology and medical implications of this remarkable new technology. Proof of principle has already been shown in animal models, and by those in other nations where stem cell research has little or no legal impediment, such as South Korea and Britain. The American scientific community, in partnership with dedicated disease advocates, bioethicists, physicians, patients, parents and policy makers, must join together to lead the discourse proactively. We must identify and cultivate champions within both parties in both state and Federal governments who will help us achieve a more favorable policy climate."

Brinkley called on scientists and academicians to stop complaining and underestimating the American public and "to begin to do what we do best—educate and advocate."

"The conference was a wonderful gathering of world class leaders in science, ethics, media, and public policy," said Judy Haley, Vice President of Texans for the Advancement of Medical Research (TAMR). "Stem cell research is complicated, so educational sessions like this are keys to separating myths from facts. We hope the entire field of stem cell research moves forward in Texas so resulting treatments and cures are available here in Texas for those suffering from incurable diseases and conditions."

Rice University planned to webcast the conference, which was to be available for public viewing in mid-December at www.ruf.rice.edu/~neal/stemcell.

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ans' health, housing, and a host of other critical programs in the VA/HUD bill in addition to us. But having said that, the hard cold reality is that we're facing a budget cut this year and the situation in Congress doesn't look any brighter next year. It's going to force the science community at large to do some hard, serious thinking about priorities we can afford."

3-D Structure of Anthrax Toxin Complex Solved

A team of researchers led by Dr. Robert C. Liddington* of The Burnham Institute has determined the crystal structure of the binding complex between anthrax toxin and one of its host receptors. Inhalation anthrax, unless diagnosed at a very early stage, is fatal: there is no existing antidote once the toxin is blood borne. The study, published online in the July 4, 2004 issue of *Nature*, offers new leads for the discovery of anthrax antitoxins that could be used in conjunction with antibiotics to treat late-stage anthrax. In a surprising twist, the new information will also help in the design of anthrax toxin as an anti-tumor agent for treatment of cancer.

Anthrax toxin is comprised of three proteins: protective antigen (PA), lethal factor (LF), and edema factor (EF). To gain entry into host cells, PA must recognize a receptor on the surface of the target cell. Once PA has bound to the cell, it then enables EF and LF to bind and form a pore through which PA forces EF and LF into the cell in a syringe-like action.

Dr. Liddington's laboratory, together with Stephen Leppla at the National Institute of Allergy and Infectious Diseases, studied the interaction of PA with the two known receptors for anthrax: TEM8 and CMG2. PA binds tightly to both receptors and can use either to transfer toxicity into the cell. The scientists were able to determine the crystal structure of the PA-CMG2 binding complex, making it possible to design small molecules that will interact with PA and prevent the binding complex from forming.

Dr. Robert C. Liddington

The two receptors are similar in how they mediate entry into the cells, but differ in important ways: The CMG2 receptor is present in most tissues, whereas the TEM8 receptor is mostly found on the cells that form the blood vessels of tumors and is upregulated during the creation of new blood vessels. This probably explains why anthrax toxin at sub-lethal doses has strong anti-tumor activity.

Dr. Leppla is now developing anthrax toxin as an anti-tumor agent. Although the PA-TEM8 complex is yet to be solved, Liddington expects the interactions to be similar to that of the PA-CMG2 complex. "We can exploit the differences to design PA molecules that bind better to TEM8 than to CMG2," says Liddington, "which would minimize the side effects of toxin binding to normal tissues."

Liddington was recently awarded a $15 M grant from the National Institute of Allergy and Infectious Diseases that supports a multidisciplinary effort focused on developing candidate antitoxins for anthrax and other potential agents of biological warfare.

*ASBMB member

Fogarty International Center Announces Research Training Grants to Tackle AIDS and Tuberculosis

The Fogarty International Center (FIC), part of NIH, has announced the funding of institutions in China, Haiti, Russia and Uganda, along with partner institutions in the U.S., in the first four comprehensive awards of the International Clinical, Operational, and Health Services Research Training Award Program for AIDS and Tuberculosis (ICOHRTA-AIDS/TB).

FIC, with co-sponsorship from nine NIH institutes and centers, the United States Agency for International Development (USAID) and the Centers for Disease Control and Prevention (CDC), will commit approximately $12 million over the first five years of the program.

"AIDS is a priority for all of NIH and the Department of Health and Human Services. Fogarty's success in forging international collaborations between foreign and U.S. institutions to help train researchers in developing countries is a key part of our fight against this terrible disease," noted Elias A. Zerhouni, M.D., NIH Director.

This innovative program supports collaborative and multidisciplinary research training in developing countries where AIDS and tuberculosis are taking an enormous toll on individuals, families and communities. It provides opportunities for health professionals to train at the masters, Ph.D., and post-doctoral levels while working on research projects related to HIV/AIDS and TB that are relevant to their country's needs.

"This program will play an important role in meeting the training needs in countries struggling to gain control of the scourge of AIDS," said Sharon Hrynkow, Ph.D., FIC Acting Director, speaking on behalf of all the program sponsors. "These first four sites will provide critically needed training in the design and conduct of AIDS and TB research to scale-up promising interventions as they are brought into health care systems."

The four projects and awardees are:

Dr. Zunyon Wu of the Chinese Center for Disease Control and Prevention (CDC) in Beijing, China, will collaborate with Dr. Roger Detels of the University of California, Los Angeles, to implement a research training program that addresses the HIV/AIDS epidemic in China. The project will set up an independent HIV/AIDS training center at the Chinese CDC. The center will assist other academic and research institutions in China in training health professionals and researchers to fight the HIV/AIDS epidemic.

Dr. Jean Pape of the Groupe Haitien d'Etude du Sarcome de Kaposi et des Infections Opportunistes (GHESKIO) will collaborate with Dr. Warren Johnson of Cornell University to build upon HIV prevention and care services in Haiti. The project involves training a cadre of research leaders while increasing research capacity of the National HIV Care and Prevention Network. This network, made up of public and private health care organizations in Haiti, will provide a standardized package of HIV care and prevention services to 300,000 people annually.

Dr. Andrei P. Kozlov of The Biomedical Center in St. Petersburg, Russia will work with Dr. Robert Heimer of Yale University. The team will develop a center of excellence, called the TB-AIDS Clinical Training and Research Unit, in St. Petersburg, Russia. This center will help train a new generation of medical scientists to respond to the emerging epidemics of TB and AIDS in Russia.

> ***"This program will play an important role ... in countries struggling to gain control of the scourge of AIDS"***
>
> **—Sharon Hrynkow, Ph.D.**

Dr. Peter Mugyenyi of the Joint Clinical Research Centre in Kampala, Uganda will work with Dr. Christopher Whalen of Case Western Reserve University. The project will broaden national capacity to meet the public health and scientific challenges of the evolving HIV and TB epidemic in Uganda. Infrastructure will be developed in Uganda to translate basic and clinical research findings into public health policy and interventions and to evaluate their effectiveness.

New Findings in Innate Immunity

Nicole Kresge, Staff Science Writer

Scientists are one step closer to deciphering the molecular signaling process controlling innate immunity with the discovery that a molecule called IRAK1 regulates the expression of the anti-inflammatory cytokine IL-10. Because atherosclerosis patients often have elevated IL-10 levels, IRAK1 may be a viable target for developing therapeutics for atherosclerosis.

The research appears as the "Paper of the Week" in the December 3 issue of *The Journal of Biological Chemistry*, an American Society for Biochemistry and Molecular Biology journal.

Innate immunity is the body's first response to infection, and it plays a major role in regulating infection, inflammation, cell growth, and apoptosis. During an innate immune reaction, macrophages, dendritic cells, and epithelial cells use a set of transmembrane receptors called Toll-like receptors (TLRs) to initiate signaling cascades.

"TLRs can sense diverse environmental cues and send signals downstream to a family of interleukin-1 receptor associated kinases (IRAKs). These IRAKs then activate and/or regulate specific cytokine gene expression," explains Dr. Liwu Li* of the Wake Forest University School of Medicine.

However, the specificity of the TLR signaling process is not clearly understood. "In the past," says Dr. Li, "it was thought that all IRAKs may play a somewhat redundant role in regulating the nuclear transcription factor κ and the expression of pro-inflammatory cytokines such as IL-1beta and TNFalpha." However, mice that lack IRAK1 can still activate κ, suggesting that IRAK1 may be involved in other activities.

Dr. Li and his colleagues discovered that IRAK1 actually activates a molecule called Signal Transducer and Activator of Transcription 3, or Stat3, which in turn activates expression of the anti-inflammatory cytokine IL-10. The scientists also found that IRAK1 can translocate into the nucleus and regulate the nuclear transcription of proteins. "Our finding sets IRAK1 apart from other IRAKs and elucidates a novel pathway in innate immunity regulation," says Dr. Li.

Because atherosclerosis patients usually have elevated serum IL-10 levels, the scientists also looked at IRAK1 levels in blood from atherosclerosis patients. They found that IRAK1 is modified and localized to the nucleus in these patients, indicating a possible link between IRAK1 regulation and the pathogenesis of atherosclerosis.

"Inflammation and infection have been increasingly shown to play a significant role in the pathogenesis and/or resolution of atherosclerosis," explains Dr. Li. "Anti- inflammatory cytokines such as IL-10 may serve as a self protective mechanism to prevent excessive inflammation and contribute to plaque stability. Indeed, patients with higher IL-10 serum levels have a better chance of recovery. Therefore, elevated IRAK1 modification and IL-10 levels observed in atherosclerosis patients may be a compensatory and self-protective mechanism."

Manipulating innate immunity may eventually be a therapeutic strategy for treating atherosclerosis. "Our study, as well as others, indicates that innate immunity alteration plays a critical role in either the pathogenesis or resolution of atherosclerosis. IRAK1 may provide a viable target for developing therapeutic interventions for atherosclerosis. Compounds or strategies directed at preventing or enhancing IRAK1 modification and nuclear entry may hold great promise in treating atherosclerosis," concludes Dr. Li.

Besides atherosclerosis, alterations in innate immunity can cause diabetes, cancer, and numerous other inflammatory disorders. Further understanding of the innate immunity process may lead to development of therapies for these diseases as well.

*ASBMB Member

Celebrating the past & looking to the future

The Journal of Biological Chemistry (*JBC*) announces two special series in honor of its Centennial.

Hear the personal experiences of prominent scientists and Nobel laureates in the Reflections series. Learn about Christian de Duve's love affair with insulin and Paul Berg's favorite experiments or find out why Donald D. Brown pays homage to the Xenopus laevis oocyte and egg.

See some of the seminal articles published in *JBC* over the past 100 years in the Classics series. Read about Esmond E. Snell's discovery of avidin or how James B. Sumner proved that enzymes are proteins.

These features can be found on the *JBC* website (www.jbc.org) under the Reflections and Classic Articles headings as well as in the journal itself.

All of this culminates in the *JBC* Centennial Celebration at the ASBMB Annual Meeting in San Francisco, April 1-5, 2006.

San Diego 2005

Brian Strahl to Receive ASBMB-Schering-Plough Award

The ASBMB-Schering-Plough Research Institute Award will be presented to Dr. Brian Strahl at the ASBMB Annual Meeting, April 2-6 in San Diego. The Award recognizes outstanding research contributions to biochemistry and molecular biology. The recipient must have no more than ten years post-doctoral experience, and the nominees and nominators need not be ASBMB members. The Award consists of a plaque, stipend, and transportation and expenses to present a lecture at the Annual Meeting. Additional expenses will be awarded for travel to attend a meeting of the recipient's choice. Recent recipients of this Award were Pehr A. B. Harbury in 2004, Catherine Drennan in 2003, John D. York in 2002, Stephen P. Bell in 2001, and Xiadong Wang, in 2000.

Strahl, who is currently Assistant Professor, Department of Biochemistry and Biophysics, University of North Carolina School of Medicine, completed his doctoral studies in molecular endocrinology at North Carolina State University in 1998, and subsequently moved to the laboratory of Dr. David Allis at the University of Virginia. Dr. Allis is an internationally recognized expert on dynamic chromatin structure and its relationship to gene transcription and other fundamental DNA processes, and in a relatively short time, Dr. Strahl emerged as a young leader in this area, which is currently a subject of intense investigation. With Dr. Allis, he co-wrote, "The Language of Covalent Histone Modifications," which was published in *Nature* in 2000 and has since become a widely cited "must read" for those concerned with chromatin structure/function. In this review, they proposed that histone proteins, which package DNA into nucleosome structures, are subject to a variety of distinct biochemical modifications that form an important epigenetic language, with subtle variations in modification producing important differences in gene expression, DNA replication, etc. They further proposed that these modifications might regulate the activity of chromatin by altering the structure of the chromatin polymer itself and/or by recruiting proteins that uniquely recognize their single or combinatorial modifications.

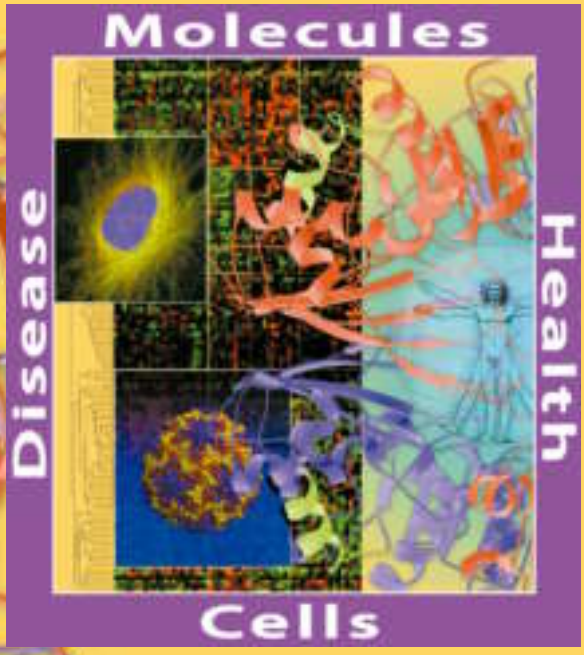
As a postdoctoral fellow, Dr. Strahl collaborated with a mass spectrometry expert to provide conclusive evidence for arginine methylation in histone proteins, a previously controversial event, and showed that this particular modification is conserved from yeast to mammals, further emphasizing its significance. He also provided evidence linking methylation of a specific arginine residue to regulation of gene transcription by showing that a nuclear transcription coactivator is the major, if not sole, mediator of this histone methylation reaction in human cells. These studies helped provide critical evidence for the importance of histone methylation in the regulation of gene transcription. In less than three years, Dr. Brian authored or coauthored ten high-impact research articles from the Allis lab, all published in top-tier journals such as *Science, Nature, PNAS,* and *Current Biology*.

Dr. Brian Strahl

Since coming to UNC, noted Dr. Allis, Dr. Strahl has continued his cutting-edge investigations of the histone code hypothesis using yeast as a model system in order to combine biochemical and genetic approaches. His current efforts are aimed at identifying cooperating proteins, pursuing roles for novel histone methyltransferases, and defining mechanisms by which histone methylation events regulate gene transcription. He is also examining the role of other histone modifications such as phosphorylation and ubiquitination. These studies promise important mechanistic insights into human biology and disease, since the protein machinery responsible for histone modifications is well conserved and methyltransferases have been strongly implicated in human diseases, including cancer.

Dr. Strahl started his own independent lab at UNC Chapel Hill not long ago, and shortly thereafter on his first try landed an NIH grant to cover his Set2/Lys36 H3 methylation work on his first try. Then, barely six months after setting up his group published a landmark paper on their work; an often-cited paper in *Genes and Development*. "Brian and I joked that his first paper published with me was published six months to the day after set foot in my lab," Dr. Allis recalled. "Now he has done it again in his own lab!"

See You in San Diego!



2005 ASBMB Annual Meeting

Held in conjunction with EB 2005

April 2-6, 2005

San Diego, CA

Meeting Organizers

Dennis R. Voelker, National Jewish Medical Research Center

Cecile Rochette-Egly, IGBMC, Strasbourg

and the 2005 ASBMB Program Planning Committee

Meeting Themes

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

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

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

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

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

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

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

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

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

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

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

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

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

Experimental Biology 2005

www.asbmb.org/meetings

ASBMB American Society for Biochemistry and Molecular Biology

San Diego 2005

DNA Replication, Interactive Repair, and Recombinational Processes

Organizer: Charles McHenry, *Professor of Biochemistry & Molecular Genetics, University of Colorado Health Sciences Center, Denver, CO*

The process of chromosomal replication is characterized by an elaborately orchestrated process driven by the sequential interactions of numerous components of protein machines. Replication is tightly regulated, at the level of the initiation at chromosomal origins, and also by checkpoints, enabling a variety of repair processes before replication is reinitiated. The symposium will begin with presentations of innovative research directed toward understanding normal replication processes. The focus will shift in the last two sessions to repair and recombinational reactions that are required to repair damage-arrested replication forks and broken chromosomes. The symposium will be of interest both to the DNA replication community, and to those interested in the broad (interdisciplinary) topics of cell cycle regulation, multi-protein assembly mechanisms, and protein machines. Each session will be expanded by selection of three additional speakers from submitted abstracts. There will also be exciting interactive poster sessions devoted to the topics of this symposium theme.

DNA Replicases

Chair: Charles McHenry

Cellular replicases comprise a sliding clamp processivity factor, a multisubunit clamp loader ATPase and a replicative polymerase. Dr. McHenry will describe evidence for a bacterial replicase being a functionally asymmetric dimer with distinguishable leading and lagging strand polymerases. He will discuss a novel kinetic partitioning mechanism used to assemble the replicase. Dr. Linda Bloom (Univ. Florida) will describe mechanistic studies directed toward understanding the temporal correlation of clamp loader-clamp binding, DNA binding, ATP hydrolysis and clamp release. Dr. Peter Burgers (Washington Univ.) will present research focusing on the use of two polymerases to deal with the strand asymmetry issue in eukaryotes. These studies have led to the discovery of an idling-extension mechanism used by the lagging strand delta polymerase to facilitate Okazaki fragment maturation together with the FEN1 nuclease.

Replication Fork Dynamics

Chair: Robert Bambara, *University of Rochester Medical Center*

This session will build on the first session to describe additional processes involved in replication fork transactions. Dr. Steve Benkovic (Penn State Univ.) will discuss the mechanism of polymerase assembly on primers, with an emphasis on the importance of suppressing polymerase activity until the replisome is assembled. He will also present research directed toward understanding timing and regulation issues required for coupled synthesis by continuous leading and discontinuous lagging strand polymerases. Dr. Xiaojiang Chen (Univ. Southern California) will discuss models for helicase action, based on X-ray crystal structures of MCM complexes and the SV40 T antigen. Dr. Bambara will describe research in which FEN1, involved in Okazaki fragment processing, serves a second role in repair when damage is encountered at the fork. In contrast to its normal replicative role, this repair process is stimulated by an alternative '911' clamp that is activated in response to DNA damage.

Dr. Charles McHenry

Initiation and Restart of DNA Replication

Chair: Mike Cox, *University of Wisconsin*

The RecA protein plays a critical role in recombinational DNA repair. Dr. Cox will present research on regulation of the RecA recombinase activity by a host of important regulatory proteins: RecFOR, RecX, DinI and RdgC. Dr. Justin Courcelle (Mississippi State Univ.) will present research on the role of RecJ protein in partially degrading damage-stalled replication forks, allowing repair enzymes to gain access to the blocking lesion. Dr. Johannes Walter (Harvard Medical School) will present recent research that has revealed an ongoing role of two proteins required for origin assembly, Cdc45 and MCM7, in vertebrate replication fork progression. The role of the MCM complex in extensive unwinding of

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Genomes and Proteomes

By Organizer: Andrew J. Link, *Department of Microbiology and Immunology, Vanderbilt University School of Medicine, Nashville, TN*

Dr. Andrew J. Link

The success of the human genome project has generated a plethora of biological information and new approaches to dissect the biology of individual cells and whole organisms. In the past 10 years, proteomics or large-scale analysis of proteins has influenced nearly ever field in biology. Advances in technologies continue to drive these highly dynamic fields. Genomic and proteomics approaches are underway to map the network of biological interactions that regulate biological processes. Deciphering genomes and proteomes and understanding how variation influences traits or predisposes individuals to disease is an ongoing endeavor. This symposium will highlight new technologies and showcase examples of how genomes and proteomes are being analyzed and used for basic sciences and medical applications.

Breakthrough Technologies

Chair, John Yates, *The Scripps Research Institute*

This session will highlight exciting new genomic and proteomic technologies that are likely to profoundly change how biological problems are addressed. Dr. Rob Mitra will discuss using polony technology or PCR colonies for high speed sequencing of DNA. Dr. Gavin Macbeth will report on the development of protein microarrays for interrogating interactions. Dr. John Yates will report on comprehensive approaches to profile complex protein samples to simultaneously identify proteins and modifications.

Single Molecule Amplification and Sequencing of Nucleic Acids
Rob Mitra, *Washington University, St. Louis*

Protein Microarrays: From Functional Proteomics to Protein Profiling
Gavin MacBeath, *Harvard University*

Towards Comprehensive Proteomics of Complexes, Organelles, and Cells
John Yates, *The Scripps Research Institute*

Deciphering Genomes and Proteomes

Chair, Eric Green, *NIH*

Interpreting genomics and proteomics information is a major challenge. This session looks at efforts to decipher and understand genomic and proteomic information. Dr. Mike Cherry will discuss the global efforts to annotate genomes. Dr. Gilbert Omenn will report on the world-wide effort to comprehensively identify the components in human plasma. Dr. Eric Green will discuss using comparative sequencing to identify functional elements in genomic sequences.

Annotating Genomes
Mike Cherry, *Stanford University*

The Human Plasma Proteome: Results From the HUPO Plasma Proteome Project
Gilbert S. Omenn, *Univ. of Michigan*

Decoding the Human Genome by Comparative Sequencing, **Eric Green,** *NIH*

Gene and Protein Networks

Chair, Andrew Link, *Vanderbilt Univ.*

Biology is driven by the complex network of interactions at the genomic and proteomic level. This session discusses approaches to identify and map gene and protein interactions that control most biological processes. Dr. Trey Ideker will discuss efforts to model and visualize complex biological networks. Dr. Andrew Link will report on applying proteomics screens to identify novel components in post-transcriptional regulation. Dr. Rich Young will discuss efforts to map transcriptional networks regulating biological processes.

Network Alignment and Other Approaches for Cross-Species Comparison of Protein Networks, **Trey Ideker,** *UCSD*

Proteomic Screens for Constructing Translational Control Networks
Andrew Link, *Vanderbilt University*

Transcriptional Regulation of Eukaryotic Genomes
Richard A. Young, *The Whitehead Inst.*

Genes, Proteins and Medicine

Chair, Denis F. Hochstrasser, *Hopitaux Universitaires de Geneve*

Genomics and proteomics are having a profound influence on the practice of medicine. This session highlights how the practice of medicine, predicting diseases, and medical diagnosis are changing using genomic and proteomic approaches. Dr. Mark Boguski will discuss the application of genomics to advance our knowledge in neurobiology. Dr. David Cox will report on identifying single nucleotide polymorphisms related to human diseases. Dr. Denis Hochstrasser will discuss the use of proteomics in medical applications.

Neurogenomics: At the Intersection of Neurobiology and Genome Sciences
Mark Boguski, *Fred Hutchinson Cancer Research Center*

Human Genetic Variation and Complex Human Disease
David Cox, *Perlegen Sciences*

Clinical Proteomic and MS Imaging
Denis F. Hochstrasser, *Hopitaux Universitaires de Geneve*

San Diego 2005

Organelle Biogenesis and Dynamics

Organizers: Carla Koehler, *University of California at Los Angeles*, and Danny Schnell, *University of Massachusetts, Amherst*

Eukaryotic cells are subdivided into membrane-bound organelles that separate and organize vast arrays of metabolic and signaling processes, providing the framework for cellular growth and differentiation. The molecular mechanisms underlying organelle biogenesis and maintenance have long been areas of intense interest among biochemists and cell biologists. A major portion of this symposium will be devoted to the latest results from studies of the many intracellular trafficking pathways that target the enzymes, membrane transporters and structural proteins to their site of function within the proper organelle. In addition, we will examine the mechanisms that organelles utilize to recognize and dispose of damaged or misfolded proteins in order to maintain the quality control of their protein constituents. The second major theme focuses on the dynamic changes of organelles in response to cellular changes that accompany growth, development and stress responses. These studies will not only highlight the underlying mechanisms by which organelles undergo morphological and functional change, but they also include investigations of the signaling networks operating between organelles that are necessary for a coordinated cellular response. Disruptions in many of the fundamental mechanisms of organelle biogenesis and dynamics that will be discussed during the symposium lead to specific diseases, making the sessions particularly apt for the four themes of the annual meeting, molecules, cells, health and disease.

Dr. Carla Koehler

Dr. Danny Schnell

Protein Targeting and Translocation I and II

In recent years, the basic view of protein targeting and translocation systems has expanded tremendously. These two sessions will focus on the mechanisms by which proteins are targeted to specific organelles and subsequently sorted to their proper organellar subcompartment. Not only do these systems transport proteins across membranes, they also decode the signals that are necessary to trigger the integration of membrane proteins into lipid bilayers. It now is apparent that translocation systems are complex molecular machines composed of functional units that interact in distinct combinations to mediate protein targeting to specific compartments. This flexibility allows the systems to manage the sorting of membrane vs. soluble proteins, to mediate targeting to different suborganellar compartments, and to respond to stress and developmental cues. These two sessions will include examples of these processes from a variety of organelles using bacterial, fungal, plant and mammalian model systems.

Session I will focus on the assembly and function of the targeting and translocation components that mediate protein import from the cytoplasm into mitochondria (Carla Koehler), chloroplasts (Danny Schnell) and peroxisomes (Suresh Subramani). Session II focuses on the complex mechanisms by which integral membrane proteins are recognized by protein translocation systems and threaded into lipid bilayers (Art Johnson and Arnold Driessen). The session also will include a presentation on intracellular signaling that uses a signaling between the endoplasmic reticulum and nucleus as a model to understand how organelles communicate with the nucleus to tailor gene expression to the demands of organelle biogenesis or stress (Peter Walter).

Protein Assembly, Maturation and Quality Control

This session will focus on the close connection between the transport and modification of proteins in two of the best-studied systems, the endoplasmic reticulum (ER) and mitochondria. Examples from the ER by Dan Hebert and Randy Hampton will focus on the mechanisms by which the translocation, modification (e.g. glycosylation) and folding of proteins are integrated. Furthermore, they will highlight examples of how the ER deals with proteins that misfold by ejecting from them from the organelle through a reversal of the translocaton process and feeding the proteins to the cytoplasmic proteasome. Finally, Thomas Langer will provide insights into the role of membrane-associated proteases in regulating membrane and organelle biogenesis in mitochondria. This session is of direct relevance to the study of human disease as each speaker draws on specific systems that are models for known human diseases.

Organelle Dynamics

The final session of the symposium will focus on the burgeoning field of organelle dynamics. These studies represent several outstanding examples of how organelle assembly, division and fusion occur and are regulated in response to cues from cellular growth and development. In contrast to the static views of organelles presented on our textbooks, these speakers will illustrate the dynamic nature of organelles. The presentations include the studies of the elaborate networks of fusing and dividing mitochondria in yeast (Jodi Nunnari), the process by which chloroplasts undergo division to increase plant photosynthetic capacity and ensure organelle inheritance (Kathy Osteryoung), and the regulation and assembly of the nuclear pore complexes that regulate transport and communication across the nuclear envelope (Susan Wente). This session is underscored by the fact that these investigators have been instrumental in transforming their fields by making key contributions to understanding the underlying molecular mechanisms that drive these complex processes.

DNA Replication continued ...

Continued from page 12

DNA, generating a signal for checkpoint activation, when the delta replicase is blocked, will be discussed.

Replication-Recombination-Repair Interactive Systems

Chair: Myron Goodman, *Univ. Southern California*

Dr. Goodman will discuss research on the role of E. coli DNA polymerase V in translesion synthesis in a process that requires monomeric RecA, distinguishing its function from that as a filament in other RecA-dependent reactions. Dr. Steve Kowalczykowski (Univ. California, Davis) will discuss his research focused on the biochemistry of recombinational DNA repair. Dr. Jim Haber (Brandeis Univ.) will discuss the repair of double-strand breaks in eukaryotes, using yeast as a model system. He will focus on gene conversion, a process in which a patch of new DNA is created by copying a donor template to repair the break. He will also discuss the special circumstances, such as repair of an eroding telomere, where only one end of DNA is homologous to the template.

Streptococcus Infects Humans

Streptococcal bacteria may infect humans by using a bacterial enzyme to "hijack" the blood-clotting system, according to new research by Howard Hughes Medical Institute scientists.

In studies published in the August 27, 2004, issue of the journal *Science*, the researchers established that the enzyme streptokinase is responsible for the bacteria's ability to infect humans while exhibiting little activity against other mammals.

The scientists genetically altered strains of mice to make the animals susceptible to infection by streptococcus. They say their strategy outlines a new path for developing animal models for human-specific microbes. The research is also likely to open the way to new understanding of the factors that enable bacteria to evolve host specificity.

Howard Hughes Medical Institute investigator David Ginsburg* led the research team, which included lead author Hongmin Sun and colleagues at the University of Michigan and Lund University in Sweden.

Dr. Ginsburg said that Hongmin Sun's achievement of constructing a transgenic mouse susceptible to streptococcus infection represents a major step not only in understanding infection by that bacterium, but in opening the way to similar studies of other bacteria.

In infecting its human host, the group A streptococcus secretes its own streptokinase, which activates the human enzyme plasminogen. In turn, plasminogen dissolves blood clots by degrading the protein, fibrin. A major question was what role streptokinase played in the bacterium's overall pathogenicity.

Dr. David Ginsburg

To develop a "humanized" mouse that would be vulnerable to bacterial streptokinase, Dr. Sun attached the gene for human plasminogen to a regulatory DNA sequence that normally activates the gene for albumin. Because albumin is produced in large amounts, the transgenic mice made significant amounts of human plasminogen.

To show that the human plasminogen was functional in the mice, Sun crossed the transgenic mice with a strain of plasminogen null mice. This cross essentially restored plasminogen function in the resulting mice. In test-tube experiments, Sun demonstrated that human plasminogen from the transgenic mice was able to dissolve blood clots when activated by streptokinase.

"The critical experiment, though, was when Hongmin infected the skin of these transgenic mice with the group A streptococcus bacteria," noted Dr. Ginsburg. "She found that the bacteria were much, much more toxic to these mice than the normal mice. This fit with the idea that streptokinase was an important component of the pathogenicity of strep."

In further experiments, the researchers found that when they removed the streptokinase gene from group A streptococci bacteria, there was little difference in their infectivity between normal and the transgenic mice.

These studies have led Dr. Ginsburg and his colleagues to theorize that streptokinase "hijacks" the human clot-forming system for the bacteria's own infective ends. "The theory is that the bacteria cause a local infection and begin to grow. Many of the bacterial products, as well as our immune cells, trigger the human clotting system, which evolved in part as a defense against such infection," explained Dr. Ginsburg. "This system produces clots in the blood vessels around the infection, closing the highways that the

ASBMB Members Elected to Institute of Medicine

Four ASBMB members were among 65 New Members and 5 Foreign Associates recently elected to theInstitute of Medicine. The ASBMB members elected were:

Robert J. Desnick, Professor and Chair, Department of Human Genetics, Mount Sinai School of Medicine, New York City.

Rowena G. Matthews, Robert Greenberg Distinguished Professor of Biological Chemistry, University of Michigan, Ann Arbor.

Charles J. Sherr, Investigator, Howard Hughes Medical Institute; and member, Department of Genetics and Tumor Cell Biology, St. Jude Children's Research Hospital, Memphis.

Arthur Weiss, Investigator, Howard Hughes Medical Institute, and Professor and Chief, Division of Rheumatology, University of California, San Francisco.

by Thwarting Blood Clotting

bacteria would use to spread. However, the bacterial streptokinase bypasses this system causing the blood clot to dissolve so the bacteria can spread."

Sure enough, when the researchers bypassed the clotting defense by injecting the streptococcus directly into the bloodstream of both normal and transgenic mice, both showed similar susceptibility to infection.

The scientists' findings highlight the evolutionary arms race between bacteria and humans. "Clearly, if we could mutate our plasminogen so it still worked, yet was resistant to a bacterial streptokinase, it would give us an advantage," said Dr. Ginsburg. "But then the bacteria could mutate their streptokinase to keep up. So, you can see how one bacterial species and one host get locked in this evolutionary dance and would evolve apart from other host-bacterial pairs—ending up with a multitude of variants of streptococci, one for each host."

Such findings also hint that subtle variations in plasminogen genes among humans could partially explain differences in susceptibility to certain infection in different people. Thus, Dr. Ginsburg's laboratory is currently exploring the genetic variations in the blood-clotting system that might affect risk factors for infection. "Although this is speculation at this point, it might ultimately be possible to tailor treatment of infections to the pattern of genetic variability in clotting genes or other pathogenicity factors," concluded Dr. Ginsburg.

**ASBMB Member*

A New Species of Amyloid Peptide

Nicole Kresge, Staff Science Writer

Scientists have identified a new, longer species of amyloid β-peptide that has the potential to be a new target for the treatment of Alzheimer's disease.

The research appears as the "Paper of the Week" in the December 3 issue of *The Journal of Biological Chemistry*, an American Society for Biochemistry and Molecular Biology journal.

One of the characteristic features of Alzheimer's disease is the deposition of amyloid β-peptides in the brain. These amyloid β-peptides are derived from a large amyloid precursor protein through a series of cleavage events. Under normal conditions, cleavage first by α-secretase and then by γ-secretase results in a soluble ectodomain, a short peptide called p3, and an intracellular C-terminal domain, none of which are amyloidogenic. Alternatively, amyloid precursor protein can be processed by the enzymes β-secretase and γ-secretase to produce a soluble ectodomain along with the full-length amyloidogenic amyloid β-peptide and the intracellular C-terminal domain.

Although amyloid precursor protein is found in many cells, its normal biological function is not well understood. "It has been suggested that amyloid precursor protein may function as a receptor or growth factor precursor," notes Dr. Xuemin Xu of The University of Tennessee. "Recent studies also suggest that the intracellular C-terminal domain of the amyloid precursor protein may function as a transcription factor."

While the exact pathogenic role of amyloid β-peptide in Alzheimer's disease has not yet been definitely established, accumulating evidence supports the hypothesis that amyloid β-peptide production and deposition in the brain could be a causative event in Alzheimer's disease. Dr. Xu explains that the literature indicates amyloid β-peptide itself could be toxic to synapses and the accumulation of amyloid β-peptide could initiate a series of events contributing to cell death, including activation of cell death programs, oxidation of lipids and disruption of cell membranes, an inflammatory response, and possibly neurofibrillary tangle formation, which is a close correlate of neuron loss. Therefore, the problem of production, accumulation, and clearance of amyloid β-peptide in the brain emerges as one of the possible rational approaches for the treatment of Alzheimer's disease.

Generally, amyloid β-peptides are around 39-43 amino acid long. Studies have shown that the longer amyloid β-peptides are more amyloidogenic and more pathogenic than the shorter ones. Now, Dr. Xu and his colleagues have discovered a new species of amyloid β-peptide that is 46 amino acids

AAMC Honors ASBMB Members

William Merrick, Professor, Department of Biochemistry, Case Western Reserve University, was recently elected to a three-year term on the Council of Academic Societies Administrative Board. The AD Board serves as the Board of Directors/Council and is an important part of the governance process. Dr. Merrick has been very active in the CAS over the years and currently serves on both the Program Committee and the CAS Task Force on Dual Degree Students and Programs.

Also at that meeting, Diana Beattie, Chair, Department of Biochemistry and Molecular Pharmacology, West Viriginia University School of Medicine, was presented with a plaque commemorating her election as an AAMC Distinguished Service Member. She was elected to this honorary position by the AAMC Executive Council in recognition of her extraordinary contributions to the AAMC over the years.

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.

Ayca Akal-Strader
University of Tennessee, Knoxville

Xian Luo
Loma Linda University

Cagdas D. Son
University of Tennessee, Knoxville

Charles E. Thomas*
University of Michigan

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

long, called $A\beta_{46}$. This $A\beta_{46}$ peptide is produced by γ-secretase at a novel cleavage site, the ζ-site. This site also happens to be the site of a mutation found in early-onset familial Alzheimer's disease called the APP717 or London mutation.

"Another well characterized Alzheimer's disease-linked amyloid precursor protein mutation, the Swedish mutation, also occurs at a major cleavage site, the β-cleavage site at the N-terminus of amyloid β-peptide," adds Dr. Xu. "Studies have shown that Swedish mutation at the β-cleavage site makes the amyloid precursor protein more susceptible to β-secretase activity. The finding that ζ-cleavage site is the APP717 mutation site suggests that the APP717 mutation may cause enhanced production of the longer amyloid β-peptide, $A\beta_{46}$, by influencing the ζ-cleavage. Therefore, this finding may open a new avenue for studying the mechanism by which APP717 mutations cause enhanced production of the longer amyloid β-peptide."

Dr. Xu and his colleagues also discovered that γ-secretase cleavage at the new ζ-site is specifically inhibited by compounds known as transition state analogs, but is less affected by compounds known as non-transition state inhibitors. Specifically, some of these inhibitors, which were previously known to inhibit the formation of secreted amyloid β-peptides, were found to cause an intracellular accumulation of an even longer amyloid β-peptide species, $A\beta_{46}$. "These novel findings provide information important for the strategy of prevention and treatment of Alzheimer's disease, aimed at the design of γ-secretase inhibitors," concludes Dr. Xu. "Since amyloid β-peptide is produced by the sequential actions of β- and γ-secretases, inhibition of these secretases to reduce the production of amyloid β-peptide is believed to be one of the more promising avenues of treatment of the disease. To date, more than one dozen γ-secretase inhibitors have been developed or identified."

by John D. Thompson, Editor

Scripps' Plans for Florida Facility Mired in Feud Over Land Use

Plans for a biotech center in Florida all but halted by opposition to the use of a rural site.

A little more than a year ago, Governor Jeb Bush, the President's brother, announced what he termed a coup as big for Florida as Walt Disney Co.'s arrival in Orlando: Scripps Research Institute of La Jolla would build a major biomedical research facility on the edge of the Everglades in Palm Beach County. Since that announcement, though, a storm of objections from environmentalists and advocates of regulated development has brought plans for Scripps Florida to a halt, at least for the foreseeable future.

What has galvanized opposition to the Scripps center and halted work for the time being is not the project itself, but the spot chosen for it: a former orange grove known as Mecca Farms. The site is 18 miles west of the city of West Palm Beach, adjacent to publicly owned conservation areas and near the scenic Loxahatchee River. Building Scripps Florida on this 1,920-acre site runs counter to mandated rural, low-density land use, environmentalists say. They also claim that it could trigger a boom that would further extend South Florida's sprawl.

For some environmentalists, the vision of building Scripps Florida and related roads, businesses, housing, schools, clinics, and shopping and recreational areas in the inland countryside constitutes the greatest flouting to date of the 1985 law that laid down the rules regulating development and land use in Florida. "They are basically putting a development the size of West Palm Beach out there," Janet Bowman, Legal Director for 1000 Friends of Florida, a group that advocates controlled growth told the *Los Angeles Times*. "Basically, they are ignoring years of growth management policy. If this is not sprawl, then I don't know what is."

That group, the Florida Wildlife Federation, and others have filed two suits in state circuit court in West Palm Beach to try to bar Scripps' use of the Mecca Farms site, claiming that the development would violate the county's own comprehensive plan.

At the moment, the biotech center's designated home is accessible only by dirt road, and lacks water, sewer service and other conveniences. Under the deal hammered out with Scripps under the governor's guidance, those improvements are supposed to be provided at taxpayers' expense, as are the 320,000 square feet of buildings Scripps plans for its offices and laboratories. The county's contribution to the project would be about $600 million; Florida's Legislature has approved $310 million in state funds.

Keith McKeown, Vice President for Communications and Public Relations at Scripps at La Jolla, declined to comment on the legal challenges filed over Mecca Farms, but said his employer remained "guardedly optimistic" the project would be allowed to proceed.

U.S. Pharmaceutical Market Growth to Slow

According to Wood Mackenzie, a provider of consulting services and research products to the energy and life sciences industries, the growth of the U.S. pharmaceutical market is likely to return a compound annual growth rate of 9.7% over the period 2003-2008, dropping below 10% for the first time in recent history.

"Medicare reform, a number of key patent expirations, and relatively slim R&D pipelines are likely to combine to impact the sales growth of the world's leading companies in the US market," said Simon Smyth, senior analyst at Wood Mackenzie Life Sciences. "However, the continued strong performance of key biotechnology companies such as Amgen and Genentech and fast-growing pharmaceutical companies such as Eli Lilly and Hoffmann-La Roche should ensure that U.S. growth continues to outpace that of the global market."

According to the recent Wood Mackenzie report, Big Pharma still faces big problems, including poor pipeline productivity. Wood Mackenzie calculated what it calls a freshness index for the top 10 pharmaceutical firms. The index is determined by the percentage of total sales represented by products launched in the previous five years.

For six of the top 10, the freshness index was roughly 10% or less and the top three (GlaxoSmithKline, AstraZeneca, and Novartis) scored under 25%. For biotechs as a whole, the report says, "As biotechs increasingly retain ownership of their developmental compounds and create more targeted blockbuster drugs, they will grow faster than pharmaceutical companies."

Dharmacon and GE Healthcare to Distribute RNAi in Japan

Dharmacon and GE Healthcare have announced an exclusive distribution agreement in Japan for Dharmacon's RNAi research products. Under the terms of the agreement, GE Healthcare will be the sole distributor of Dharmacon's RNAi products in Japan.

"As an innovator in the field of RNAi committed to expanding our global presence, it is fitting that Dharmacon is joining with GE Healthcare to distribute our products to the Japanese market," said Leland Foster, president and chief executive officer of the Biochemicals group of Fisher Scientific International Inc., which includes Dharmacon. "GE Healthcare is a preeminent supplier of life sciences research products in Japan, and we are very pleased that their expertise and strong on-the-ground presence will be mobilized to support the growth of our RNAi product line in one of the world's most important research markets."

"GE Healthcare has built its respected position in the demanding Japanese research market by providing world class products and premiere customer support," said Keiko Hattori, president of Japan for the Life Sciences division of GE Healthcare. "By adding Dharmacon's leading siRNA technology to our product portfolio, we will address the growing demands of our Japanese customers for state-of-the-art gene silencing technology."

Agilent and ExonHit Working to Optimize Microarray Technology for Splice Variant Analysis

Agilent Technologies Inc. and ExonHit Therapeutics, have announced a research collaboration to combine Agilent's microarray platform and ExonHit's alternative RNA splicing technologies and expertise. This collaboration explores the development of a microarray-based solution that will enable scientists to properly monitor the expression of splice variants.

Splice variants are variable sequences of RNA produced from the same gene in DNA, resulting in the creation of different proteins potentially affecting cellular regulation. Scientists developing therapeutics are increasingly interested in this emerging field as the expression of splice variants can provide novel targets, may indicate disease states, and can be altered by exposure to drugs and toxins.

Agilent and ExonHit are working together to optimize microarray design, reagent protocols and data analysis methods for splice variant studies. While developing alternative RNA splicing, ExonHit realized that the proper characterization of splice variant expression required dedicated profiling platforms. The company has received notice of the allowance of its patent, which broadly claims nucleic acid arrays that enable the detection of alternative RNA splicing events via either intron or exon and splice junction-specific probes.

Initial results from an experimental splicing array of G-protein coupled receptors, designed by ExonHit and produced by Agilent pursuant to the collaboration, were presented at Splicing 2004, an annual symposium on alternative RNA splicing. The array detected multiple isoforms of several genes, and showed good reproducibility and specificity. The companies are expected to work with early test sites to generate additional experimental results.

Georgia Medical College Profit Hits $34 Million

The Atlanta Journal Constitution reported in late November that, "Just five years ago, the Medical College of Georgia was on the edge of financial collapse....State officials took a drastic step, severing ties between the medical center and school, allowing the center to operate as a private enterprise. Within two years, the medical center was in the black. Last year, MCG Health Inc., recorded a $34 million profit. Meanwhile, the medical college is gaining national prominence, having recruited some of the nation's top cardiologists, neurologists and oncologists from prestigious institutions. "

Foreign Student Enrollment in U.S. Declining

By John D. Thompson, Editor

The latest edition of Open Doors' annual report on academic mobility reported a 2.4% decrease in enrollments by students from outside the U.S. in academic year 2003-04. That was the first drop since the 1971-72 academic year and follows upon a year of almost no growth in foreign enrollment.

The November 19 Chronicle of Higher Education, quoted Peggy Blumenthal, Vice President of the report's publisher, the Institute of International Education (IIE), as describing the slump in foreign enrollment as a "wake-up call." The report, Open Doors Two Thousand Four, discusses reasons for the decrease in foreign students in the United States. These include difficulty in getting a visa, higher costs, competition from schools in other English-speaking nations, and the perception of some that foreign students are no longer welcome in the United States.

Columnist Thomas Friedman, wrote in the December 4 *Washington Post*: "If we don't do something soon and dramatic to reverse this 'erosion,' Shirley Ann Jackson, President of Rennselaer Polytechnic and also President of the American Association for the Advancement of Science, told me, we are not going to have the scientific foundation to sustain our high standard of living in 15 or 20 years."

The IIE said this was the first drop in the number of foreign students in more than 30 years. A total of 572,509 foreign students attended American colleges and universities in the 2003-04 academic year, down from 586,323 in 2002-03, and 5% fewer undergraduates from other countries than the year before. However, the number of foreign graduate students increased by 2.5%.

For the third year, India sent the most students to the United States, just under 80,000. That was a 7% increase from the year before. China sent the next highest number, 61,000, but that was down 5% from the preceding year. South Korea was third, with 52,000 students, up 2%, and Japan was fourth, with 40,000 students, an 11% decrease from the year before.

Another survey of 350 institutions, conducted jointly by the American Council on Education (ACE), the Association of American Universities (AAU), the Council of Graduate Schools (CGS), NAFSA: Association of International Educators, and the National Association of State Universities and Land-Grant Colleges (NASULGC), found similar declines in foreign student enrollment.

Of 250 institutions responding, nearly half (47%) indicated a decline in applications, 38% said application rates had not changed, and 14% indicated an increase in application numbers. Of 130 doctoral/research institutions that responded, 59% reported a decline, 28% no change in application numbers, and 11% reported an increase.

All of the 19 that are ranked among the 25 research institutions that enroll the most international students had declines in international graduate applications. Nine of these reported decreases of 30% or more.

Of 216 institutions responding about applications from Chinese graduate students, 48% reported a decline in applications. Declines in applications were more dramatic among the 25 research institutions that enroll the most international students. All 17 institutions that responded to this question indicated declines, with 13 reporting more drastic declines in applications from Chinese students than from their international graduate applicants.

Career Opportunities

LABORATORY RESEARCHER

Researches effects of targeted developmental drugs in the treatment of breast cancer using in vitro/in vivo models. B.S.in Biomed. Sci.,Biochem., or Interdisc. Natural Sci., and 3 yrs exp. in human cancer-related research, including independently performing westerns,and confocal and electron microscopy. 40hr/wk. $35K/yr. Send resume: Moffitt Cancer Ctr, attn: C.R.Schmitt.12902 Magnolia Dr., SRB2, Tampa,Fl 33612

RESEARCH ASSISTANT/ASSOCIATE

Univ of Virginia Health System

The Thoracic Oncology research lab at the University of Virginia–Department of Surgery is looking for a Research Assistant or Associate. The focus of the lab is on transcription and chromatin modifications in lung cancer with an emphasis on basic mechanistic aspects of lung cancer as well as the translational research avenues, including drug development.

To qualify as an Assistant, applicant must have a master's degree or equivalent and as a Research Associate a doctoral degree or equivalent. Successful candidate will be expected to perform standard molecular biology assays, apoptosis and cell survival assays and will work with lung cancer mice models. In addition, the candidate will be involved in grant preparation, research design, reviews of the literature, and in teaching postdoctoral fellows. Position is open until filled.

Please send CV to:
Sharon Jordan, Department of Surgery
PO Box 800709, UVA Health System
Charlottesville, VA 22908-0709

The University of Virginia is an Equal Opportunity/Affirmation Action Employer.

BIOCHEMIST

The Department of Biology of the University of New Brunswick seeks applicants for a tenure track position in Biochemistry. The successful candidate will be expected to develop a strong research program examining biochemical processes in any biological system.

Since this position is central to the Biology-Chemistry degree program, the candidate will be expected to teach a core biochemistry course and to develop other courses in support of this program. A PhD is required and post-doctoral experience is strongly preferred.

Information about the Biology Department can be obtained at www.unb.ca/fredericton/science/biology. All qualified applicants are encouraged to apply, however, Canadian and permanent residents will be given priority. The University is committed to the principle of employment equity.

The closing date is 1 February 2005, or whenever a suitable candidate is found. To apply, send a letter describing your research and teaching interests, a curriculum vitae with the names and addresses of three referees, three representative publications, and a statement of teaching philosophy to:

S. Heard, Chair, Dept. of Biology, University of New Brunswick, Mail Bag Service #45111, Fredericton, N.B. Canada, E3B 6E1.

Applications may also be submitted electronically to biochair@unb.ca.

WEST VIRGINIA SCHOOL OF OSTEOPATHIC MEDICINE

Biochemistry Position Available

Assistant/Associate Professor

The Division of Functional Biology of the West Virginia School of Osteopathic Medicine invites applications for a tenure-track position. The successful applicant must have a Ph.D. in Biochemistry/Molecular Biology expertise (or willingness to develop expertise) in Nutrition preferred. Experience with development of Web-based teaching material is a plus.

The successful applicant will team teach first and second year medical students in the traditional curriculum's biochemistry course, will serve as a facilitator in the problem-based curriculum, and will perform other academic administrative duties (for example, course/system coordinator) as assigned. Mode of professional development is flexible; some research opportunities are available.

Salary and rank commensurate with experience and includes excellent fringe benefit package.

For a unique opportunity to really make a difference, qualified applicants may apply by submitting a current resume, including statements of teaching experience and research interests, and three letters of professional references to: Chairperson, Biochemistry Search Committee, C/O Personnel Office, Box S, WVSOM, 400 North Lee Street, Lewisburg, WV 24901. Applications accepted until position is filled.

The West Virginia School of Osteopathic Medicine is an Affirmative Action/Equal Opportunity Employer and encourages applications from all protected classes.

Calendar of Scientific Meetings

MARCH 2005

FEBS Advanced Lecture Course

March 12–17 • Wildbad Kreuth, Germany
Origin and Evolution of Mitochondria and Chloroplasts
Deadline for application and abstract submission: January 31, 2005; Contact: Prof. J. Soll, Botanik, LMU, München
Menzinger Straße 6780638, München, Germany
Ph: +49 89 17861 244; Fax: +49 89 17861 185
Email:evo05@lrz.uni-muenchen.de

CSBMCB Sponsored Meeting on Cellular Dynamics

March 16–20 • Banff Centre, Banff, Alberta, Canada
This Canadian Society of Biochemistry, Molecular and Cellular Biology sponsored meeting will feature cutting-edge sessions on Nuclear structure, Organelle Inheritance, Imaging Technologies, Protein Folding, mRNA Localization, Organelles of the Secretory Pathway and Systems Approaches to Cell Biology. Keynote Speaker will be Günter Blobel.
Meeting organizer: Email: rick.wozniak@ualberta.ca
Website: www.csbmcb.ca/2004Meeting/index.html

Horizons in Molecular Biology Decoding Nature: Hierarchy of Interactions

March 17–19 • Max-Planck Institute for Biophysical Chemistry in Göttingen, Germany
Email gpmolbio@gwdg.de
Website: www.horizons.uni-goettingen.de

APRIL 2005

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

April 2–6 • San Diego
Nobel Laureates Michael S. Brown and Joseph L. Goldstein will open the ASBMB Annual Meeting with the Herbert Tabor/Journal of Biological Chemistry Lecture.
Contact: ASBMB 2005, 9650 Rockville Pike, Bethesda, MD 20814-3008; Ph: 301-634-7145; Email: meetings@asbmb.org
Website: www.asbmb.org/meetings

The 46th ENC Experimental Nuclear Magnetic Resonance

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

MAY 2005

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

May 8–12 • EuroMedLab, Glasgow, UK
Contact: Jordanhill Campus Southbrae Drive Glasgow 2, UK
Email euromedlab2005@meetingmakers.co.uk
URL http://www.glasgow2005.org

From Gene to Genome: Heredity and Society

May 26–28 • Palais de Congrès, La Grande Motte, France
The half-century long success story of genetics and genomics has had and will continue to have a profound impact on society. It is time to recall how the science of genetics has evolved, and modified several fields of society such as medicine, law, ethics, behaviour. Taking advantage of the 40th anniversary of the Nobel prize awarded to a team from the Pasteur Institute, the French Society for Genetics has invited prominent geneticists, historians and philosophers to address these issues. Contact: Christophe Schwob
Ph: +33 4 95 09 38 00; Fx : +33 4 95 09 38 01
Email : c.schwob@mcocongres.com
Website: www.genetogenome.org

JUNE 2005

7th Annual Plant Sciences Institute Symposium; Meristems 2005

June 2–5 • Iowa State University, Ames, Iowa
Abstracts due April 1, 2005; Registration Deadline May 2, 2005
Student Travel Grants: Applications due April 1, 2005
Contact: Plant Sciences Institute Symposia, Symposium Office, 3208 Molecular Biology Building, Iowa State University, Ames, Iowa 50011-3260; Ph: 515-294-7978; Fax: 515-294-2244
Email: pbmb@iastate.edu
Website: www.bb.iastate.edu/~gfst/phomepg.html

Glycoproteomics—Protein Modifications for Versatile Functions

June 28–30 • Dubrovnik,Croatia
For information: Email: glauc@pharma.hr; Ph: 385 1 4818 757
Website: http://bmb.pharma.hr/glyco2005/

JULY 2005

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

July 2–5 • Budapest, Hungary
Contact: Ms. Franciska Morlin, Chemol Travel Congress Dept. H-1366 Budapest, P.O.Box 28, Hungary
Ph:+36-1-266-7032, Fx: +36-1-266-7033
Email: incoming@chemoltravel.hu; www.febs-iubmb-2005.com

7th International Symposium on Biocatalysis and Biotransformations

July 3–8 • Delft, Netherlands
Contact: Biotrans 2005 Secretariat, Department of Biotechnology, Julianalaan 67 2628 BC, Delft, The Netherlands
Email biotrans2005@tnw.tudelft.nl
Website: www.biotrans2005.bt.tudelft.nl/

BioScience2005 - From Genes to Systems

July 17–21 • Glasgow, UK
Focus topics for the meeting: Cell architecture: from structure to function; The nucleus: chromatin, recombination and repair; Cellular information processing; Proteins in disease; Stem cells and development. Plenary speakers include: Robert J. Lefkowitz, Wolfgang Baumeister, P. Leslie Dutton, Walter Kolch, and David Stuart. Poster abstract deadline: April 15, 2005, Early registration deadline: May 23, 2005
For more information: BioScience2005, Biochemical Society, c/o Commerce Way, Colchester, Essex CO2 8HP
Ph: +44 (0)1206 796351; Fx : +44 (0)1206 798650
Email: info@BioScience2005.org; www.BioScience2005.org

AUGUST 2005

Ninth International Congress on Amino Acids and Proteins

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

SEPTEMBER 2005

Second World Congress on Synthetic Receptors

September 7–9 • Salzburg Congress Centre, Salzburg, Austria
Topics: New approaches in supramolecular chemistry, Theory and practice of self-assembly, Design of synthetic receptors using combinatorial approaches
Molecular imprinting, Nanosystems, Engineered proteins, nucleic acids and saccharides as receptor and catalytic systems, Engineered biomolecules capable of manifesting an additional function, e.g. signal, transduction (molecular wire) or mechanical action (e.g. molecular arms), and Innovation and exploitation.
Call for Papers Abstract Deadlines: 25 March 2005 (oral and poster papers)
For information: Conference Secretariat, Elsevier, The Boulevard, Langford Lane, Kidlington, OxfordOX5 1GB, UK
Tel: +44 (0) 1865 843691; Fax: +44 (0) 1865 843958
Email: jm.seabrook@elsevier.com
Website: www.syntheticreceptors.elsevier.com

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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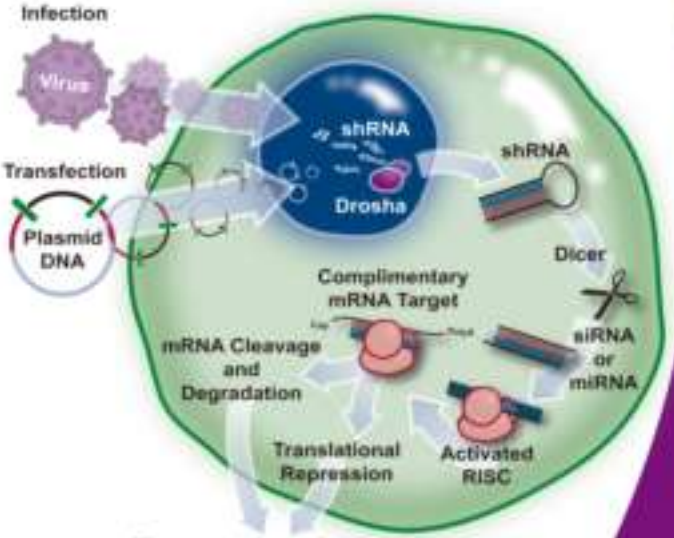

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