

JULY 2005


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# ASBMB Goes to China



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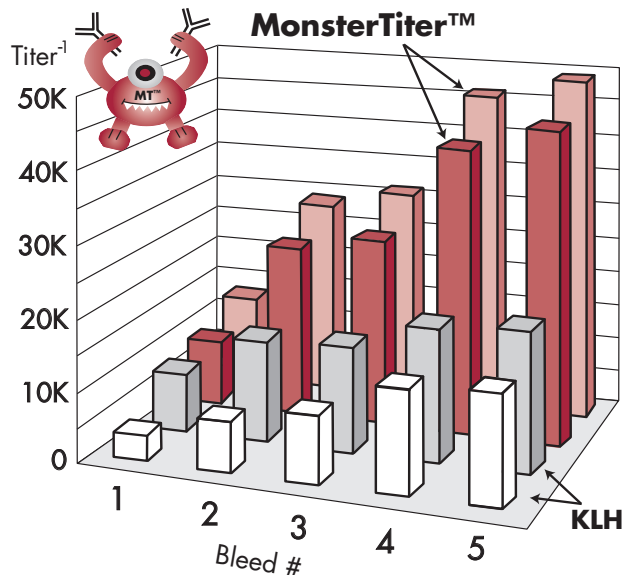
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# ASBMB *Today*

AMERICAN SOCIETY FOR BIOCHEMISTRY AND MOLECULAR BIOLOGY

JULY 2005,  
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## features

4 ASBMB Urges Reforms in Visa Policies

5 House Passes Stem Cell Bill

8 MCP Hosts Protein Identification Workshop

10 Focus on the Future; Shape the Debate

14 From the Yin-Yang of Cyclic Nucleotides  
to Nuclear Receptor Phosphorylation

18 Research on Model Organisms

19 Vital Step in Cell Migration Described

22 New Polysaccharide May Help Combat  
Multidrug Resistance

12



**ON THE COVER:**  
**ASBMB Goes to China**  
**Article page 2**  
**Photos page 12**



AWARDS OF EXCELLENCE:  
MOST IMPROVED MAGAZINE  
COLUMNS & EDITORIALS  
DESIGN & LAYOUT



BRONZE AWARD WINNER 2003

## departments

3 From the Desk of the President

4 News from the Hill

6 NIH News

20 Biotech Business

23 Career Opportunities

24 Calendar

14





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# ASBMB

I have recently returned from an extraordinary visit to the People's Republic of China, as a member of an ASBMB delegation, to begin a dialog with biochemists and molecular biologists there and leaders in the Chinese life science Societies. My message this month provides a snapshot of that visit and what we learned.

The visit was initiated and organized by Dr. Duanqing Pei, Deputy Director of the Guangzhou Institute of Biomedicine and Health (GIBH) of the Chinese Academy of Sciences in Guangdong Province. The GIBH is a new Institute dedicated to building a world-class research organization focused on biomedicine and health; Dr. Ling Chen is the first Director General of the Institute. The GIBH is committed to promoting academic exchanges between China and the rest of the world. The purpose of the visit of the ASBMB delegation was to explore how we and their Societies can interact and how we can help the Chinese in their goal to publish in international journals and make an impact on science that is heard around the globe.

The 'ASBMB delegation' consisted of: Judith S. Bond, President ASBMB, Associate Editor of *The Journal of Biological Chemistry*, and Chair of Biochemistry and Molecular Biology, Penn State University College of Medicine.

Ralph A. Bradshaw, Editor of *Molecular and Cellular Proteomics*, Professor of Physiology and Biophysics, University of California, Irvine.

Edward Dennis, Editor of the *Journal of Lipid Research*, Distinguished Professor of Chemistry, Biochemistry and Pharmacology, School of Medicine University of California at San Diego.

Sharon Stack, Editorial Board Member of the JBC and Associate Professor

of Cell & Molecular Biology, Northwestern University Medical School.

We visited three cities in China during the week of June 3–10, 2005. Each of us presented our latest research and described the journals that we represent at each site. Then we had informal conversations with many of the leaders and scientists, and tours of their research facilities. Our Chinese colleagues were eager for us to see the extensive investment that the government has put into buildings, equipment and personnel to fuel the sciences. It was indeed impres-



ASBMB Delegation with Chinese colleagues from China National Center of Biomedical Analysis. Dr. Fuchu He, Director of the Center is third from the left.

sive growth, and the energy and time that the faculty members and trainees are putting into their work is also impressive. A priority has been set for work in proteomics and stem cell research, and the recruitment of productive Chinese nationals who have had successful scientific training in the USA is the base for the growth of the faculty.

### First Stop: Beijing

In this capital of the nation, we were whisked off to a banquet dinner, immediately upon arrival in China, hosted by Depei Liu, President of Peking Union Medical College and President of the Chinese Academy of Medical Sciences. We will work toward the participation of his scientists and trainees at our ASBMB

# Goes to China

meetings. During the morning of the first full day in Beijing, our 'delegation' presented lectures to a full auditorium of students and faculty in the new Life Science Building at Peking University. Lunch was hosted by the President of Peking University, Zhihong Xu. After lunch Sharon and I had a delightful visit to the Forbidden City, hosted by Zengyi Chang, Professor of Biochemistry and Molecular Biology at Peking University, while Ralph and Ed explored the ancient streets of old Beijing.

Then a visit to the China National Center of Biomedical Analysis. Fuchu He, the Director, led a tour of these facilities. Dr. He is also President of the Institutes of Biomedical Sciences of Fudan University, and Chair of the HUPO (Human Proteome Organization) Human Liver Proteome Project. This project is an international effort to identify all the proteins encoded in the human genome. The vision is to generate "a comprehensive functional map of the liver, to expand the liver proteome to 'Physiome' and 'Pathome,' and to accelerate dramatically the development of diagnostics, prevention and therapeutics towards liver diseases." With the array of equipment (e.g., mass spectrometers, super computers) available, the dedication of the leaders, and the work ethic of the trainees and staff, there is little doubt that they will be successful in reaching their goals. Our 'delegation' was impressed when we visited this institute on a Sunday evening, when it was buzzing with people working at the benches.

Before leaving Beijing, Dr. Zengyi Chang led us on a tour of Peking and Tsinghua Universities—both striking mixtures of building styles, preserving the old/traditional styles and contrasting contemporary (e.g., Russian) architecture. The juxtaposition of the 'old charm' and the 'new efficiency' is com-

mon in China with the 'new world' rapidly winning out.

## Second Stop Guangzhou

The city of Guangzhou is located in the Pearl River delta, near Hong Kong, and is the region's key trading port, formerly known as Canton. Guangzhou is the capital of Guangdong province. Spurred by the outbreak of SARS in 2003, the local authorities have initiated several projects to strengthen its research capability in biomedicine and health. There is major development of biomedical research parks in this area. The Department of Science and Technology of Guangdong Province hosted our visit, and sponsored our presentations at the 'Guangdong Oriental Biomedicine Conference 2005.' Ming Zhang, deputy director general of the department welcomed us on behalf of the local authorities. Dr. Ling Chen moderated our presentations. Again the lecture room was packed with students and faculty from GIBH and other local universities and institutes.

Then, we visited the modern campus of GIBH in the Science City Section of Guangzhou. Dr. Chen gave a brief introduction of the institute and its principal investigators and led a tour of the facilities. The GIBH started operations a year ago, and under the direction of Dr. Chen, has grown to include 15 principal investigators, mostly recruited from overseas. Dr. Chen and his colleagues have launched major initiatives in cancer, infectious diseases and traditional Chinese medicine. Members of the delegation interacted with GIBH principal investigators informally to discuss collaborations and further academic exchanges. Scientists at GIBH have identified mutations in the EGFR kinase domain that appear to be unique for Chinese lung cancer patients. Targeted therapies based on specific kinase inhibitors may offer hope for lung cancer patients in China. That evening

members of GIBH hosted us on a Pearl River cruise complete with an impromptu birthday party for Sharon Stack!



Dr. Judith Bond

## Last Stop Shanghai

In Shanghai we were welcomed by members of the Shanghai Institutes for Biological Sciences (Jiarui Wu, Vice President of the SIBS) and the Chinese Society of Biochemistry and Molecular Biology (Genjun Xu, President of the CSBMB). The CSBMB was founded in 1979, is a member of the IUBMB, and will host the IUBMB meeting in Shanghai in 2009. The CSBMB sponsors meetings, and publishes two journals: the *Chinese Journal of Biochemistry and Molecular Biology* and the *Chemistry of Life*. In Shanghai the science is well established and the scientists are associated with centers focusing on different areas such as Biochemistry, Cell Biology, Biotechnology, Plant Physiology, and a new Neuroscience Institute. The scientists take pride in their scientific achievements and international publications, and have much to be proud of. The mini-symposium that the ASBMB delegation participated in also had speakers from the SIBS. The president of the SIBS, Dr. Gang Pei, hosted lunch on our final day in Shanghai, and confirmed the wish for interactions and support of our Societies.

Overall, our visit to the world's most populous country and fastest growing economy provided the clear message that Chinese science has gone global, and is on its way to contributing to scientific advances in a major way. Biochemistry and molecular biology are fundamental to their growth, and we expect that we will see the products of their labor through collaborations, presentations at our meetings and manuscripts in our journals.

For more pictures, see page 12.

Judith Bond, President of the ASBMB



by Peter Farnham, CAE, ASBMB Public Affairs Officer

# ASBMB Urges Reforms in Visa Policies for Foreign Students, Scholars

**O**n behalf of the Society, ASBMB President Judith Bond has signed a document calling for reforms in the U.S. visa system. ASBMB was one of a group of 40 leading academic, science, and engineering associations that urged the U.S. government to accelerate its effort to reform the visa process for international students, scholars, and researchers. The full statement is available on the ASBMB website under the "What's New" column.

The May 18 statement is a follow-up to one issued last year by a coalition of ASBMB and many of the same groups. The statement expressed appreciation for "significant recent improvements to the U.S. visa system" but pointed out that "considerable barriers remain." The statement said that additional steps are needed to help dispel the "misperception that our country does not welcome these international visitors, who contribute immensely to our nation's economy, national security, and higher education and scientific enterprises."

The misperceptions caused by these barriers, the statement said, "must be dispelled soon, or we risk irreparable damage to our competitive advantage in attracting international students, scholars, scientists, and engineers, and ultimately to our nation's global leadership."

The organizations represent nearly all of the higher education and research communities, as well as many businesses and industries vital to the U.S. economy. The groups, led by the Association of American Universities (AAU)

and the American Association for the Advancement of Science (AAAS) (staff of which drafted the statement), made six recommendations for reducing or eliminating barriers that they said cause undue hardship for the type of visitors, who for decades have helped to sustain the nation's leadership in science and innovation.

The group made the following recommendations:

- ❖ Extend the validity of Visas Mantis security clearances for international scholars and scientists from the current two-year limit to the duration of their academic appointment. This would be similar to the extension provided recently for international students. The change "would prevent redundant security checks that can waste resources and cause unnecessary delays and hardships," the group wrote.
- ❖ Allow international students, scholars, scientists, and engineers to renew their visas in the U.S. Visitors who leave the country for any reason, such as attending an academic conference or visiting family, need a visa to return. Currently, the visa renewal process must be initiated and completed outside the U.S., usually in the applicant's home country. The group proposes allowing individuals to complete, or at least initiate, the process before leaving the U.S., to facilitate their return and enable them "to continue their studies and research uninterrupted."
- ❖ Renegotiate visa reciprocity agreements with key sending countries to

extend the duration of visas for citizens of each country and permit multiple entries on a single visa. The U.S. maintains reciprocal visa agreements with other countries under which U.S. policy toward visitors from those countries matches their policy toward U.S. citizens. Agreements with some countries, such as China, are very restrictive. Negotiations with China have already begun.

- ❖ Amend inflexible requirements that lead to frequent student visa denials. Current law requires student visa applicants to demonstrate that they have a residence and employment opportunities to return to in their home country, and that they intend to return. Nearly half of the visa denials for international students from certain countries occur on the basis of this requirement. The group recommended that Congress amend the law to focus less on these criteria and more on applicants' financial ability and intent to fulfill a course of study in the U.S. They said this change would help to prevent the loss of many highly qualified students.
- ❖ Develop a national strategy to promote academic and scientific exchange and to encourage international students, scholars, scientists, and engineers to pursue higher education and research opportunities in the U.S. The strategy, the group said, should include visa reforms as well as other efforts by both the government and the academic community to "counter prevailing negative per-

*Continued on page 6*

# House Passes Castle/DeGette Stem Cell Bill

**T**he House approved H.R.810, the Stem Cell Research Enhancement Act, on May 24 in a surprisingly bipartisan vote. The bill passed 238-194, with 50 Republicans joining all but 14 Democrats.

H.R.810, introduced by Reps. Michael Castle (R-DE) and Diane DeGette (D-CO) would allow human embryonic stem cell research to be conducted on surplus embryos in cold storage at IVF clinics. Embryos slated for such use would have to be identified as no longer going to be used, the donors would have to sign informed consent agreements, and there could

*Bush's latest statement appeared to firmly slam the door shut on any compromise.*

be no monetary incentive to donate the embryos. Estimates are that as many as 400,000 such embryos are currently in storage. The vast majority of these will be destroyed without ever being brought to term.

ASBMB President Judith Bond applauded the bill's passage on May 25, stating: "On behalf of ASBMB, I thank the House of Representatives for the strongly bipartisan vote on the Castle/DeGette bill. The fact that many members of both parties joined together to support this important legislation accurately reflects the support a majority of the American people have for medical research, and the promise of stem cell research in particular.

"We hope the Senate will quickly take up the legislation and pass it forthwith.

"ASBMB also urges the President not to veto the bill, but rather, work with the legislation's supporters in the House and Senate—many of whom are senior Republicans—to come to an agreement on how to expand medical research in this most promising area.

"Expanded opportunities to conduct federally-funded research on human stem cells will pay off for our country by greatly expanding the range of treatments for many of the illnesses that continue to plague our citizens."

The House floor debate was passionate on both sides, and got quite emotional with several members coming close to tears as they described illnesses suffered by family members, and how they consequently wanted research to proceed. Opponents were equally as passionate, citing their view that embryonic stem cell research entails the destruction of human life and that this is morally and ethically wrong, regardless of whatever good the research might accomplish.

The President has vowed to veto the bill should it reach his desk, a position he made clear yesterday in a photo op with parents and their children who had been adopted as frozen embryos (Bush referred to them as "snowflake babies"). Republican supporters of H.R.810 are reportedly going to talk with the President to see if there is a compromise position that could be adopted, to avoid a veto.

The House also passed a second stem cell bill, introduced by Rep. Christopher Smith (R-NJ). Smith's bill would establish a bank in which cord blood cells would be maintained. The bill was widely seen as an alternative to the Castle/DeGette bill, and many believed it was introduced in hopes that Repub-

licans would support it in lieu of H.R.810. However, many Republicans said they would support both bills.

To see how your representative voted on the bill, H.R. 810, see <http://clerk.house.gov/evs/2005/roll204.xml>.

The stem cell issue has now gone to the Senate, where Senator Sam Brownback (R-KS) has vowed to filibuster it. Brownback has introduced legislation in the past two congresses to ban embryonic stem cell research. Senator Orrin Hatch (R-UT), a prominent backer of embryonic stem cell research, believes he may have the votes to invoke cloture, which would cut off a filibuster should one be launched. It is unclear whether stem cell research supporters have the votes to override the filibuster if invoked; it takes 60.

At a press conference held to discuss the need for quick action on the bill, Senator Arlen Specter (R-PA) who is suffering from Hodgkin's Disease and currently undergoing chemotherapy was particularly passionate. He said that when he looks in the mirror these days he hardly recognizes himself (he has lost most of his hair and appears to have aged dramatically over the past year). He called support for stem cell research critical for patients who were very ill, including "myself."

Bush reiterated his vow to veto the bill. There had been a trace of ambiguity in his first statement on the matter, his latest statement appeared to firmly slam the door shut on any compromise. Press reports indicated that Rep. Dave Dreier (R-CA), chairman of the House Rules Committee and a prominent right-to-lifer, will work with former First Lady Nancy Reagan to try to convince the President to soften his stand. ❧

# NIH Researchers Discover How Insulin Allows Entry of Glucose into Cells

**R**esearchers from the National Institutes of Health have discovered the critical sequence of events by which insulin stimulates the entry of glucose into fat cells.

The study, appearing in the May 9, 2005 *Journal of Cell Biology*, was conducted by researchers from the National Institute of Child Health and Human Development and the National Institute of Diabetes and Digestive and Kidney Diseases.

"This finding provides useful information for understanding disorders in which cells have difficulty using insulin, such as insulin resistance and type 2 diabetes," said NICHD Director Duane Alexander, M.D.


Glucose is a nutrient that cells need to survive, noted the study's corresponding author, Joshua Zimmerberg, Chief of NICHD's Laboratory of Cellular and Molecular Biophysics. Glucose is ferried through the cell's outer covering, or membrane, by a family of molecules known as glucose transporters. In the study, the researchers discovered how glucose transporter 4 (GLUT 4) carried insulin into fat cells.

Previously, scientists had learned that, within the cell, GLUT 4 is contained in the membrane of tiny sacs known as vesicles. Another author of the current study, Dr. Samuel Cushman of NIDDK's Diabetes Branch, had found earlier that GLUT 4 was transferred from the vesicles within the cell to the cell membrane, when the vesicles combined, or fused with, the membrane. Researchers had been unable to determine, however, where in the cell the vesicles were stored and how insulin stimulated them to fuse with the cell membrane.

In the current study, the NIH researchers observed fat cells taken from mice and learned that the GLUT 4 vesicles are highly active. They discovered that, although a few vesicles are scattered throughout the cell, the majority circulate just under the cell's surface. The vesicles travel along a railroad track-like network of molecules known as microtubules. When insulin binds to the cell's outer surface, those vesicles immediately stop moving, tether to the cell's inner surface, then fuse with the cell membrane. GLUT 4, contained in the vesicles' membrane, then enters the cell membrane, where it ferries glucose into the cell.

The researchers made their observations using total internal reflector flo-

rescent microscopy. This consists of aiming a laser beam at an angle at the glass cover slip beneath the microscope, explained the last author of the paper, Dr. Vadim A. Frolov, Ph.D., of NICHD's Laboratory of Cellular and Molecular Biophysics and the Russian Academy of Science in Moscow. The light bounces off the cover slip, away from the microscope's lens. However, residual energy from the light passes through the cover slip, to the cell beneath, illuminating the area just below the cell's surface while leaving the inside of the cell dark.

"When we started the experiment, we thought that the vesicles would be stationary," Dr. Zimmerberg said, "but they looked like comets streaking by." 

## Visa Policies continued ...


*Continued from page 4*

ceptions of studying and conducting research in the United States..."

❖ The government should not require that export licenses be obtained for international scientists and engineers to use equipment for unclassified, fundamental research in the U.S. The Department of Commerce is considering a new requirement that export licenses be obtained before certain foreign nationals may use specialized scientific equipment for unclassified, fundamental research. It would apply even to researchers who had undergone a Visas Mantis security review. The group argued that such a requirement could further discourage top international scientists and engineers from working in the U.S.

"We reiterate our commitment to work with the federal government to improve the visa system," the group

statement concluded. "That system should maintain our nation's security by preventing entry by those who pose a threat to the United States and encouraging the entry of the brightest and most qualified international students, scholars, scientists, and engineers to participate fully in the U.S. higher education and research enterprises. Such a system will foster American scientific and economic competitiveness. We commend the federal government for the improvements made to the visa system to date, and we look forward to continuing to work together for these further needed changes."

ASBMB has recently conducted a survey of biochemistry department chairs at graduate and medical schools on visa problems they have experienced for foreign scholars and students. A report on the results of this survey will appear in the next issue of *ASBMB Today*. 



# Harmful Chemicals May Reprogram Gene Response to Estrogen

**N**ew research shows that exposure to harmful chemicals and drugs during critical developmental periods early in life may actually “reprogram” the way certain genes respond to the female hormone estrogen. This genetic reprogramming may determine whether people with a genetic predisposition for a disease actually develop the disease.

The new research shows that when rats with a genetic predisposition to uterine tumors also receive an early-life exposure to diethylstilbestrol (DES), a synthetic form of estrogen linked to vaginal cancer, the incidence of uterine tumors rises to almost 100 percent. By comparison, slightly more than half of the unexposed animals, those having only the genetic defect, developed the uterine tumors.

DES is a drug that was prescribed for women from 1938 to 1971 to prevent miscarriages and premature deliveries. Daughters of women who used DES are at increased risk for reproductive tract abnormalities, pregnancy complications such as ectopic pregnancies and preterm deliveries, infertility, and a rare vaginal and cervical cancer called clear-cell adenocarcinoma. Other research conducted by NIEHS scientists indicates that women exposed to DES in utero have a higher risk of uterine fibroids.

The National Institute of Environmental Health Sciences provided funding to researchers at the University of Texas M.D. Anderson Cancer Center for the two-year study. The study results were published in the May 2005 issue of the *Proceedings of the National Academy of Sciences*.

“This study is telling us that an environmental reprogramming of a normal

response, combined with an inherited gene defect, work together to promote cancer,” said NIEHS Director David Schwartz. “If this model is correct, it will help doctors determine which individuals are more likely to develop cancers of the uterus, breast and prostate.”

The finding should alert doctors to ask more questions about a patient’s early-life exposures to chemicals and other harmful agents in order to better predict that person’s cancer risk.

“Most people with a family history for a particular disease are concerned about their recent exposures to harmful agents in the environment,” said Cheryl Walker, Professor of Molecular Carcinogenesis at the Anderson Cancer Center and lead author on the study. “We are just beginning to realize that exposures received decades earlier, during critical developmental stages, may be much more important in determining who develops cancer as an adult.”

The researchers used a special strain of rats with a defect in a gene called Tsc-2 (tuberous sclerosis complex 2) that made them more susceptible to uterine leiomyomas, benign tumors that are common in women over 30 years of age. These rats were then treated with DES during days 3, 4 and 5 of life, during a critical period of uterine development.

Once the rats reached adulthood, almost 95 percent had developed the uterine tumors. Furthermore, the tumors were much larger and more numerous than those in genetically defective rats not receiving the DES treatment. “These data suggest that environmental exposures during development of the uterus can interact with a preexisting genetic susceptibility to increase the risk of dis-

ease,” said Walker. “We are looking at a new kind of gene-environment interaction that determines who gets cancer and who doesn’t.”

According to Walker, the increase in frequency and size of the uterine tumors is due to DES’ ability to influence estrogen, a female hormone that is involved in promoting the growth of tumors by regulating the activity of key genes involved in cell growth. “We found that the DES treatment somehow ‘reprogrammed’ how these genes respond to estrogen, making them much more responsive to estrogen than normal,” he reported. “We realized that the DES exposure enabled estrogen to drive the tumor development when combined with a genetic predisposition.”

While DES exposure can lead to the development of vaginal and cervical cancers, the fact that most DES-exposed women did not develop the cancers suggests that genetic predisposition is an important part of the equation.

This is not the first study to suggest that cancer risk is influenced by both genetic and environmental factors. A 2003 study of Jewish women born with a defect in BRCA1, a gene linked to inherited forms of breast and ovarian cancer, showed that those women born before 1940 had a much lower risk of developing breast cancer than women born after 1940. The researchers believe this discrepancy is due to differences in diet, exercise, hormonal factors and chemical exposures.

Walker believes more research needs to be done to test this concept, and said, “NIEHS is partnering with the National Academy of Sciences to fund additional research on early-life exposures and cancer risk in human populations.”

# MCP Hosts Protein Identification

Organizers: Mike Baldwin, Ralph A. Bradshaw, Al Burlingame, and Steve Carr.

**T**he field of proteomics covers a wide range of endeavors employing an impressive array of technologies and experimental paradigms. However, central to these efforts is the identification of proteins and the co-/post-translational modifications that characterize their mature (active) forms as well as their dynamics in response to extracellular cues. Indeed, the value of most large scale proteomics experiments hinges to a considerable degree on the accuracy of these determinations. Although there are a number of ways to do this, mass spectrometry, and in particular tandem mass spectrometry (MS/MS), has become the core technology because of its efficiency, accuracy and sensitivity. When coupled to various separation methodologies and appropriate isotopic labeling, it can produce hundreds of identifications and quantitative measurements from a single experiment. These are generally based on fragmenting the proteins in the sample with a highly specific enzyme such as trypsin and separation of the peptides followed by selective 'sequencing' in the mass spectrometer. The sequence ion series are then compared to a data base for final putative identification. A variation on this methodology that requires only a single stage of MS (i.e., to obtain m/z and intensity data) is peptide mass mapping, which is quite effective in identifying proteins in simple mixtures, such as found in spots from 2D gels, and depends on matching the masses of the peptides against those calculated theoretically from suitable databases.

The power of these approaches is already considerable and they certainly have not been maximally developed or exploited. Even so, their application to finding new and more effective bio-

markers for diagnosing difficult to detect diseases, e.g ovarian cancer, as one use is already a major enterprise worldwide. It is not unreasonable to expect these and related efforts to multiply in the coming years. However, there are problems associated with these approaches that are required for large scale experiments and they have already begun to manifest themselves. The most serious of these is the large and growing number of misidentifications. These arise for a variety of reasons, most related to human error, which can range from poor sample preparation, incorrect standardization of the instrument, and poor quality data, to over extending the capacity of the identification software and even errors in the databases themselves. Unfortunately some of this incorrect information is finding its way into the literature and is thus threatening the integrity of the scientific record. Given the size of typical experiments and the speed with which data can be collected, this can not be seen as either a minor issue or a passing phenomenon.

About two years ago, the editors and associate editors of MCP began to seriously consider this problem and what could be done about it. It was their conclusion that there were several responses possible but that defining a set of criteria for the publication of such data was an important place to begin. Accordingly, an ad hoc committee composed of several editors and interested colleagues, chaired by Steve Carr of the Broad Institute of MIT and Harvard (and an Associate Editor of MCP) labored diligently to produce a working set of guidelines. These were adopted and promulgated by MCP, along with an explanatory document, (Carr et al. 2004), The need for guidelines in publication of peptide and pro-

tein identification data, *Mol. Cell. Proteomics* 3, 531-33), as a point of departure. Several meetings, forums and discussions followed that underscored the seriousness of the problem and that generally recognized the Carr guidelines as an important beginning.

Although these guidelines were useful to the editors and reviewers of MCP, it was clear from the outset that guidelines for MCP alone would not act as a general solution to the larger problem. What was required was a refinement of the Carr guidelines into a more universal set of guidelines and their broad adoption by all journals interested in the publication of such data. This of course included not only the other journals devoted to proteomics but also journals such as the *JBC*, *Science*, *PNAS*, *Cell*, *Nature*, etc. that publish limited numbers of protein identification papers (but ones that are generally important). To achieve this conversion, it was clear that we would need a group of individuals that were representative of the 'stakeholders' in this problem, to wit, editors/referees/publishers, vendors of germane instruments, software developers/purveyors, organizations (e.g. the Human Proteome Organization (HUPO) and the European Bioinformatics Institute (EBI)) and most importantly practitioners of the art. It was also clear that the group had to be limited in size if an actual document was to be produced, even in draft form. After some discussion, Mike Baldwin, UCSF (and a member of the MCP Board) 'accepted the baton' and agreed to be the chief organizer. In a little more than two months, a suitable venue was identified (La Maison de la Chimie, Paris), an appropriate cast identified and confirmed (30 participants from all over the world) and an

# Workshop

agenda set. The meeting took place May 12-13, and with a great deal of hard work from all concerned produced the desired draft.

Although built on the framework of the Carr guidelines, the new document is considerably modified and extended. It deals with issues not covered in the original guidelines, such as quantitation, and should, when completed, provide a rigorous but useable set of instructions to authors that will help enormously in standardizing the protein identification literature and eliminating misidentifications. The discussions also underscored some of the remaining problems that presently lie outside the scope of the guidelines and solutions for them. One of these is

the issue of depositing raw data at a site that can be linked to a journal but that is separate from it. MCP is exploring developing a modest test of such a site in coordination with the Broad Institute that could, if successful, grow into a major operation with substantial and widespread support.

The draft document produced in Paris will for the next three months or so be very widely circulated to a much larger group of interested parties for comments, criticisms and suggestions. These will be incorporated as appropriate by the four subgroups present at the Paris meeting (into the sections that they produced) to yield the final draft. This document will then be circulated to all germane publishers/editors for their ratification (and

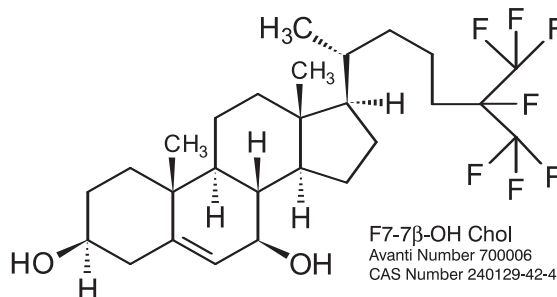
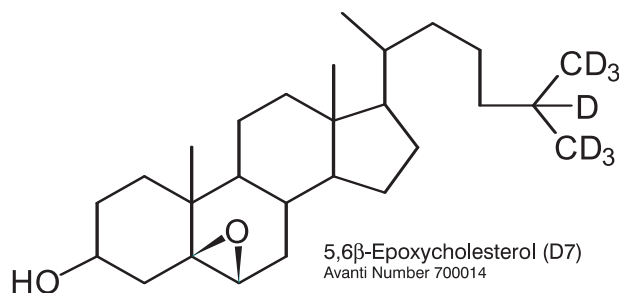
hopefully adoption). It is our intention that the entire process be completed by January 1, 2006.

The overall success of the Paris meeting cannot be judged until the editorial process is complete and the final document is in hand. However, based on the enthusiasm of the participants as we finished up the initial draft, prospects for bringing these standards into general use seem quite high. Sufficiently so that we closed the workshop in the finest French tradition—with a glass of champagne!

The organizers and the ASBMB are grateful to Prof. Pierre Potier and Ms. Helene Waisman for making the facilities of La Maison de la Chimie available and for their excellent support throughout the meeting. ☺

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# The Education and Professional Development Theme for the 2006 Meeting: Focus on the Future, Shape the Debate

By Ellis Bell, Chair, Education and Professional Development Committee

**T**he 2006 Meeting in San Francisco marks a special occasion: the centenary of the Society, a celebration of the past and a focus on the future. The Education and Professional Development Committee is sponsoring three major symposia, and two plenary talks, one where the Society's new Education Award will be presented for the first time, and, in conjunction with the Minority Affairs Committee, a symposium focusing on outreach and public awareness, and the Undergraduate Poster Competition. As part of the focus on the science done primarily in undergraduate institutions there will also be a MAC-EPD jointly sponsored symposium featuring faculty and student speakers presenting the results of NIH- and NSF-funded research at undergraduate institutions.

The meeting will start on Saturday, April 1, with the Undergraduate Poster Competition, organized, as in the past several years, by Phillip Ortiz, Mark Wallert, Joe Provost, and Marilee Benore Parsons. At the San Diego meeting over a hundred posters by undergraduates across the country were presented and the competition involved some 40 judges selecting 4 awardees. The Poster Competition, which started in 1997, has steadily involved increasing numbers of students, and over 200 undergraduates are expected to participate next year in San Francisco. In San Diego, this event was sponsored in part by 10 graduate programs: Auburn University, Brigham Young University, National Institutes of Health Graduate Partnerships Program, Pennsylvania State University, Texas A&M University, University of New Mexico School of Medicine, University of North Dakota, School of Medicine and Health Sciences, University of Texas Southwestern Medical Center at Dallas, University of

Texas Health Science Center at San Antonio, and Virginia Tech. This sponsorship enabled undergraduates to talk to program directors and graduate admissions directors, as well as to graduate students who also attended the competition.

The timing and the format of the Poster Competition in San Francisco are designed to maximize the networking opportunities for the undergraduates and undergraduate faculty, and to allow the Society to open its centennial meeting by focusing on the future—the undergraduates who will become the next generation of molecular life scientists.

The competition will start at 1 p.m. and as in the past several years will involve two judging sessions, one from 1 p.m. to 2:30 p.m. and a second from 3:00 until 4:30 p.m. Between the two judging sessions there will be a 30-minute break with refreshments. As in San Diego, the Graduate School sponsors of the event will be in the event hall, and undergraduate students and their faculty mentors will have the opportunity to talk with them throughout the afternoon. A new feature of the Undergraduate Poster Competition will be a plenary talk for the participating undergraduates and their faculty by Nobel Laureate Edmund Fischer which will

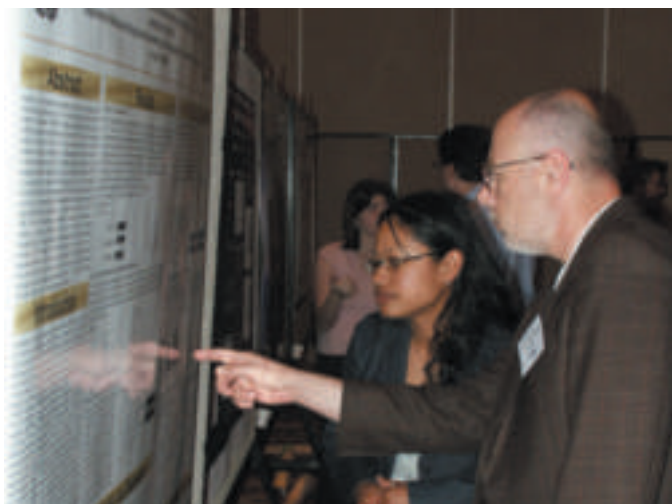
*ASBMB President Judith Bond chats with Peter Kennelly, Chair of Biochemistry at Virginia Tech, who participated in the grad tables at the Poster Competition.*

begin at 4.45 p.m., and lead into the opening plenary of the meeting at 6 p.m. where ASBMB President Judith Bond will announce the four undergraduate first place awards. Following this session will be a catered reception, for which participating undergraduates and their faculty mentors who have registered for the meeting will receive complementary invitations.

In addition to this focus on undergraduates on the opening day of the meeting, there will be a symposium on Monday morning, April 3, featuring invited undergraduates and faculty from primarily undergraduate institutions talking about the science being done in these institutions that is sponsored by NSF and NIH. These talks will highlight research conducted by undergraduates in four major areas: Protein Structure and Function, Signal Transduction, Gene Regulation, and Cellular Biochemistry. Undergraduate speakers will be invited based upon the abstracts submitted for the Undergraduate Poster Competition.

Clearly the expanding involvement of undergraduates in the meeting is part of the "focus on the future" in the title. What about the "shape the






*Judge discussing poster with student.*

debate” component? The formal symposia sponsored by the Education and Professional Development, and Minority Affairs Committees throughout the meeting will be helping to shape the debate in the arenas of public awareness of science, with a symposium organized by Mike Cox, University of Wisconsin, on evolution; a symposium focusing on outreach and service learning organized by Neena Grover of Colorado College and Thomas Landefeld, California State University, Dominguez Hills. The needs for industry will be addressed in a session chaired by Ron Niece, Research Resource & Technologies, and Greg Bertenshaw, Clearant Inc. The morning of the final day of the meeting will address “The Classroom of the Future: Who we Teach, What we Teach and How we Teach,” with presentations by National Academies of Science President Bruce Alberts, Ken Wesson, and Diane O’Dowd from UC Irvine.

In addition to the formal symposia being organized, there will be opportunities for faculty and students to network throughout the meeting with NSF and NIH program officers, graduate school representatives, and of course with the speakers from the various sessions.

The Undergraduate Poster Competition and the various Education, Professional Development and Minority Affairs components of the 2006 meeting offer an exciting venue for both undergraduates and their faculty mentors to present their science and to network and connect with their futures. As in the past, ASBMB has a number of travel awards to assist student and undergraduate faculty attendance at the meeting. The Undergraduate Affiliates Network (UAN) program also offers travel awards to participating schools and programs. Application dates for the various travel awards are before the abstract submission dates, so keep an eye on the ASBMB web page, [www.asbmb.org](http://www.asbmb.org), *Enzymatic*—the UAN newsletter, and *ASBMB Today* for more information in the coming months.

Be part of the celebration; help shape the future.  
See you in San Francisco. 



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As part of the 2005–06 Centennial Celebration of ASBMB and the *Journal of Biological Chemistry* (JBC) we are asking you to tell us what it was like:

- ✦ At the Atlantic City meetings.
- ✦ When you gave your first lecture at an ASBMB Annual Meeting.
- ✦ Serving as an ASBMB officer or Council member.
- ✦ Getting your first paper accepted—or rejected—by the *JBC*.
- ✦ Great teachers and professors who were ASBMB members and what you learned from them.
- ✦ The first ASBMB meeting you attended.
- ✦ Why you recommended ASBMB membership to students.
- ✦ What ASBMB membership has meant for you and what it can mean to today’s undergrads and postdocs.

These are just some of the things we are looking for to help us in celebrating our Centennial and to tell your fellow members and potential new members about what ASBMB means in terms of camaraderie, research, and science’s contribution in making this a healthier and happier world.

Please send your comments and any photos you have—particularly those from years past—via email to John D. Thompson, Editor, *ASBMB Today*, at [jthompson@asbmb.org](mailto:jthompson@asbmb.org).



# ASBMB

## Beijing



**Above: President Bond with Professor Zhihong Xu.**



**Above: Duanqing Pei and Sharon Stack.**



**Above: Ralph Bradshaw and Ed Dennis.**



**ASBMB Delegation with Chinese colleagues from China National Center of Biomedical Analysis.**



**Professor Genjun Xu and Professor Jianli Wu**



# Goes to China

*Dr. Ling Chen, Director of the Guangzhou Institute of Biomedicine and Health with Dr. Ed Dennis.*



## Guangzhou

*ASBMB Bond, Dr. Gang Pei, ASBMB Stack, Professor Jiarui Wu.*



*Above: ASBMB delegation at the GIBH; Director Ling Chen in the middle.*

## Shanghai



*Celebrating Sharon Stack's birthday on a Pearl River cruise.*



*ASBMB delegation and Shanghai scientists discuss future joint activities.*

# Reflections of a French Woman: From the Yin-Yang of Cyclic Nucleotides

By Cécile Rochette-Egly  
Institut de Génétique et de Biologie Moléculaire et Cellulaire

*When I was asked to write this article, I re-read some of my early publications and I realized that, although the topics and the approaches appeared to be different from what I am doing right now, in fact there was an undoubtable evolutionary link: signaling pathways and cell fate through phosphorylation processes. That is the extraordinary and fascinating aspect of research, work is constantly in progress. If some questions are solved, other are continuously asked, opening new horizons and increasing the complexity of the systems.*



*The IGBMC (Institute of Genetics and Molecular and Cellular Biology) located in Illkirch just outside the city of Strasbourg, France, was inaugurated in October 1994. It was a stunning accomplishment by Pierre Chambon who succeeded in building the first public research institute in France to be funded with private industry money. Ten years later, the IGBMC counts more than 500 scientists and according to the Institute for Scientific Information, its productivity (publications in journals with an impact factor—20) ranks fourth in the world among institutions of molecular biology and genetics and second outside the United States.*



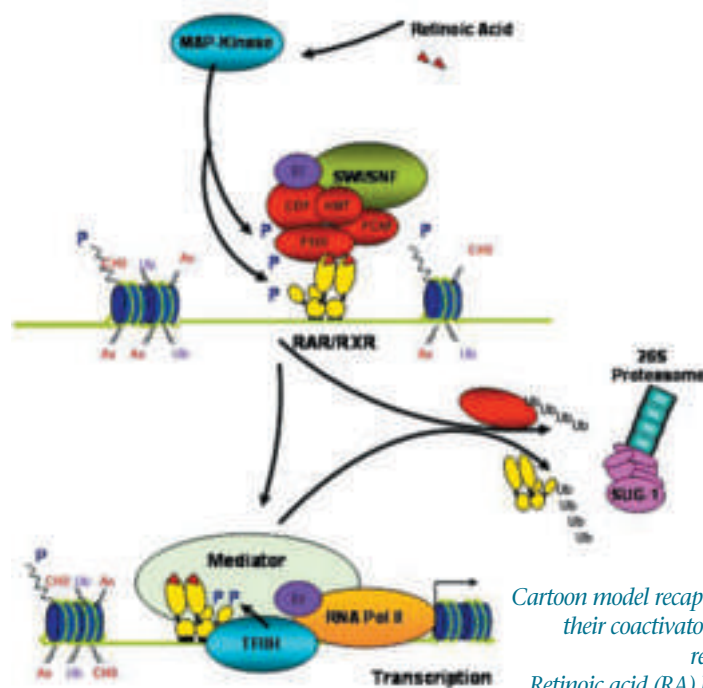


# to Nuclear Receptor Phosphorylation

## Cyclic nucleotides as second messengers: the yin and the yang

After studies in pharmacy, in the late seventies, I was introduced to research by Dr. Monique Castagna in Villejuif. At that time, in Paris, only men were teaching science at the university and were team leaders. She was one of the few women with a research position and getting research funding was rather difficult. She was just coming back from Dr. E.G. Krebs' laboratory where cAMP-dependent protein kinase was characterized and located in the adenylate cyclase pathway.

At that time the new concept was that cyclic nucleotides, cAMP and cGMP were the second messengers necessary and sufficient to transduce a signal from the membrane. As these messengers depicted reciprocal variations in response to a signal, their action was named Yin-yang, which according to Oriental concepts is the symbol of opposed forces. In that context, I studied the production of cyclic nucleotides in response to Phorbol esters, interferon or hormones, in relation to their effects on cell growth and differentiation. This work highlighted cyclic nucleotides, not really as "second messengers" but rather as "regulators" of several physiological functions. However at that time, the general significance of cyclic nucleotides and their fundamental mechanisms could not be appreciated due to the lack of the adequate tools.



Cartoon model recapitulating how RARs and their coactivators are phosphorylated in response to Retinoic Acid.

Retinoic acid (RA) binds to cognate nuclear receptors bound at response elements located in the promoters of RA-target genes. Then liganded RARs trigger a dynamic and coordinated recruitment of a series of coactivators which will methylate, acetylate, and ubiquitinate histones and remodel nucleosomes. RA also activates p38MAPK which phosphorylates both RARs and their coactivators. Phosphorylation cooperates with the ligand for signaling the destruction of coactivators by the proteasome.

This process continues many times with the purpose of recruiting all the coactivators with an essential function in chromatin remodeling, leading to the displacement of impeding nucleosomes within the proximal promoter region and thus facilitating the arrival of RNA PolII and GTFs. At this step, TFIID becomes able to interact with NRs and the cdk7 kinase subunit phosphorylates their AF-1 domain. This phosphorylation process participates to the assembly of the transcriptional preinitiation complex (PIC). Then RARs are degraded by the ubiquitin proteasome system facilitating transition to elongation and providing an efficient mechanism for attenuating the transcription signal.

## Signaling to the nucleus: Phosphorylation of nuclear retinoid receptors

The best way to make progress in signaling was to associate my knowledge in cell biology with the new tools of molecular biology. Thus I joined the group of Pierre Chambon who has been "riding the big waves of molecular biology" for more than 30 years. One can imagine how honored I felt, especially as a young women entering this chapel of uncompromising men, working day and night. However such a context was the major challenge for women of my generation, holding two professions—research and family.



*Dr. Rochette-Egly, at far right, with her lab members. In front row are (from left to right) Jean-Luc Plassat, Engineer; Annie Bauer, Engineer; Nathalie Bruck, Ph.D. student; and Emilie Gaillard, Ph.D. In rear are Pd. D. students Gaetan Bour and Sebastien Lalevée.*



In 1988, the genes encoding the nuclear receptors for retinoic acid (RARs) had been just cloned in Chambon's lab and I had been assigned to characterize the corresponding RAR proteins. During the next decade, this field evolved very rapidly with our discovery that RARs, which work as ligand-dependent transcription activators, are phosphoproteins and that such phosphorylation processes cooperate with retinoic acid for transcription through controlling the dynamism of RAR association/dissociation with coregulators and their degradation by the ubiquitin-proteasome pathway.

I made, in collaboration with my husband's group, the novel and rather unexpected discovery that RARs are phosphorylated by the cdk7/cyclin H complex within the General Transcription Factor TFIID. The interesting feature of this finding is that the phosphorylation process results from a docking of TFIID subunits to RARs, allowing the efficient recognition of the phosphorylation site by the cdk7 kinase subunit. Ongoing studies performed in the field revealed that TFIID-mediated phosphorylation of RARs occurs when both the receptors and TFIID are recruited at the response element and the promoter respectively, subsequent to the ordered and coordinated recruitment of a series of coactivators remodelling the chromatin structure and thereby paving the way for the transcription machinery and TFIID. We concluded that, in fine, phosphorylation by TFIID is crucial for the transcriptional activity of RARs and therefore for the antiproliferative and differentiative action of retinoic acid.

The most plausible hypothesis is that this is done through helping or alleviating interactions with other transcription regulators, thereby improving the formation of the Preinitiation complex (PIC).

However, complexity came with the finding that RAR-mediated transcription is also influenced by additional phosphorylation processes involving MAPKs. Indeed, we recently evidenced that RA can rapidly activate p38MAPK. The mechanism of this activation has not been elucidated yet, but p38MAPK can phosphorylate the RAR gamma isotype at a serine residue adjacent to the cdk7 site. Phosphorylation by both cdk7 and p38MAPK is necessary to control the dissociation of repressors and to signal the ubiquitylation and subsequent degradation of the receptor by the ubiquitin-proteasome pathway. It remains to be determined whether this dual phosphorylation controls the recruitment of complexes with ubiquitin-ligase activity. In fact, complexity is still increasing since RA-activated p38MAPK also phosphorylates RARs coactivators, thereby indirectly controlling RAR transcriptional activity.

Finally, as the logical result of my previous work, I found that the cAMP-dependent protein kinase (PKA) also

phosphorylates RARs in response to cAMP signaling. The pertinence of this observation was that phosphorylation by PKA propagates an allosteric signal influencing the conformation of distinct surfaces involved in the recruitment of TFIID subunits and thereby phosphorylation by the cdk7 subunit. We reconstituted a cascade, where cyclicAMP is indeed a second messenger influencing cellular functions through the phosphorylation of transcription activators such as RARs and thereby the expression of a battery of target genes.

## **Motivation and funding**

During the last decade, science progressed very fast and my group opened new horizons on how RAR transcriptional activity is regulated. We demonstrated that the action of the ligand, retinoic acid is not restricted to orchestrating a series of coregulator exchanges allowing chromatin remodelling and paving the way for the recruitment of the transcription machinery. Indeed, we found that Retinoic acid also makes RAR able to be phosphorylated by the cdk7/Cyclin H subcomplex of the General Transcription Factor TFIID and by p38MAPK.

These new data added new pieces to the puzzle through the demonstration that phosphorylations cooperate with the ligand for transcription of retinoic acid target genes. Though the importance of these phosphorylation processes is becoming increasingly clear, the complexity is also increasing, and the challenge of the future will be to answer newly arising questions, such as whether phosphorylations by TFIIH and by p38MAPK occur in the same time-slot and how they control the dynamics of the association/dissociation of coregulators and which ones. The final important point is that many RA-resistant tumoral processes are characterized by amplified or aberrant kinase activities, raising the hypothesis that other kinases can target RARs and providing new insight into cancer mechanism and therapy.

### Women still under-represented, but making progress

At the European as well as at the international point of view, I am one of the few women in the field of nuclear receptors. Moreover, at the IGBMC, which is composed of 7 departments with 39 teams, only 20 percent of the team leaders are women. There is no doubt that such an under-representation is not due to the fact that women are less competent or less qualified than men, but reflects unconscious thinking and behaviors on both the men's and women's sides. Indeed, during the last decades women had to outperform men in order to obtain equivalent scientific recognition. I must admit that today, in the French university and

academic system, among the under-thirties, women are even more represented than men. However, they are still under-represented in the higher tenure positions and as speakers in scientific conferences.

What will be the future for the new generations? In preparation for this, the European Commission has announced its intention to ensure a better integration of women scientists in the new Sixth Framework Program (2002-2006). Similar ideas have been taken up in France by the Agence Nationale de la Recherche. As a result, the participation of women in peer-review panels and in assemblies has markedly increased (from 10 percent to 20 percent) during the last few years. At the American level, ASBMB contributes efficiently in this as international meetings are co-organized by a man and a woman. ♪

## 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.

Daryl L. Arkwright-Keeler  
Western Michigan University

Iva Dostanic  
University of Cincinnati

Scott J. Salsman  
University of Oklahoma

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

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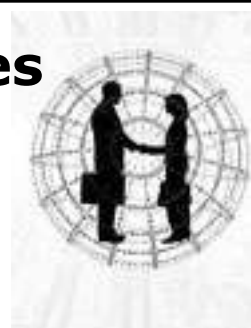
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# The Prognosis for Research on Model Organisms

**T**hough more than millions of described species live on Earth, most basic knowledge about the properties of cells has come from study of just a few “model organisms,” including the bacterium *Escherichia coli*, the yeast *Saccharomyces cerevisiae*, the nematode worm *Caenorhabditis elegans*, the mustard plant *Arabidopsis thaliana*, the fruit fly *Drosophila melanogaster*, and the mouse *Mus musculus*. But investments in biomedical research often are justified through their potential applications to human disease. As researchers increasingly gain the ability to study diseases directly in humans, will research on model organisms decline?

That’s unlikely, says Stanley Fields,\* a Howard Hughes Medical Institute investigator at the University of Washington, and Mark Johnston at Washington University School of Medicine in St. Louis, in an article published in the March 25, 2005, issue of *Science* entitled, “Whither Model Organism Research?”

“Funding pressures and calls for translational research are orienting research toward humans and human diseases,” said Dr. Fields. “But there’s still a lot to be gained by studying model organisms.”

With that said, however, Fields and Johnston believe that within the next few decades, research into model organisms will reach a pivotal juncture. Starting with yeast and progressing through the more complex organisms, the basic biology of model organisms will be “solved,” they said. In other words, biologists will understand, at least in outline, all of the basic mechanisms of the cell, including the functions of nucleic acids and proteins, the signaling pathways by which cells communicate, and the selective expression of subsets of genes.

“Our contention is that at some point, no basic biological processes in these organisms will be obscure,” said Dr. Fields, who has spent much of his career studying genetic processes in yeast. “Within twenty to thirty years, for example, we predict that there won’t be key biological processes in yeast that we don’t understand, even if we don’t know every detail of those processes. At that point, we will have to face the fact that we have been very successful in what we set out to do,

*“Funding pressures and calls for translational research are orienting research toward humans and human diseases. But there’s still a lot to be gained by studying model organisms.”*

*—Stanley Fields*

and we’ll have to move on.”

“Some people will say that to speak in terms of a ‘solution’ is ridiculous, but I believe they are wrong,” said Dr. Johnston, also a specialist in yeast genetics. “Of course, you can always find more detailed questions to answer. But the basic biology of these organisms will be understood at a reasonable level of detail.”

Once that biology is understood, the character of model organism research inevitably will change. In some cases, the quantity of research on an organism may decline, as happened with *E. coli* in the 1980s. However, Fields and Johnston insist that model organisms will remain critical to future investigations of

human biology, for five main reasons.

First, model organisms will continue to provide insights into basic cellular processes, even after the organisms’ basic molecular mechanisms have been solved. For example, when a human gene involved in a disease is identified, researchers often will be able to examine the function of a homologous gene in model organisms. “For basic cellular processes, you want to work with the simplest organism that carries out that process,” said Fields.

Second, biologists will continue to use model organisms to examine disease processes more directly. For instance, Alzheimer’s disease, Parkinson’s disease, and Huntington’s disease all involve misfolding or aggregation of proteins, and similar molecular malformations occur naturally or can be induced in yeast, worms, and flies. Model organisms have genes involved in aging that may play analogous roles in humans. Studies of yeast will shed light on diseases caused by single-celled organisms, just as studies of fruit flies could help control the mosquitoes that carry malaria.

Third, model organisms will be essential to understanding the complex biological networks that control life processes. Basic cellular processes such as DNA replication involve elaborate molecular mechanisms with many components acting in multiply connected ways. Studying how these networks operate “will bestow upon biologists the predictive powers and design capabilities long held by physicists and engineers,” Fields and Johnston write. In particular, study of molecular networks will be essential in understanding complex diseases, which result from the effects of many

*Continued on next page*

# Vital Step in Cellular Migration Described by UCSD Medical Researchers

**A**vital molecular step in cell migration, the movement of cells within the body during growth, tissue repair and the body's immune response to invading pathogens, has been demonstrated by researchers in the University of California, San Diego (UCSD) School of Medicine. Published in the March 27, 2005, online edition of *Nature Cell Biology* and the journal's April print edition, the study describes how the interaction of alpha4 integrin adhesion receptor with a protein called paxillin creates directional movement of a cell by inhibiting a protein called Rac.


"Understanding how this protein contributes to directional movement of a cell provides a new insight into cell migration and ultimately could lead to therapeutic interventions in autoimmune diseases such as multiple sclerosis and Crohn's disease," said the paper's first author Naoyuki Nishiya, a

postgraduate researcher in the lab of senior author Mark Ginsberg,\* UCSD professor of medicine. "Since cell migration plays an important role in the immune response, as leukocytes move toward targets, a therapy that stops that movement could potentially help in autoimmune disorders where the body's immune system incorrectly attacks the body's own tissue."

From the genesis of human life to birth and beyond, cell migration is a complex, extremely important process that is not completely understood by researchers. In order to move, a cell must be polarized so that the molecular processes at the front end and back end are different, leading only to forward movement. One of the first steps in cell migration is the initiation of activity by Rac that extends protrusions out of the cell. These protrusions serve as tractor sites for migration as the cell moves toward its intended tar-

get. If Rac were active throughout the cell, it would extend protrusions in all directions, in essence keeping the cell in one place.

Until now, researchers have had limited understanding of the molecular mechanism that inhibits Rac activity in the back of the cell, to maintain directional movement. In laboratory experiments with human and animal cells, the UCSD team discovered that the alpha4 integrin recruits enzymes that block Rac activity only at the rear of a crawling cell.

The scientists noted that alpha4 integrins are widely expressed in neural crest cells, immune system leukocytes (such as T cells), striated and smooth muscle, and neurons. For this reason, they believe the mechanism used by alpha4 integrins to localize Rac activity may participate in a wide variety of cell migratory and pathfinding events. 

\*ASBMB member

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*Continued from previous page*  
genes and environmental influences working together. "Model organisms will be the proving ground for studies of complex diseases, which is the frontier in biology," said Johnston.


Fourth, critical questions of biological variation and diversity will be investigated using model organisms. Biological traits can change depending on small differences in large numbers of genes. These relationships will need to be understood in model organisms before diversity in other organisms can be understood, said Fields and Johnston.

Fifth, model organisms will remain the proving ground for developing and

testing new technologies. Already, model organism research has led to the ability to isolate and manipulate genes, purify and characterize proteins on a large scale, and profile and control gene expression. Indeed, the more that is known about model organisms, the more useful they will be in developing new technologies, and "the people who had the biggest impact on biology have been the people who have developed new tools," said Johnston.

"Ten or twenty years from now we probably wouldn't come up with the same list" of potential uses for model organisms, said Fields. "Other areas that we could have mentioned include

infectious diseases, the development of immunity, and ecological systems — how organisms fill niches." As Fields and Johnston write in their paper, exploring these and other research areas, both in model organisms and in the great many largely unstudied organisms, "is certain to occupy [biologists] for a long time."

According to geneticist Maynard Olson at the University of Washington, Fields and Johnston's paper is "interesting, constructive, and provocative." It asks "new kinds of questions," which helps push biological research in new directions. 

\* ASBMB member.

by John D. Thompson, Editor

## Cardiovascular Drug Market to Top \$100 Billion by 2008

The world market for prescription cardiovascular medications, which topped \$75 billion in 2004, will surpass the \$100 billion mark by 2008, according to a new report released June 9. However, growth in the market is uneven—certain therapeutic classes are on the decline while some niche areas show double-digit annual growth, according to the study by Kalorama Information, a division of MarketResearch.com.

The study, *The Worldwide Market for Prescription Cardiovascular Drugs*, found that generic competition will significantly impact established areas of

cardiovascular therapy, such as diuretics, which will record negative growth over the next five years. Newer emerging therapeutic classes are driving the market forward and more than making up for the losses. Antiplatelet agents, for example, have shown nearly 20 percent annual growth over the past three years and will continue to post strong revenue growth through 2009 with at least six new drugs in late-stage clinical trials or awaiting approval.

“The aging population is driving the cardiovascular market forward as a whole,” notes Mary Anne Crandall, the

principal author of the study, “But it’s the new drugs and, particularly, new combination products that are changing clinical practice and providing the major opportunities for manufacturers.”

The study examined eight major segments of the cardiovascular market, including cardiac glycosides and positive inotropic agents, antihypertensives, antiarrhythmics, vasodilators and peripheral vasodilators, antihyperlipidemics, blood modifiers, diuretics, and other cardiovascular drugs. In addition, the report details epidemiology and demographics, covers major trends—such as OTC statins, combination product development, and potentially new approaches to hypertension—and provides competitive market share for the major players in each segment.

## Biotech Stocks Are Standing Still, Why?

If you look at Genentech’s performance on Wall Street so far this year, you might conclude that biotech stock may be a sure thing. As of mid-June, Genentech’s shares had soared 49.2%, to \$81.25. This can be attributed to upbeat news reports about its drugs to treat cancer and macular degeneration.

This is the sort of news that typically pulls in investors, but the average for biotech stocks overall seems less appealing. The American Stock Exchange Biotechnology Index, which includes Genentech, was up just 1.1% since January, and the NASDAQ Biotechnology Index was down 11.7%.

On June 13, *BusinessWeekonline* commented that investors have become more picky when it comes to biotech. Rather than buying stocks based on news about a firm’s drug-development strategy, they’re turning to companies with actual products. It quoted Dallas Webb, Senior Vice-President of Equity Research for financial services provider Stanford Group Co., as stating, “People

aren’t listening as much to the hype.”

Biotech investors have also been turned off by the FDA’s recent crack-down on drug safety. “Not only are they afraid the FDA will be cautious about approving new drugs, but they’re afraid [the agency] will attack drugs that are already on the market,” said Alex Zisson, a partner at venture-capital firm Thomas, Mc Nerney & Partners. The consequences can be bleak, as Biogen Idec Inc. shareholders learned in February when the firm pulled its multiple sclerosis drug, Tysabri, off the market when a couple of patients developed a potentially fatal side effect. Shares nosedived 42.5%, to \$38.65, that day.

*BusinessWeekonline* suggested that investors might regain some confidence in the sector if the small companies start scoring some successes. Unfortunately, the vast majority of biotech companies still don’t have any FDA-approved products, which means they remain years away from profitability.

## Advancis Launches Antibiotic in the U.S.

DataMonitor reports that Advancis Pharmaceutical has launched an oral formulation of the respiratory tract infection drug Keflex in the U.S. Keflex is approved for treatment of respiratory tract infections caused by *S. pneumoniae* and *S. pyogenes*; otitis media due to *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*; and skin and soft tissue infections due to *staphylococci* and/or *streptococci* as well as several other bacterial infections.

Keflex Powder is now available in 125 mg/5 mL and 250 mg/5 mL strengths in two bottle sizes, 100ml and 200ml.

Advancis acquired Keflex from Eli Lilly in July 2004. The product launch completes the process it has been working on to commercialize an oral form of the drug.



## FDA Official Sees Genetics as Key to Personalized Healthcare

Within the next five years, pharmacogenomics will take a stronger hold in medicine, with genetics becoming key to drug development and providers moving toward a more personalized approach to healthcare, a U.S. Food and Drug Administration (FDA) official pre-

dicted at the May Bio-IT World Conference + Expo in Boston.

“I think we’re going to see some rapid changes” in how genetics is used in healthcare and drug development, said Lawrence Lesko, Director of the FDA Office of Clinical Pharmacology and Biopharmaceuticals in the

Center for Drug Evaluation and Research. The FDA is focused on the role of genetics and the emerging importance of pharmacogenomics, which are drugs developed using genetics, and is putting into place related guidelines and regulations, said Lesko, offering an overview of what the FDA has done recently in that regard.

As for genetic testing, Lesko forecast that standard test platforms will be adopted in the next few years and there also will be more complete testing available to patients. As an offshoot of that progress, problems with interpreting test results will be lessened as vendors “are going to see a business here.” There already are point-of-care testing systems hitting the market, and those will become more widespread and reliable, as will predictive algorithms for test interpretation.

Pharmacogenomics also will be incorporated into guidelines for standards of care, Lesko said. Although in somewhat limited use today, genetics testing enables doctors to alter drug dosages based on a patient’s genome, which can reveal, among other things, how well an individual will tolerate particular drugs.

Support for genetics-based medicine must come from insurance providers before “personalized medicine” becomes the norm, he said. Insurers are beginning to provide reimbursement for genetics testing and other elements of personalized medicine, Lesko said. Such medical care involves taking into account not only an individual’s genome, but also other aspects of the patient, including age, weight and family history.

### UNC, Wilmington Focusing on Marine Biotechnology

North Carolina, is one of 20 states with a coastline and the ocean and its products are an important element of the North Carolina economy. The University of North Carolina, Wilmington (UNCW), is currently striving to take advantage of the state’s ocean resources by exploring three areas of marine biotechnology.

Speaking at a recent biotech business conference UNCW Chancellor Rosemary DePaolo outlined the institutions goals as:

**Mariculture:** Research in this area can help sustain harvestable marine species, such as flounder and black sea bass.

**Biosensor technology:** Monitoring the health of the ocean and intra-coastal waterways by using detectors that can warn of pollution, the approach of harmful algal blooms, the invasion of new species, and other possible threats.

**Potential drug discovery:** By examining cultured marine microbes obtained from the ocean, the potential for new drugs is possible. The ocean, with its immense biodiversity, appears to offer a

great potential source of new leads for the pharmaceutical industry. UNCW scientists are placing their research emphasis on organisms that will yield value-added products. Examples include drugs from the sea like the cystic fibrosis therapeutic agents, nutraceuticals like omega fatty acids as dietary supplements, and food fishes from mariculture.

A key element in UNCW’s strategy is the Center for Marine Science, an interdisciplinary program that provides research opportunities for faculty, visiting faculty, graduate and undergraduate students, and postdocs. Core resources and other research-enhancing activities and facilities have been developed to optimize the Center for creative endeavors. Interdisciplinary research has been emphasized through unique projects, and shared equipment is purchased on an annual basis. “The spectroscopy core facility is one of the finest in the Southeast,” said DePaolo, “and the laboratories look more like biomedical and molecular laboratories than field marine laboratories.”

# New Polysaccharide May Help Combat Multidrug Resistance in Cancer

By Nicole Kresge, Staff Science Writer

**I**n a recent study published in the *Journal of Biological Chemistry*, scientists report that a molecule previously thought to play a purely structural and inert role in cells is actually involved in multidrug resistance in cancer. Using antagonists for this molecule, the researchers were able to sensitize drug resistant breast cancer cells to chemotherapeutic drug treatment.

The research appears as the "Paper of the Week" in the May 27 issue of the *Journal of Biological Chemistry* (2005, 280: 20310-20315), an American Society for Biochemistry and Molecular Biology journal.

Multidrug resistance is very common in most types of cancers, making it one of the leading problems in cancer therapy. It is often caused by an increase in the cell's production of proteins that transport drugs out of the cell, preventing the drugs from combating cancer.


Previously, Dr. Bryan P. Toole\* and his coworkers, Drs. Suniti Misra and Shibnath Ghatak, of the Medical University of South Carolina noticed that small pieces, or oligomers, of a polysaccharide called hyaluronan were able to sensitize drug-resistant breast cancer cells to several different chemotherapeutic drugs. He believed that the polysaccharide oligomers were binding to a receptor for hyaluronan (called CD44) and preventing it from initiating a signaling cascade that would result in drug resistance.

"It is very surprising that hyaluronan is involved in drug resistance,"

admits Dr. Toole. "Most scientists think of hyaluronan as a structural and inert molecule. In adult tissues it plays two roles. First, it assists in tissue hydration and in biophysical properties such as resilience. Second, it forms a template to which matrix proteins attach and form important extracellular structural complexes." Hyaluronan also accumulates around the outside of cells during disease processes such as early atherogenesis, persistent inflammation, and cancer. In recent years, however, hyaluronan has also been shown to induce signaling pathways in inflammatory, embryonic and cancer cells.

In their current *Journal of Biological Chemistry* paper, Dr. Toole and his colleagues report on further studies which indicate that hyaluronan increases the cellular production of a multidrug transporter protein by binding to CD44. They discovered that antagonist molecules that bind to hyaluronan and prevent it from interacting with CD44 were able to sensitize multidrug resistant breast cancer cells to chemotherapeutic drugs. The researchers also found that increasing hyaluronan synthesis in cells increased resistance to drug treatment.

"Our work indicates that hyaluronan antagonists, for example small hyaluronan oligomers, reverse the malignant properties of cancer cells, including proliferation, invasiveness, and drug resistance," explains Dr. Toole. "Hyaluronan oligomers are non-toxic, non-immunogenic, and readily appli-

cable to several proliferative disease processes, especially cancer. We are hoping that hyaluronan antagonists can be used in conjunction with chemotherapy such that much lower and less toxic doses of chemotherapeutic agents can be used." 

\*ASBMB Member


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## Former JBC Editorial Board Member Honored by University of the Pacific

The University of the Pacific has appointed Dr. Giuseppe Inesi the recipient of the Dr. Earl R. and Tannia Hodges Endowed Chair in Physiology. Dr. Inesi, a professor of physiology, became the first named endowed chair at the Arthur A. Dugoni School of Dentistry.

A portion of the Hodges' gift to Pacific will be utilized to promote advanced scholarship, teaching, research and outreach in physiology for a five-year period.

Dr. Inesi has taught at Pacific for 33 years, one of the longest serving faculty members at the School of Dentistry. During his tenure at Pacific, he is credited for securing and renewing an NIH program grant for his research on calcium transport proteins.

An accomplished educator and research scientist, he has authored nearly 200 articles in medical, dental and scientific journals, while holding positions on several editorial boards including that of *The Journal of Biological Chemistry*. 

# Career Opportunities

## UNIV OF MICHIGAN

The University of Michigan, College of Pharmacy, invites applications for a senior level Endowed Professorship position and a junior level Endowed Assistant Professorship position in the Department of Pharmaceutical Sciences (<http://sitemaker.umich.edu/pharmaceuticalsciences>).

### Ara G. Paul Assistant Professorship

This tenure-track position in the College of Pharmacy will also have a joint appointment with the new Life Sciences Institute (<http://www.lifesciences.umich.edu/institute>).

Applicants should have research expertise in one of the pharmaceutical sciences as well as genetics and genomics as applied to the pharmaceutical sciences. A focus in one or more of the following areas is preferred: cellular and molecular membrane transport, cellular enzymatic activation and metabolism of pharmacological agents, and cellular or sub-cellular targeting to enhance drug efficacy.

### Ara G. Paul Professorship

This position is in the College of Pharmacy with a joint appointment with the new Life Sciences Institute ([www.lifesciences.umich.edu/institute](http://www.lifesciences.umich.edu/institute)).

Applicants must have outstanding research expertise in one of the pharmaceutical sciences as well as genetics and genomics as applied to the pharmaceutical sciences. A focus in one or more of the following areas is preferred: cellular and molecular membrane transport, cellular enzymatic activation and metabolism of pharmacological agents, and cellular or sub-cellular targeting to enhance drug efficacy.

Applicants for both positions must demonstrate a strong record of leadership in research and professional activities and a strong commitment to graduate training and teaching.

Interested individuals should send curriculum vitae, future research plans, and three representative publications to the Search Committee Chair via US Mail and email a PDF file to [tjasin@umich.edu](mailto:tjasin@umich.edu)

The Search Committee will begin reviewing applications immediately and

preferential treatment will be given to those applications received before August 1, 2005. Submit the requested information to: Professor Gordon L. Amidon, Search Committee Chair, College of Pharmacy, The University of Michigan, 428 Church Street, Ann Arbor, MI 48109-1065. Telephone 734-615-3749; Fax: 734-615-6162; email: [tjasin@umich.edu](mailto:tjasin@umich.edu).

The University of Michigan is an Equal Opportunity / Affirmative Action Employer.

## PLANT BIOCHEMICAL GENETICS, ASSISTANT PROFESSOR in BIOCHEMISTRY

### University of Nebraska-Lincoln

A joint, tenure-track Assistant Professor in Biochemistry position is currently available in the Plant Science Initiative and Department of Biochemistry at the University of Nebraska-Lincoln. The position is 80% research/20% teaching. As part of a newly emerging Nutritional Genomics Center, the successful candidate is expected to maintain a vigorous research program focused on biochemical genetics of plants. Research may include plant secondary metabolism, metabolic profiling, nutritional genomics, and

genetic regulation of plant metabolism. Teaching responsibilities include teaching one graduate or undergraduate level course annually in a relevant area, and mentoring students. A Ph.D. and post doctoral experience in plant genetics, biochemistry or related field is required. Salary is commensurate with qualifications and experience. Review of applications will begin June 20, 2005, and continue until the position is filled or the search is closed. Applicants should go to <http://employment.unl.edu/> and complete the Faculty/Administrative Information form and then send complete application file, consisting of a statement of research interests, CV and arrange for three letters of recommendation be sent, to Search Committee Chair, Assistant Professor Biochemical Genetics, N300 Beadle Center for Genetics Research, University of Nebraska-Lincoln 68588-0660. UNL is committed to a pluralistic campus community through affirmative action and equal opportunity and is responsive to the needs of dual career couples. We assure reasonable accommodation under the Americans with Disabilities Act. Contact Dr. Sally Mackenzie at (402) 472-6997 or [smackenzie2@unl.edu](mailto:smackenzie2@unl.edu) for assistance.

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# Calendar of Scientific Meetings

## AUGUST 2005

### **Ninth International Congress on Amino Acids and Proteins**

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

### **2005 International Gap Junction Conference**

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

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

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

## SEPTEMBER 2005

### **Second World Congress on Synthetic Receptors**

**September 7–9** • Salzburg Congress Centre, Salzburg, Austria  
Abstract Deadlines: 25 March 2005 (oral and poster papers)  
For information: Conference Secretariat, Elsevier, The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, UK  
Tel: +44 (0) 1865 843691; Fax: +44 (0) 1865 843958  
Email: jm.seabrook@elsevier.com  
Website: [www.syntheticreceptors.elsevier.com](http://www.syntheticreceptors.elsevier.com)

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

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

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

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

### **International Conference on Enzyme Technology RELATENZ 2005**

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

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

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

## OCTOBER 2005

### **Supramolecular Chemistry**

**October 14-19** • Obernai (near Strasbourg), France  
A European Science Foundation conference. For information:  
Ph: +33 (0)3 88 76 71 35; Fx: +33 (0)3 88 36 69 87  
Email: [conferences@esf.org](mailto:conferences@esf.org)

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

**October 21-22** • North Carolina Biotechnology Center, Research Triangle Park, NC. 2005  
Deadline for registration and abstract submission: July 1  
Email: [stu\\_maxwell@ncsu.edu](mailto:stu_maxwell@ncsu.edu)  
Website: <http://www.med.unc.edu/pmbb/nc-rna-soc.html>

## NOVEMBER 2005

### **International Workshop on Biosensors for Food Safety and Environmental Monitoring**

**November 10-12** • Agadir, Morocco  
Contact: Université Hassan II-Mohammedia, Faculté des Sciences et Techniques, B.P. 146, Mohammedia, Morocco  
Email [a.amine@univh2m.ac.ma](mailto:a.amine@univh2m.ac.ma)  
Website: [www.univh2m.ac.ma/biosensors](http://www.univh2m.ac.ma/biosensors)

## DECEMBER 2005

### Xth PABMB Congress: Panamerican Association for Biochemistry and Molecular Biology

December 3-6 • Hotel del Bosque, Pinamar, Province of Buenos Aires, Argentina

Organized by the Argentinian Society for Research on Biochemistry and Molecular Biology (SAIB). The Congress will consist of five Plenary Lectures, eighteen Symposia, nine sessions of oral communications, and three poster sessions.

For more information contact:

SAIB President. Ernesto Podestá: ernestopodesta@yahoo.com.ar  
SAIB Secretary Carlos Argaraña: carga@dqbf.fcq.unc.edu.ar, or  
PABMB Chairman Juan José Cazzulo: jcazzulo@iib.unsam.edu.ar  
website: <http://www.saib.org.ar>

### Non-Vesicular Intracellular Traffic

December 15-16 • Goodenough College, London, UK  
Contact: Meetings Office, Biochemical Society, 3rd Floor, Eagle House, 16 Procter Street, London, WC1V 6NX  
Email: [meetings@biochemistry.org](mailto:meetings@biochemistry.org)  
Website: [www.biochemistry.org/meetings/focused.htm](http://www.biochemistry.org/meetings/focused.htm)

## FEBRUARY 2006

### Third International Conference on Ubiquitin, Ubiquitin-like Proteins, and Cancer

February 9-11 • The University of Texas M. D. Anderson Cancer Center, Houston, Texas

This meeting will celebrate the Nobel Prize awarded to Avram Hershko, Aaron Ciechanover, and Irwin Rose for their discovery of the ubiquitin pathway and the 10th anniversary of the discovery of SUMO/Sentrin and NEDD8

Application and Abstract Submission Deadline: Friday, November 11, 2005; For information contact: Amy Heaton Program Manager, Department Of Cardiology University of Texas M. D. Anderson Cancer Center  
Tel: 713-745-6826; Fax: 713-745-1942  
Website: [www.sentrin.org](http://www.sentrin.org)

## MARCH 2006

### Gordon Research Conference (GRC) on New Antibacterial Discovery & Development

March 5-10 • Ventura Beach Marriott, Ventura, California  
For Information: Email: [trevor.trust@astrazeneca.com](mailto:trevor.trust@astrazeneca.com)  
Website: [www.grc.org/programs/2006/antibact.htm](http://www.grc.org/programs/2006/antibact.htm)

## RNAi2006: Advances in RNA Interference Research

March 22-23 • St. Anne's College, Oxford, UK  
Conference Organizer: Muhammad Sohail  
Biochemistry Department, University of Oxford  
Tel: +44 1865 275225; Fax: +44 1865 275259  
Email: [muhhammad.sohail@bioch.ox.ac.uk](mailto:muhhammad.sohail@bioch.ox.ac.uk)  
Website: <http://libpubmedia.co.uk/Conferences/RNAi2006HomeMay2005.htm>

## APRIL 2006

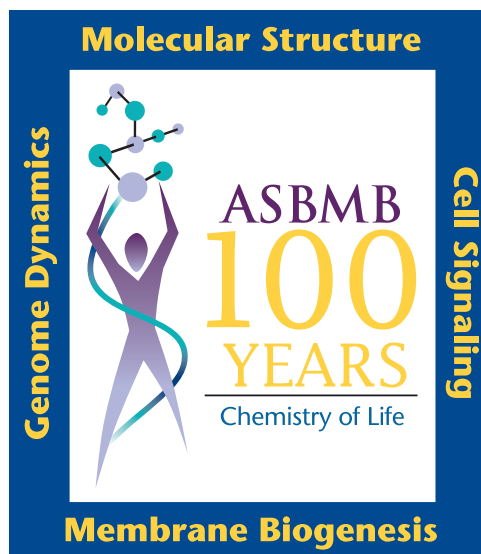
### ASBMB/JBC Centennial Celebration Held in Conjunction with EB 2006

April 1-5 • San Francisco  
Contact: ASBMB 2006, 9650 Rockville Pike  
Bethesda, Maryland 20814-3008  
Ph: 301-634-7145; Email: [meetings@asbmb.org](mailto:meetings@asbmb.org)  
Website: [www.asbmb.org/meetings](http://www.asbmb.org/meetings)

## OCTOBER 2006

### International Conference of Immunogenomics and Immunomics

October 8-12 • Budapest, Hungary  
A joint meeting of 2nd Basic and Clinical Immunogenomics and 3rd Immunoinformatics (Immunomics) Conferences  
Email: [diamond@diamond-congress.hu](mailto:diamond@diamond-congress.hu)  
Website: [www.bcii2006.org](http://www.bcii2006.org)



# ASBMB/JBC Centennial Celebration

*Honoring 100 Years of Achievements and Contributions to Science*



Join us for the ASBMB/JBC Centennial Celebration to honor a century of achievements and contributions of The American Society for Biochemistry and Molecular Biology (ASBMB) and *The Journal of Biological Chemistry (JBC)*. This grand event will be held next year at the ASBMB 2006 Annual Meeting (April 1-5, 2006, San Francisco, CA, in conjunction with Experimental Biology 2006).

- Special publications which tell the history of ASBMB and *The JBC*. A collection of Classics, Reflections, scientific landmarks, and the many contributions to science that have been made by ASBMB members.
- Lectures and commentary by scientific luminaries.
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