AUGUST 2006

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ASBMB Today

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AMERICAN SOCIETY FOR BIOCHEMISTRY AND MOLECULAR BIOLOGY

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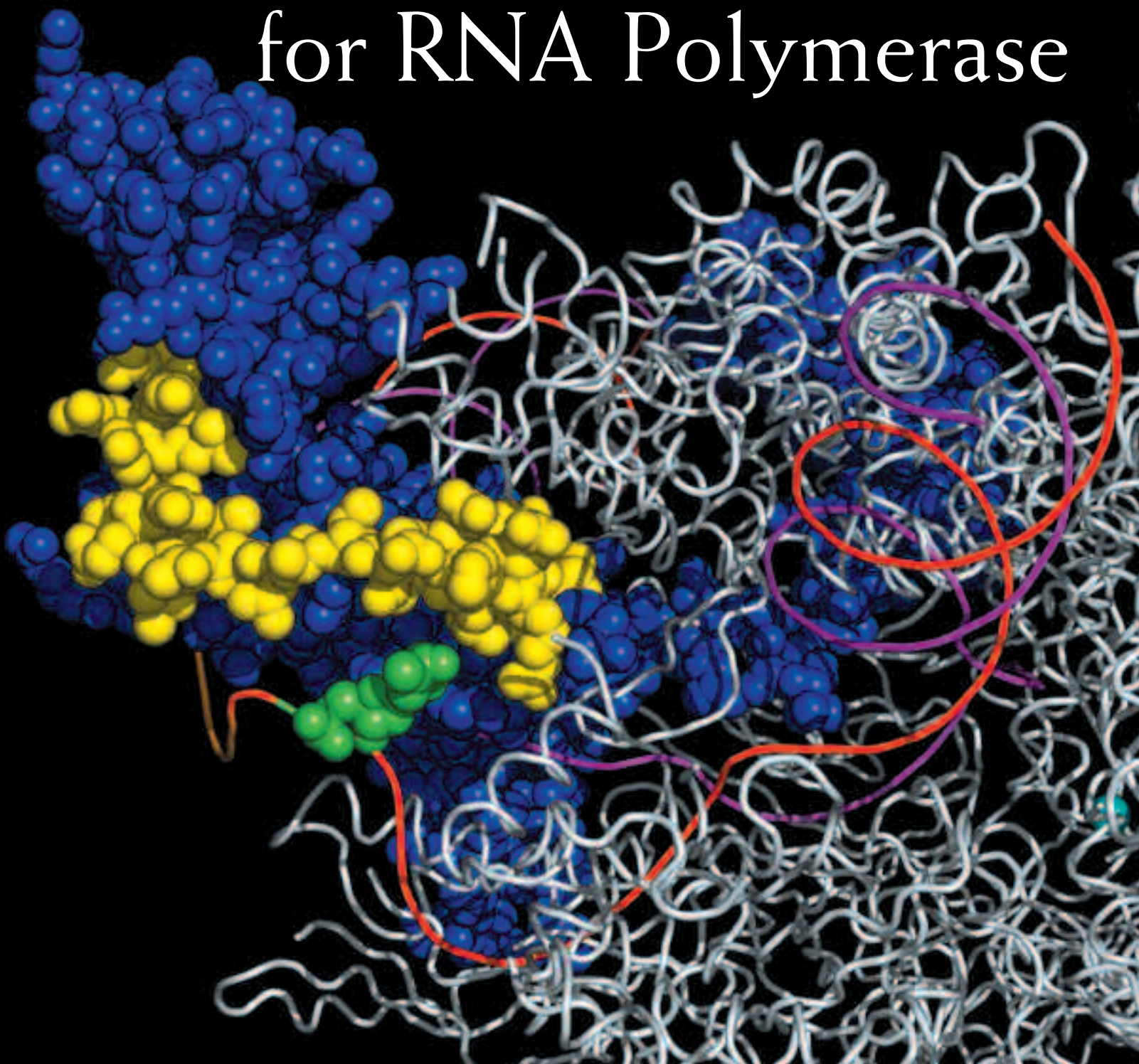

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ASBMB Today

AMERICAN SOCIETY FOR BIOCHEMISTRY AND MOLECULAR BIOLOGY

AUGUST 2006
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features

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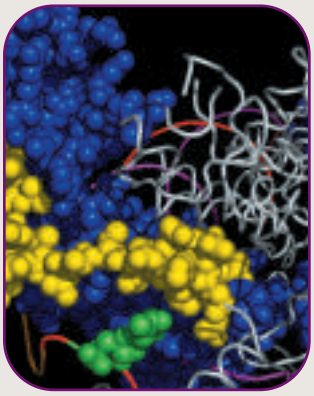

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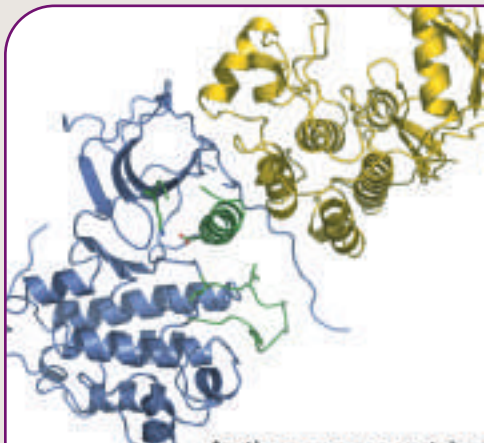

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NIH's 'Flat Budget'

Dear ASBMB Members,

As all of you undoubtedly know, the 2007 NIH budget is flat (which is actually a reduction when biomedical inflation is taken into account) and success rates are low. Under these circumstances, there are extraordinary stresses on all aspects of the system.

Senator Tom Harkin (D-IA) said recently that the doubling of the NIH budget was not intended to be a one-time action. The doubling provided new infrastructure at a time when medical research was producing major advances, especially in this era of genomics and informatics, and was not meant to simply level off, let alone be eroded through actual budget decreases and high biomedical inflation. But that is what is happening.

Unfortunately, this backsliding is destroying many of the exciting opportunities that were created by the doubling, which was completed in 2003. Many institutions across the country have made major investments in infrastructure in recognition of the new opportunities unfolding at NIH, and it will be an economic disaster not to capitalize on these investments by failing to fund the scientists who have made and continue to make scientific breakthroughs.

One of the most important things we can do as scientists is to continue to get the word to the American people and to Congress about the extraordinary benefits of biomedical research. Judy Bond, our Past President; Bob Palazzo, incoming FASEB President-Elect; Barbara Gordon, Pete Farnham, and I recently visited NIH Director Elias Zerhouni to ask what we can do to help. His number one plea to us was to act in our own communities to make the point about the impact of biomedical research on our economy. The doubling of the NIH budget was a highly leveraged investment in job and infrastructure creation that directly impacted our communities. We need to reach out to Congress, as well as our regional business leaders, and remind them of this.

We are very far removed from the "ivory tower" days when scientists did not have to communicate the importance of their research. Yet, there continues to be ebbs and flows in how activist we were at communicating this message. There was a tremendous push among scientists in the '90s to educate Congress about the importance of biomedical research, spearheaded by FASEB, Research! America and many scientific societies including our own. The doubling directly resulted from those efforts. Unfortunately, I think many of us in the biomedical research community got complacent during the doubling era, and only now realize that without more activism amongst us at the local level, the enormous progress we have made will be increasingly eroded. Thus, it is now time to get active again, particularly in our own districts.

The economic message is not complicated. The local benefits of investment in biomedical research through the doubling include job creation, training of creative and talented future scientists, infrastructure development, a healthier population that lives

Dr. Heidi E. Hamm

Is a Reduction

longer, better, healthier lives, and, as President Bush mentioned in the State of the Union Address, the positive impact of all these things on the competitiveness of our nation in the world.

Consider the Following:

Increases in life expectancy in the United States between 1970 and 1990 were worth roughly $2.8 trillion dollars a year. This huge sum represents a rate of return on the research investment of greater than a hundred to one!

Reduced mortality from cardiovascular disease alone was estimated to be worth $1.5 trillion a year.

Improvements in life expectancy account for nearly half of the actual gain in U.S. living standards during the past 50 years.

The likely returns from future medical research are so high that the payoff for any plausible portfolio of investments will be enormous. For example, research that would lead to reducing cancer deaths by as little as 10% would be worth $4 trillion.

Given the obvious economic benefits of increased biomedical research, as well as the trouble for our competitiveness in the long term if we continue to allow our once substantial lead to disappear, I propose that we not only begin to engage in local advocacy for biomedical research ourselves, but that we also get our students and postdoctoral fellows engaged in this outreach. We need to begin to make pests of ourselves on this issue to each representative in a Congressional district that has active biomedical researchers in it. Members of Congress are usually in their home districts from Thursday evening to Monday evening each week, and it's much easier to get to talk to them personally there than in Washington. Regular meetings with members of Congress while they are at home have the potential to be an enormously effective weapon that biomedical research has not used as effectively as it might have in recent years.

ASBMB has recently posted on its website a set of resources and a list of "talking points" that you can print out and give to your students and take with you as you meet with your congressional representative. We expect this material will make your visits easier; please let us know what other data would be useful! In addition, I will soon send each of you a query about your willingness to participate in this grass-roots effort. My goal is to have several ASBMB members in each Congressional district where research is taking place meet with their member of Congress, get to know him or her, establish a good relationship, and to contact them at critical times in the budget process.

We are now in such a critical time. The President proposed that NIH be flat-funded for 2007—without even an inflationary increase—and the House of Representatives has gone along with this proposal. Prospects are slightly better in the Senate, but we expect no good news in this regard until Fall at the earliest. Thus, the sooner you can arrange to contact your Member of Congress on this point, the better. The ASBMB Staff can help you with these meetings; please contact Pete Farnham, pfarnham@asbmb.org, at society headquarters for assistance if needed.

You will note elsewhere in this issue of *ASBMB Today* that Dr. Zerhouni has given us a lengthy interview, in which he specifically addresses the seriousness of the situation and the need for scientists to speak out and get active locally. We hope you will take his plea to heart.

In short, we are faced with very difficult times at NIH these days, in spite of the doubling that was completed only three years ago, and we need your help to begin to alleviate these hard times—they will not go away by themselves!

Next month I will be speaking to you about the plight of the individual investigator in an era such as we are experiencing now—more money than ever (or close to it) but funding success rates in the single digits in many institutes with little prospect of improvement in the short term.

Rest assured that ASBMB is working very hard on multiple fronts to address this situation, but we need your help. Please do what you can, not only for you and your colleagues now, but for the next generation of biomedical researchers who in the future will be impacted by decisions Congress—and we in the biomedical research community—make today. If you feel particularly motivated, we are looking to make some new appointments to the Public Affairs Committee and we would be pleased to hear from any of you who have an interest in serving on this committee or in some of its activities.

Heidi Hamm
ASBMB President

by Peter Farnham, CAE, ASBMB Public Affairs Officer

ASBMB Interviews NIH Chief

The ASBMB leadership met with NIH Director Elias Zerhouni in early June to discuss a variety of issues of concern and interest to individual investigators. During that interview, Dr. Zerhouni agreed to respond to questions for an article in ASBMB Today. The following are the questions and Dr. Zerhouni's responses.

ASBMB: Given the current difficult budget situation, what are your top priorities for NIH?

ZERHOUNI: I am often asked to explain the apparent paradox of an NIH budget that doubled while the success rates for investigators has dropped by a third. Many in Congress and the Administration feel that they have fulfilled their promise to NIH. Scientists on the other hand feel that getting funded by NIH has gotten much harder than the doubling would have led them to believe. The fundamental reason driving the difficult times we are facing is that the number of yearly applications to NIH has almost doubled between 1998 and 2006 from 24,000 to 46,000 per year and the number of individual applicants grew from 19,500 to nearly 32,000. At the same time each grant has become more costly due to natural inflation and the increasing complexity of research projects. In fact more growth in the number of applications for NIH grants occurred in the two years following the doubling than in the entire five years of the doubling period. This surge in demand occurred just when budget growth slowed dramatically below inflation due to a combination of Federal and trade deficits, defense and homeland security needs, preparation for pandemic flu, and natural disasters, such as hurricane Katrina. This growth in demand for grants is due to a real expansion of research capacity across the country thru the building of numerous new research facilities and the recruitment of new faculty at academic institutions. All of us have had the opportunity to witness the many construction sites on our campuses. According to the AAMC, over $15 billion of new research facilities have been developed between 1999 and 2007 as compared to $3.2 billion between 1990 and 1997. This growth is in response to the national need for more research in biology and health, the extraordinary scientific opportunities for progress and the stimulus of the growing NIH budget. Obviously, because it takes time to build laboratories and recruit faculty, there was a lag time between growing budgets during the doubling and growing demand. In challenging times such as these, it is critical to develop adaptive strategies and priorities based on sound analysis and key principles.

First, we must hold to our core values and mission. At NIH it is the support for fundamental discoveries and the generation of new knowledge for the improvement of health. We need to support a research portfolio that includes a breadth of scientific disciplines, research mechanisms, and public health priorities and insure that we maintain a strong basic science core through these difficult times. For example, the percentage of basic science research was 53.9% before the doubling and is now 55.8% and will reach 56.1% next year.

Second, we need to protect the future by preventing the loss of a generation of new, young scientists entering research and that these young people are being nurtured to independence earlier rather than later in their career. To this end, we created early this year a new mechanism, the "Pathway to Independence" award that is designed to support a mentored investigator and bridge his or her work to a point of independence. We expect to award 150-200 of these each year for the next five years.

Third, we need to focus on the core issue facing us and that is balancing supply and demand for investigator initiated grants by ensuring a larger number of competing research project grants. We need to prioritize projects, to maintain investigator-initiated success rates to the greatest extent possible. For example in 2007, even with a flat budget we will increase the number of RPGs by 3%. We are also working in multiple ways to improve the effectiveness of our peer-review processes. For example, we are piloting a more rapid cycle for reapplication for new investigators in 40 review sections and hopefully will expand that pilot further if it is successful.

Fourth, we must continue to engage in pro-active communication about the tremendous benefits of the public's investment in NIH-supported research at local, state and national levels. We are providing a growing resource about these results on a new site: www.nih.gov/about/researchresultsforthepublic/index.htm. and I invite you to read my testimony to Congress this year on http://olpa.od.nih.gov/hearings/109/session2/testimonies/overview.asp

Finally, we must promote a compelling NIH's vision for the future — a future where medicine and health will be transformed through discovery to a more predictive, personalized, preemptive and participatory form of healthcare.

It is in times such as these that great communities demonstrate their leadership capabilities and I am confident that as in previous crises, our community will do so.

ASBMB: There is an impression in the community that the number of R01s is dropping to levels below pre-doubling levels. Would you like to comment?

ZERHOUNI: The *total* number of actively funded R01s grew during the doubling period from about 20,000 to about 28,000 or 40% while the average cost of grants grew by over 30%, but the number of new R01s and equivalent mechanisms funded per year dropped 13% from the end of the doubling in FY2003 to FY2005 (7430 new awards in FY2003 compared to 6463 awards in FY2005).

In FY2005, the number of *new* awards was 5% greater than the number at the start of the doubling in FY1998. Although this data may appear discouraging at first glance, it reflects in part the natural budget cycles of NIH. In 2005, we are recycling funds from grants that started in FY 2000 and 2001 when the doubling had not reached its peak. As we recycle budgets from future years, we will be able to increase the available pool. For example, in 2007 we plan to increase the number of new and competing RPGs by 3% because we will be recycling the 2002-2003 budget dollars. I would like to remind our investigators of both our eagerness to fund outstanding investigator initiated research and our advice to work directly with program officers. Furthermore, I want to reassure the community that our commitment to the R01 mechanism remains intact and that we are making every effort to sustain the likelihood of being funded for individual investigators as we know that original research springs from this mechanism. Despite the great increase in demand, we have been able to preserve a success rate of about 20% for applications and about 25% per applicant in 2006.

ASBMB: Are you concerned about the fate of junior investigators seeking their first NIH grant under the current circumstances?

ZERHOUNI: The NIH has been concerned for many years about the fate of applications from junior investigators. The NIH launched the New Investigator Research Award in 1975 and the First Independent Research Support and Transition Award (FIRST) in 1988. Beginning in 1998, the NIH extended special review and funding incentives previously reserved solely for FIRST awards to nearly all applications submitted by new investigators. When I became director of the NIH, I launched a series of initiatives and made very clear my concern about not only new investigators but also the rising age at which independent funding is achieved. As a result of these efforts, slightly more than 30 percent of the competing research grants in FY 2005 supported projects for new investigators. This year the NIH announced a new program called the Pathway to Independence Award

Dr. Elias Zerhouni

(http://grants.nih.gov/grants/guide/pa-files/PA-06-133.html) that provides continuing support for the final stages of postdoctoral training and transitions into an independent research grant, once a suitable tenure track position has been identified. The NIH remains committed to the enrichment of the scientific workforce with talented, new investigators.

ASBMB: Some investigators with grants above the 20th percentile are not receiving competitive renewals this year because of lack of funds. Some extramural researchers are proposing that any investigator whose grant applications are rated above the 20th percentile get at least one application funded. Could you comment?

ZERHOUNI: NIH Institutes and Centers award grants on the basis of scientific and technical merit, and programmatic considerations. We believe this to be the best way to ensure that the biomedical research enterprise remains rigorous and flexible, even in these tough

times. In fact, in FY2005, NIH funded 92% of competing renewal RPGs and 91% of new competing RPGs that scored in the top 20 percentile or better. These percentages have dropped since the end of the doubling. In 2003, we funded 97% of competing continuing RPGs and 98% of new competing RPGs that scored in the top 20 percentile or better. Even though the playing field has become more competitive, these funding rates are still quite high.

ASBMB: There is concern that NIH is targeting more funding through the use of Program Announcements. Could you comment?

ZERHOUNI: With rare exceptions, Program Announcements (PAs) do not set aside funds. They merely signal an Institute or Center's interest in a particular area of science. Requests for Applications (RFA) rely on set aside funds. The number of Research Project Grants (RPGs) funded through RFAs has remained relatively steady at approximately 10% of the RPGs funded. In absolute terms, unsolicited awards increased the most, increasing by $7.4 billion from 1995 to 2005. In contrast, funding through RFAs increased by only $1.5 billion during the same period. The best indicator is that since 2003, we have been very careful about the rapport between solicited and unsolicited research is that today 93% of R01s are unsolicited as opposed to 91% at the beginning of the doubling.

ASBMB: Management of NIH is a great challenge given that the Institutes and Centers (ICs) are rather independent entities. How do you attempt to unify the ICs when opportunities arise for breakthrough science that crosses interdisciplinary lines?

ZERHOUNI: The NIH Institutes and Centers (ICs) are experiencing a renaissance in collaboration. The ICs are increasingly drawn together by scientific opportunity that crosses their specific mission area. Some have proposed that institutes be merged into larger entities for greater synergy. I happened to believe that a functional mechanism that identifies emerging areas of science, roadblocks, or opportunities or pilots that no single institute can address, but that all of NIH should address is a better approach than wholesale mergers of institutes. This is why we pioneered the concept of an NIH Roadmap and encouraged institutes to develop ways to address cross-cutting challenges such as the obesity epidemic. Obviously, this should not be done at the expense of the creativity that comes from a decentralized system. Nonetheless, I feel that a small percentage of the NIH budget should be used to support, through wide and transparent consultations, the scientific community's most urgent needs—needs that could not be addressed by a single or a few Institutes—and that would benefit the entire biomedical research enterprise. For example, in seeking input from the research community, we heard that there was a need to support innovative and high-risk research, to stimulate interdisciplinary research, to stimulate the basic science of complex biological systems, and to create a better infrastructure for clinical and translational science. The NIH Roadmap is not a single large initiative but a balanced set of priorities with 40% of its budget dedicated to basic science, 40% to translational science, and 20% to high risk and interdisciplinary pilot projects such as the Director's Pioneer Award pilot. NIH is implementing these recommendations through a variety of mechanisms, including program project grants, R01s, centers, and contracts. By the second year of the Roadmap, 379 new awards were issued–56 of them to investigators new to the NIH-at 134 institutions in 33 states. Finally, it is worth noting that the Roadmap was well received by Congress and the Administration and served as an important part of the rationale for NIH's small increases in 2004 (up 2.9%) and 2005 (up 1.9%).

NIH also launched the Office of Portfolio Analysis and Strategic Planning (OPASI) to provide the NIH and its constituent ICs with the methods and information necessary to manage their large and complex scientific portfolios. It also identifies, in concert with other inputs—important areas of emerging scientific opportunities or rising public health challenges, and assists in the acceleration of investments in these areas, focusing on those involving multiple ICs. Although OPASI will not have grant-making authority, OPASI will provide an "incubator space" for trans-NIH initiatives, and support priority projects on a time-limited basis (5 to 10 years). This process has essentially two goals: to allow new science that falls through the cracks to be funded quickly, and to make sure new ideas have a chance.

OPASI builds upon the model of the NIH Roadmap for Medical Research and will coordinate with NIH Institute and Centers (ICs) and external stakeholders to identify research priorities that will ultimately improve NIH's ability to be nimble, dynamic, and responsive to emerging scientific opportunities and public health needs. OPASI will solicit regular input from the biomedical and behavioral research community, including proposals from individual scientists, stakeholders and organizations outside NIH; a regular, Roadmap-like planning process; data about the burden of illness; as well as considerable input from IC directors and such NIH Office of the Director components as women's health, behavioral science, and AIDS research.

ASBMB: If you could send a message to the NIH extramural scientists what would that be?

ZERHOUNI: Communicate with your local community. Share the results of your research efforts and those of NIH sponsored research. Demon-

strate to them how our work at the NIH and NIH- supported institutions is making a difference in the lives of our citizens. I would encourage them to use our funding website for continuously updated information: http://grants1.nih.gov/grants/financial/index.htm. Get informed about the true state of affairs by communicating often with us and do not over react to seemingly overwhelming bad news. We are a strong community. With clear leadership and resilience, we will overcome these challenges.

ASBMB: If you could send a message to graduate students and postdocs who want to pursue careers in basic biomedical research, what would that be?

ZERHOUNI: Stay the course. There will continue to be opportunities for productive careers in biomedical research. Be assured that one of NIH's main concerns is not to lose new investigators. The NIH is supportive of developing new research careers and recently launched the Pathway to Independence Awards, which is an innovative initiative allowing us to grant R01-equivalent funding earlier in the career path of postdocs. We're going to reserve 150 to 200 grants a year for postdocs who are finishing their training in any discipline. We want to continue to support the up-and-coming best and brightest biomedical researchers.

ASBMB: Are there any other points you'd like to make?

ZERHOUNI: I truly believe that NIH is the best investment the public makes in the future. The strong support that NIH received over the doubling period is due to the value placed in the NIH for biomedical research by the American people, the Congress, and Administrations—past and present. But these are uncertain times for federally-supported biomedical research. There are many competing national priorities that demand resources. We need to work together as a community, to ensure that we can capitalize on the strides we have made in understanding human health and identifying, ameliorating or curing disease. At the same time, NIH and the research community needs to do a better job of explaining the importance of the nation's investment in biomedical research to the public, patients, and policy makers in clear, compelling, and relevant terms. We must make our progress explicit and understandable to the public. We must nurture the public's understanding of science, and we must continue to earn the public's trust.

by Peter Farnham, CAE, ASBMB Public Affairs Officer

Senate Passes Stem Cell Bill; Bush Veto Follows Immediately

The Senate on July 18 passed H.R. 810, the Stem Cell Research Enhancement Act which had passed in the House last year. The Senate voted 63-37 in favor of the bill. The vote cleared the way for a conference and the dispatch of the bill to the White House—where President Bush promptly vetoed it as expected. The House immediately attempted an override, but it failed by more than 50 votes. The Senate is thus unlikely to take up an override attempt.

H.R.810, introduced last year by Reps Mike Castle (R-DE) and Diane DeGette (D-CO) passed the House of Representatives in May 2005 by a healthy majority of 238 votes, including 50 Republicans who went against their leadership to support a bill that would overturn President Bush's decision on stem cells announced on August 9, 2001, which would only allow federal funding for research on stem cells derived from lines developed before that date.

The bill allows federal funds to be used to conduct research on stem cell lines developed from cells taken from left-over blastocysts slated for destruction at *in vitro* fertilization clinics. There are approximately 400,000 such blastocysts in cold storage in clinics around the country, most of which will never be used in fertilization procedures. The bill also includes safeguards, such as requiring a donator to give her written informed consent, and also that no payment be given for the donation.

Majority Leader Bill Frist (R-TN), in a July 18 column in *The Washington Post*, noted that he supported H.R.810 because he hoped that the loss of life involved—destruction of the embryo to obtain stem cells—could be redeemed "in part by using these embryos to seed research that will save lives in the future."

Frist also observed that "The debate over embryonic stem cell research will never prove simple. Congress isn't always the best forum to hash out complicated bioethical issues. But it appears inevitable that we will confront these questions time and again as science advances."

After the veto

Unfortunately, the President has vowed to veto any bill that overturns or loosens his stem cell policy of August 2001. Senator Arlen Specter (R-PA) implored the President on July 17 to reconsider his veto threat, "comparing the president's position to those who opposed Columbus, locked up Galileo, and rejected anesthesia, electricity, vaccines and rail travel", according to a *Post* columnist writing about the debate. Such attitudes "in retrospect look foolish, look absolutely ridiculous," Specter said.

Former First Lady Nancy Reagan, a strong supporter of embryonic stem cell research, was also expected to call the President to make a final appeal, but in the end, virtually all observers expected a veto—the first of the Bush Presidency. Furthermore, the veto is likely to stick.

In the House, supporters of the bill would need 290 votes to override, which is 52 more votes than H.R.810 received when it passed last year. This is very likely too much of a deficit to overcome.

The chances for a successful override are better in the Senate; however, the Senate may not even try, given that there are numerous other pressing matters demanding its attention and a successful override would almost certainly do no good, given an override's poor prospects in the House. In addition, the agreement by which H.R.810 reached the Senate floor specified that after the vote, the issue would not come up again this year. A veto override attempt can be construed as a violation of that agreement.

Although the issue may be dead in the Congress this year, it will be alive and well during the upcoming mid-term elections. The public supports stem cell research by majorities exceeding 60 %; thus, Democrats are sure to make political hay out of the issue on the hustings this Fall.

Two other bills were considered along with H.R.810. One encourages development of methods of obtaining stem cells that do not involve destruction of blastocysts; the other prevents scientists from implanting human embryos in order to abort them for experimentation—or, "fetal farming," as opponents of stem cell research characterize this concept. Both of these bills passed unanimously and the President is expected to sign them.

FASEB Members Press Legislators On Importance of Medical Research

By Jon Retzlaff, FASEB Director of Legislative Relations

In a continuing effort to make policymakers aware of the importance of biomedical, physical sciences and agricultural research, FASEB's Office of Public Affairs coordinated its second annual Capitol Hill Day, on June 5-6. FASEB's Board and Science Policy Committee members met with 20 Congressional offices to discuss how research is improving lives, reducing the burden of illness, and improving the economy. In coordination with Capitol Hill Day, FASEB issued a media release that was featured in numerous news outlets, including *Research Day USA* and *Inside Higher Education*. FASEB also released several new advocacy products, including a brochure titled *Science Fortune: How Unpredictable Research Advances Have Saved Millions of Lives* and a statement of principles related to reauthorization of the National Institutes of Health (NIH). These materials are available in the advocacy resources section of the FASEB website, opa.faseb.org

Over the course of two days, scientists from more than a dozen states visited with the offices of Congressional leaders, appropriators, authorizers and other members of Congress who have expressed an interest in medical research. The lawmakers included House Speaker Dennis Hastert (R-IL); House Majority Leader, John Boehner (R-OH); House Energy and Commerce Ranking Member, John Dingell (D-MI); Senate Majority Leader Bill Frist (R-TN); Senate Appropriations Chairman, Thad Cochran (R-MS); Representatives Fred Upton (R-MI); Diana DeGette (D-CO); Jim Leach (R-IA); Jim Cooper (D-TN); Virginia Foxx (R-NC); Ed Markey (D-MA); Mark Kirk (R-IL) and Chris Van Hollen (D-MD); and Senators Maria Cantwell (D-WA); Richard Durbin (D-IL); Mike DeWine (R-OH); Richard Burr (R-NC); Chuck Hagel (R-NE); Patty Murray (D-WA) and Barack Obama (D-IL).

Prior to dispersing for the meetings, former Illinois Congressman John Edward Porter provided FASEB leaders with the keen insight he gathered during his 20 years in Congress. During the six years he served as Chairman of the House Labor, Health and Human Services, Education and Related Agencies (L/HHS) Appropriations Subcommittee, Congressman Porter was the force in the House the behind doubling of NIH's budget.

Porter suggested that FASEB scientists and clinicians provide examples of how research discoveries are generating scientific opportunities that may provide hope for millions of Americans. He praised President George W. Bush for proposing to double the National Science Foundation and Department of Energy's Office of Science budgets over ten years, but encouraged FASEB society scientists to explain that all areas of research should be similarly supported, including biomedical research.

Late in the afternoon on June 6, participating FASEB Board Members came together to present the FASEB Public Service Award to Representative Mike Castle (R-DE) for his extremely effective leadership and outstanding commitment to health programs, including medical research funded by NIH. Castle helped organize moderate Republicans to gain assurances from House leaders that an additional $7 billion would be made available for important health and education programs during the FY2007 appropriations process. In additional, Castle is co-author of H.R. 810, the Stem Cell Research Enhancement Act, which passed the House of Representatives by an overwhelming majority last year, but now languishes in the Senate.

Representative Mike Castle (center) receives the 2006 FASEB Public Service Award, presented by members of the FASEB Board of Directors. At his left is FASEB President Leo Furcht and at his right is FASEB Board member Paula Stern.

The Power of Setting a Deadline

By Jodi Hirschman

Career Insights:
How People Choose What to Do Next

By The ASBMB Education and Professional Development Committee

Traditionally, most biologists have followed a somewhat linear career path, where graduate school led to a postdoctoral fellowship, which then led to a tenure-track position doing research in an academic setting. A biologists' path on the tenure-track also seemed straightforward: an assistant professor became an associate professor (mostly accompanied by tenure) and, one day, a full professor. The only question appeared to be whether to pursue one's career in a basic science department, a medical school or a research institute.

This is, of course, an over-simplification of the career choices open to biologists in the past, and it falls short in describing what we do today. This mythical portrayal of a biologist does, however, illustrate the fact that most of us know scientists who are currently engaged in academic research; it is relatively straightforward to find someone who is willing to help us weigh the pros and cons when we are making the decision that would take us along a similar career path.

However, these days many people at various points in their career are facing an array of choices and decisions beyond this traditional academic research career track. These decisions are often not straightforward and it is not always obvious how to go about making the right choice.

In an effort to highlight the fact that many people have faced these decisions and weighed the various options, we approached a number of biologists who have gone through this process and made interesting career choices, and we asked them to write a short piece describing their jobs and the considerations that went into their career decisions. We will be featuring these articles in a new *ASBMB Today* column called Career Insights, and they will also be available on our website at www.asbmb.org.

This month, we hear from Jodi Hirschman, a curator at the *Saccharomyces* Genome Database. In the coming months we will have articles from a public policy analyst and two people who work at biotech companies. We hope that these articles will provide a glimpse into the complexity of the career paths facing us these days and illuminate what goes into the decisions we all have to make at various points in our careers.

One night in the fall of 1997 I came to the decision that my tenure as a postdoctoral researcher was over—I would be leaving the lab by the following spring whether I had found a job or not. It wasn't that I was unhappy in the lab; on the contrary, it was a very friendly and productive place to work. But I was a 41-year old mother of two boys, and I had been a postdoc for many years. I was ready for new, and hopefully more profitable, scientific horizons. And, although no one was pushing me, I also knew it was time to offer up my lab bench to new blood.

The decision, however wacky it seemed at the time, led me to research unusual job opportunities and think creatively about possibilities. I had been looking for the "right" job for a while, but the pressure of finding that one great job had not actually helped me to define what was right for me at all. Now I decided that the next step didn't have to be an impressive leap forward professionally, it just had to be a next step in the shaping of my career. I never dreamed I would move into such a rewarding future.

During the years I spent as a graduate student and a postdoc, career opportunities in biology expanded dramatically. When I started grad school, the predominant jobs were in academics and we all assumed we would eventually start our own labs at universities or teach in undergraduate colleges. But biotechnology created interesting, new possibilities in industry, and over the years those jobs became very attractive. Then came the era of genomics, and with it the release of vast amounts of data that needed organization. Suddenly companies and universities had a new job to offer biologists: the curation of scientific data into genome databases. That's where I've found a home.

Just before my deadline for leaving the lab, I was offered a part-time position at Proteome, Inc. as a contract curator. My job was to read papers about yeast and extract a variety of information from the papers into a yeast genome database. For me, reading papers and summarizing information seemed like a dream job and I found it thoroughly

Dr. Jodi Hirschman

enjoyable. I stayed with Proteome and soon my part-time position became a full-time editorial position at a professional salary level. A few years later I accepted a position as a curator for *Saccharomyces* Genome Database, a different yeast database developed by Stanford University, and that's where I work now. My job still involves reading papers and summarizing information, but it also includes many other interesting tasks like developing database tools for curation and for our users, so I'm gaining bioinformatics skills as well.

My leap-of-faith decision in the fall of 1997 led to exciting work that has kept me at the forefront of advances in biological research. I could never have imagined doing this work when I was pondering my future during graduate school—these jobs simply didn't exist. But here they are, offering rewarding professional alternatives to biologists who want to try something new!

Jodi Hirschman, Ph.D. is a Senior Scientific Curator for the Saccharomyces Genome Database (SGD) at the Department of Genetics, Stanford University School of Medicine. Dr. Hirschman earned a B.S. in Bacteriology at the University of Wisconsin, Madison and a Ph.D. in Bacteriology at the University of California, Davis. She was a postdoctoral researcher in the laboratories of Dr. Fred Winston and Dr. Duane Jenness. She can be contacted at jodi@genome.stanford.edu.

Transcriptional Regulation by Chromatin and RNA Polymerase II

A Special ASBMB-Sponsored Symposia Cosponsored by Upstate Inc.

Organizer: **Ali Shilatifard**, St. Louis University School of Medicine

Transcriptional regulation by eukaryotic RNA polymerase II (RNA Pol II) is a multifaceted process requiring the collective action of numerous transcription factors to ensure proper synthesis of messenger RNA (mRNA). In addition to Pol II associated transcription factors, chromatin and its posttranslational modifications play a pivotal role in regulating gene expression.

In this post-genomic era, many laboratories are feverishly working to further characterize epigenetic regulatory mechanisms such as chromatin structure/modifications and other factors influencing RNA Pol II activity. Given the implications of defining molecular mechanisms of gene expression by chromatin and RNA Pol II, and its impact on our understanding of cellular development and disease pathogenesis, ASBMB is bringing together investigators from various, related areas of research for a focused meeting entitled, **Transcriptional Regulation by Chromatin and RNA polymerase II**- November 2 to November 5 at Kiawa Island resort in South Carolina. This meeting will be organized by Dr. Ali Shilatifard, Saint Louis University Medical Center and Saint Louis University Cancer Center, and is cosponsored by Upstate Inc.

Although several invited speakers will attend this meeting, a large number of talks will be chosen from submitted abstracts. Therefore, there will be ample opportunity for oral and poster presentations. Confirmed speakers include: Drs. Roger Kornberg, Shelley Berger, Steve Buratowski, Bradley Cairns, Joan Conaway, Ronald Conaway, Sharon Dent, Barbara Graves, Ktaherine Jones, Tony Kouzarides, Robert Roeder, Ramin Shiekhattar, Henk Stunnenberg and Jerry Workman.

Dr. Ali Shilatifard

The plenary lecture, **Chromatin and Transcription**, by Professor Roger Kornberg, Stanford University, will describe recent work from his laboratory on the structural basis of gene regulation by RNA Pol II, its associated factors, and chromatin.

Defining how changes in chromatin and chromosomes structure regulate transcription and development will be the focus of the first session, **Chromosome, Chromatin and Transcription I.** This session will be chaired by Dr. Sharon Dent, MD Anderson Cancer Center. Dr. Rober Roeder, Rockefeller University, will chair the second session, **Transcriptional Initiation/Activation and Chromatin.** This session will focus on the role factors involved in the regulation of initiation and activation of transcription. The third session, **Transcriptional Elongation and Termination**, will be chaired by Dr. Ronald Conaway, Stowers Institute, and will bring together the diverse biological roles of Pol II elongation factors and chromatin in proper regulation of gene expression.

The fourth session, **Chromosome and Chromatin Modifications**, will be chaired by Dr. Tony Kouzarides, Gurdon Institute. Presentations in this session will be focused on recent studies on histone and transcription factor modifications and mRNA synthesis regulation. Dr. Ramin Shiekhattar, Wistar Institute, will chair the fifth session, **Chromosome and Chromatin Demodifications**, which will explore macromolecular complexes involved in unmodifying posttranslationally modified histones. Dr. Shelley Berger, Wistar Institute, will chair the sixth session, **Chromosome, Chromatin and Transcription II**, which will explore the role of many macromolecular complexes implicated in transcriptional regulation. In the penultimate session, **Chromatin, Transcription and Development**, recently identified roles for chromatin and transcription factors in development and disease pathogenesis will be discussed.

Finally, in the last session of the meeting, Dr. Dorit Zuk, Editor, *Molecular Cell*, will chair an interactive review session with attendees on what was discussed throughout the meeting and future questions to be addressed in the field.

For more information and to register, please visit the meeting site (www.assbmb.org). A large portion of oral presentations will be selected from submitted abstracts. Status (talk/poster) of abstracts will be posted on the ASBMB website by late September.

All registrations and abstracts MUST be submitted by the abstract deadline, September 8. Due to space limitation (approximately 250 participants), we anticipate an oversubscription for this meeting. In this event, we will make a concerted effort to ensure that every research group wishing to participate will be represented.

See you at Kiawah Island in November!

SAVE The DATE

April 28 – May 2, 2007

Washington, DC

2007 ASBMB ANNUAL MEETING

ASBMB

Chemistry of Life

Metabolism Is Coming Back Into Vogue

Organizer: Jared Rutter, University of Utah School of Medicine

I wish I had a dollar for every time I have heard someone express the sentiment, "Metabolism is coming back into vogue." A number of factors have contributed to this resurgent interest in metabolism. First, metabolic regulation is clearly of immense importance for human disease. It has long been appreciated that the so-called "metabolic diseases" are manifestations of metabolic dysregulation. It is now becoming increasingly clear, however, that many other human conditions, including cancer and aging, are intricately related with metabolic regulation. Metabolism is rearing its ugly head in all kinds of field, again contributing to its rediscovery. It seems a weekly occurrence that an unexpected "housekeeping" metabolic enzyme is discovered as a component of a signaling complex or as a regulator of a seemingly unrelated cellular process. As long as biologists continue to rediscover that the "metabolic" half of the cell and the "signaling" half of the cell actually reside in the same cell, metabolism will continue to share the center stage.

The Metabolism Sessions will first highlight some of the mechanistic aspects of metabolic regulation both at a biochemical and cellular level. We will then move to a discussion of how these phenomena impinge upon human health and disease. These discussions will address not only the "how" of metabolic regulation, but also the "why" and "what next."

Metabolic Sensing and Signaling

This session will focus on metabolic sensory systems that are used by the cell to monitor nutrient and metabolic status and elicit the appropriate response. Specifically, the three invited speakers will discuss different protein kinases that function in metabolic sensing and signaling. Dr. David Carling (Imperial College, London) will discuss the regulation of the AMP-activated protein kinase, AMPK. Dr. Michael Hall (University of Basel, Switzerland) will discuss the role of the TOR protein in controlling cell growth both in yeast and mammals. Dr. Jared Rutter (University of Utah) will describe the role of PAS kinase in controlling metabolic homeostasis.

Dr. Jared Rutter

Molecular and Cellular Aspects of Metabolic Disease

This session will discuss the mechanisms and pathophysiology of metabolic diseases, specifically diabetes, obesity and cancer. Dr. Craig Thompson (University of Pennsylvania) will discuss metabolic aspects of cell growth and proliferation. Dr. Morris Birnbaum (University of Pennsylvania) will analyze the role of insulin in regulating liver metabolism and the derangement of this regulation in diabetes. Dr. Marc Montminy (Salk Institute) will describe the role of a family of transcriptional coactivators (TORCs) in controlling energy and glucose homeostasis.

Mitochondria in Health and Disease

Mitochondria are the crux between cellular respiration (life) and apoptosis (death), and hence play a key role in the pathogenesis of metabolic disorders. This session, to be chaired by Dr. E. Dale Abel (University of Utah School of Medicine), will focus on recent developments that reveal novel signaling mechanisms linking mitochondria to diabetes and insulin-resistant states. Dr. Abel will present data that demonstrates a role for insulin, growth factor signaling and PI3 kinase in the regulation of mitochondrial oxidative capacity and integrity in the heart. Dr. Nika N. Danial (Dana Farber Cancer Institute, Harvard Medical School) will discuss novel roles for the pro-apoptotic BCL-2 family protein BAD in the regulation of mitochondrial glucose metabolism, and an unexpected role in the regulation of beta cell function and insulin secretion. Dr. Antonio Vidal-Puig (Cambridge University, U.K.) will present new insights regarding in vivo roles of PGC-1, an important transcriptional co-activator of mitochondrial genes.

Aging and Metabolism

Metabolic pathways are tightly regulated by nutrient and hormonal fluctuations that impact on organism longevity. Dr. Pere Puigserver (Johns Hopkins Univ. School of Medicine) will chair this session and present mechanistic insights in how a key transcriptional coactivator, PGC-1, controls metabolic genes in response to nutrient deprivation. Dr. Andy Dillin (Salk Institute) will speak about his lab's studies using worms to elucidate how the insulin pathway influences life span and its potential effects on disease. Dr. Steve Helfand (Brown University) will present novel genetic pathways that mediate life span extension in flies. Dr. Richard Weindruch (University of Wisconsin) will discuss how calorie restriction causes major macronutrients shifts in mammals to allow survival during periods of food scarcity.

ASBMB Annual Meeting

April 28 - May 2, 2007 in Washington, DC

Protein Synthesis, Folding, and Turnover

Organizers: James R. Williamson, Rachel Green, Jonathan Weissman, Christopher Hill

The Protein Synthesis, Folding, and Turnover Theme at the ASBMB meeting will cover exciting aspects of the biogenesis and turnover of proteins. There are four sessions that serve as the focus of this broad area for this year's symposium:

Molecular Mechanisms of Protein Biosynthesis
(Chair: Rachel Green, Johns Hopkins)

Co- and Postranslational Folding
(Chair: Jonathan Weissman, UCSF)

Protein Modification and Turnover
(Chair: Chris Hill, Utah)

The Ribosome and Translation
(Chair: James R. Williamson, Scripps)

The Biosynthesis session will cover exciting new mechanistic aspects of translation. Rachel Green will chair the session, and present her work on the molecular mechanism of translation and peptide bond formation. Dan Herschlag (Stanford) will present his work exploring the role of RNA binding proteins that interact with the 3'-untranslated regions of mRNAs in regulating translation. Tim Nilsen (Case Western) will present new results in the rapidly developing area of micro-RNAs regulattion of translation.

The Folding session will cover several aspects of protein folding and misfolding inside cells. Jonathan Weissman will chair the session, and present his studies on how cells recognize aberrant misfolded forms and then respond to restore the homeostasis of protein folding. Ulrich Hartl (Max Planck) will present his work on how chaperonin molecules select their substrates and subsequently assist protein folding. Elizabeth Craig (Wisconsin) will discuss how the specialization of Hsp70's in evolution allows for a broad spectrum of function on many types of substrates.

The Modification and Turnover session will be chaired by Chris Hill who will present his structural work on the activation of the proteosome. Also, in this session, Tom Rappoport (Harvard) will present functional and structural studies that illuminate how proteins are inserted into membranes. Chris Lima (Sloan Kettering) will describe his structural investigations into the protein modification machinery in the SUMO modification pathway.

The Ribosome session will cover several exciting aspects of the ribosome and translation. Jody Puglisi (Stanford) will present single molecule fluorescence data reporting on the conformational changes that take place during each round of peptide bond formation during translation. Jamie Williamson (Scripps) will present isotope pulse chase data that reveal the process of ribosome assembly. Nahum Sonenberg (McGill) will describe novel translation regulation pathways for initiation of protein synthesis.

Dr. James Williamson

There is a strong synergy of this symposium with the RNA Theme Symposium, organized by Kristen Lynch (UT Southwestern). There is a convergence of our understanding of the regulation of translation by both RNAs and proteins, and speakers from both these Symposia will address complementary aspects of this exciting and emerging area. Overall, the Protein Synthesis, Folding, and Turnover Theme Symposium will provide a broad and balanced overview of the many facets of the life cycle of a protein, from its birth on the ribosome, adolescence during folding, adulthood during function, to old age and the inevitable turnover.

Protein 'Engines' Accelerate Pancreatic Cancer

Cancer Research UK scientists have discovered that a family of proteins found in pancreatic cancer cells may contribute to the aggressive nature of the disease.

Researchers, supported by the North West Cancer Research Fund and the Medical Research Council, were able to track the proteins, called CapG and Gelsolin, in tissue samples from normal and cancerous cells. They found abnormally high concentrations of both proteins in the tumour tissue.

CapG and Gelsolin have roles in regulating cell movement. This study suggests that the proteins' involvement in moving cells around the body contributes to pancreatic cancer spreading through the pancreas and to other areas of the body.

Dr Eithne Costello and colleagues, based at the Division of Surgery and Oncology at the, University of Liverpool, carried out experiments reducing the amounts of CapG and Gelsolin in pancreatic cancer cells in the laboratory, and found the spread of cancerous cells could be reduced. In addition, they found that pancreatic cancer patients have better prospects when the level of Gelsolin protein is low or undetectable.

They also made the unexpected discovery that the amount of CapG found in the nucleus of the cancerous cells was proportional to the size of the tumour. This could mean that this protein is closely linked to aggressive tumour growth as well as spread.

Three ASBMB Members Receive Gairdner Awards

Alan Hall, Thomas D. Pollard, and Joan A. Steitz are among the five scientists who have been awarded the prestigious 2006 Gairdner International Award in recognition of their contributions to medical science.

Thomas D. Pollard

Pollard, Sterling Professor and chair of the Department of Molecular, Cellular and Developmental Biology at Yale University, was recognized along with Hall, chair of the Cell Biology Program at Memorial Sloan-Kettering Cancer Center in New York, for "discoveries related to understanding the cytoskeleton of the cell and the basis of cell motility and its relevance to human disease."

Joan A. Steitz

Steitz, Sterling Professor of Molecular Biophysics and Biochemistry at Yale University and a Howard Hughes Medical Institute investigator, was honored for her "discovery of the reactivity of autoimmune sera with nuclear riboprotein particles and elucidation of the rules of small nuclear RNA in gene expression."

The Gairdner Foundation was created in 1957 by Toronto businessman James A. Gairdner, a successful stockbroker and industrialist. The first Gairdner International Awards were presented in 1959 to recognize achievement in medical science. Since then, the awards have become one of the most prestigious international awards in medical research, recognizing outstanding contributions by medical scientists worldwide whose work will significantly improve the quality of life. Of the 279 Gairdner winners, 65 have gone on to win the Nobel Prize.

Dr. Alan Hall

Each Gairdner awardee receives the award, which carries a cash value of $CDN 30,000, at a gala dinner held in the fall at the Four Seasons Hotel in Toronto. The awardees are chosen in a two-stage process by members of two medical advisory committees, made up of leading medical scientists from both Canada and the international scientific community.

Aussie Scientists Ungagged

Australia's Commonwealth Scientific and Industrial Research Organization (CSIRO) completely rewrote its policy on public comments by staff in mid-July, after admitting that the existing policy had discouraged staff from speaking about their research in public.

CSIRO CEO Geoff Garrett had asked a panel of scientists led by chemist Tony Haymet, the organization's director of science and policy, to consult with staff over the policy. After holding 10 separate meetings, they came to the conclusion that CSIRO needed to reaffirm its trust in its scientists.

"The common denominator was that [staff] felt the old policy was contradictory," Haymet told *The Scientist*. While its preamble was very positive about communicating science to the wider community, he said it also included a series of negative rules about what was not permitted.

The review panel recommended that the policy, in place since 2004, be redrafted. The CSIRO board agreed, and "as a result of the review we have totally rewritten our policy," Garrett said in a statement. "The new rules don't require staff to seek permission from management before speaking publicly. We have taken out the word permission. Scientists are CSIRO's frontline communicators, and we trust them to discuss their science, even in potentially controversial areas."

The policy change is good news, but staff will want to see the policy's words translate into a deeper cultural change, said Michael Borgas, an atmospheric research scientist at CSIRO and president of the organization's staff association.

Others were concerned that the policy tells CSIRO staff not to advocate, defend, or canvass the merits of government or opposition policies. Ian Lowe, president of the Australian Conservation Foundation, warned that ministers in the past have seen any comment on the need to reduce greenhouse emissions as a challenge to policy. He said that he would like to be reassured that scientists will be free to tell the public what the science says, even if that makes politicians uncomfortable.

Eat Less, Weigh More?

Working with genetically engineered mice, Johns Hopkins scientists have interfered with the brain's ability to control an animal's response to a high-fat diet. The report, published in May 9 issue of the *Proceedings of the National Academy of Sciences*, is based on the identification of a gene, CPT1c, which the brain needs to manage body weight.

Fatty acid synthesis in the central nervous system is implicated in the control of food intake and energy expenditure. An intermediate in this pathway, malonyl-CoA, mediates these effects. Malonyl-CoA is an established inhibitor of carnitine palmitoyltransferase-1 (CPT1), an outer mitochondrial membrane enzyme that controls entry of fatty acids into mitochondria and, thereby, fatty acid oxidation.

CPT1c is a brain-specific enzyme with high sequence similarity to CPT1a, found in the liver, and CPT1b, found in muscle. All three CPTs bind to malonyl-CoA. However, CPT1a and CPT1b catalyze acyl transfer from various fatty acyl-CoAs to carnitine, whereas CPT1c does not. These findings suggested to M. Daniel Lane, professor of biological chemistry in the Institute for Basic Biomedical Sciences at Hopkins, that CPT1c has a unique function or activation mechanism.

Lane and his colleagues produced a targeted mouse knockout (KO) of CPT1c to investigate its role in energy homeostasis. They found that CPT1c KO mice have lower body weight and food intake, which is consistent with a role as an energy-sensing malonyl-CoA target.

Mice lacking the CPT1c gene were the same length as their littermates who carry normal copies of the gene but on average weighed 15 percent less when fed a low-fat diet. Further analysis revealed that when deprived of food for four hours prior to feeding with standard laboratory mouse chow, the knockout mutant mice ate about 25 percent less food than their normal siblings.

Paradoxically, CPT1c KO mice fed a high-fat diet were more susceptible to obesity, suggesting that CPT1c is protective against the effects of fat feeding. CPT1c KO mice also exhibited decreased rates of fatty acid oxidation, which may contribute to their increased susceptibility to diet-induced obesity. These findings indicate that CPT1c is necessary for the regulation of energy homeostasis.

"We think our study reveals a direct weight management pathway," says Michael Wolfgang, Ph.D., a postdoctoral fellow in the Department of Biological Chemistry at The Johns Hopkins University School of Medicine and an author on the report. "CPT1c seems to allow the body to respond immediately to the level of nutrients and fat in the bloodstream."

Hopeful that the discovery has broad implications for understanding the genetic underpinnings of obesity and weight management, the Hopkins investigators say the work affirms the central role of the brain in managing hunger and satiety and offers up new targets for drugs that manipulate CPT1c. But none have been developed so far, says Wolfgang.

"How do you know when to stop eating?" asks Lane. "The liver sure isn't going to tell you, it just keeps storing fat as long as the body is well fed." Instead, he notes, it is the control regions of the brain, namely the hypothalamus, that governs eating behavior.

"We are beginning to understand what the hypothalamus inputs are, but unlike the liver, where nearly the whole organ is involved in the same thing, the brain is very specialized and only a few neurons do very specific things," says Lane. The researchers hope to further understand how malonyl-CoA and CPT1c function to control body weight and appetite.

Dr. M. Daniel Lane

M. Daniel Lane received B.S. and M.S. degrees from Iowa State University and a Ph.D. degree from the University of Illinois. He was a Senior Postdoctoral Fellow with Feodor Lynen at the Max-Planck Institute Für Zellchemie in Munich. Following faculty positions at Virginia Polytechnic Institute and New York University School of Medicine, he joined the faculty of the Johns Hopkins University School of Medicine and later served as DeLamar Professor and Director of the Department of Biological Chemistry from 1978 to 1997. He is presently Distinguished University Service Professor at Johns Hopkins. In 2002 he received an honorary degree Doctor of Humane Letters, from Iowa State University, his alma mater.

Lane was elected to membership in the National Academy of Sciences (1987) and was elected as a Fellow of the American Academy of Arts and Sciences (1982) and of the American Society of Nutritional Sciences (1996). He received the Mead Johnson Award from the American Society for Nutritional Sciences in 1966 for his research on biotin-dependent enzymes; and in 1981 the ASBMB William C. Rose Award for his work on the insulin receptor. In 1990-1991, Lane served as President of ASBMB. He has presented many named lectureships (including the Feodor Lynen Lecture in Germany in 1999) and served on numerous editorial boards including the *Journal of Biological Chemistry* and the *Annual Reviews of Biochemistry*. Currently he is Associate Editor for *Biochemical and Biophysical Research Communications*.

Researchers Find New Clues To Biochemistry of Anti-Aging

University of Wisconsin-Madison researchers have found that sirtuins, a family of enzymes linked to gene silencing, cell cycle regulation, fatty acid metabolism, lifespan extension, and apoptosis, may control the activity of metabolic enzymes.

Published in the July 5 issue of the *Proceedings of the National Academy of Sciences*, the study is the first to show that sirtuins directly control acetyl-CoA synthetases in mammalian cells.

The finding, which shines a spotlight on enzymes only recently thought to play a role in the biochemistry of "anti-aging," has attracted the interest of biotechnology companies seeking to make drugs that delay the aging process and age-related diseases. The drugs could target the metabolic enzymes to produce health benefits.

"Sirtuins are very enticing because of their ability to slow the aging process," says John Denu, Associate Professor of Biomolecular Chemistry at the UW-Madison School of Medicine and Public Health (SMPH) and lead author on the study. "They also have great potential for promoting healthier aging by giving us a better understanding of—and possibly suggesting treatments for—metabolic diseases such as diabetes and neurological disorders such Alzheimer's and Huntington's diseases."

Denu and his team, who have published widely on sirtuins, conducted studies using mouse cells to learn exactly which molecular players sirtuins act on directly. Previous studies suggested that sirtuins control genes indirectly in the cell nucleus. The first hint that sirtuins might directly control metabolic pathways came from earlier work in bacteria done by UW-Madison bacteriology professor Jorge Escalante.

The researchers found that sirtuins directly controlled acetyl-CoA synthetases by activating these metabolic enzymes through deacetylation. Specifically, SIRT1 controlled acetyl-CoA synthetase-1 and SIRT3 acted on acetyl-CoA synthetase-2. Acetyl-CoA synthetases control lipogenesis and are transcriptional targets of insulin action.

Denu says it is not clear what role acetate metabolism may play in the little-understood sirtuin molecular system that seems to confer so many advantages, but a connection to diabetes and aging does exist. Studies from the 1960s and early 1990s showed that diabetics and aged individuals exhibit a decreased ability to utilize acetate, he notes.

"Although the molecular links still must be established, appropriate control of our bodies' metabolic processes is essential to life extension and healthy aging," he says. "The observation that caloric restriction extends life span and appears to reduce the risk of diabetes in animal models only underscores the importance of metabolic pathways."

ASBMB member John Denu is Associate Professor in the Department of Biomolecular Chemistry at the University of Wisconsin-Madison Medical School. He joined the Department of Biochemistry and Molecular Biology at Oregon Health and Science University as Assistant Professor in 1996 and subsequently became an Associate Professor in 2002. Denu received his B.S. in Biochemistry in 1988 from the University of Wisconsin-Madison and his Ph.D. in Biochemistry and Biophysics from Texas A&M University-College Station in 1993, and subsequently did his postdoctoral work at the University of Michigan-Ann Arbor.

Denu has authored or co-authored over 70 publications. He is currently interested in studying the mechanisms and biological functions of reversible protein modifications that modulate signal transduction and chromatin function. His laboratory uses methods derived from biochemistry, genetics, proteomics, and enzymology, as well as mammalian tissue culture system and yeast as a genetically tractable system to explore biological function. The American Cancer Association awarded Denu the Young Investigator Award from 1997-2000 and the Research Scholar Award from 2001-2004.

Dr. John Denu

Scientists Identify New Regulation Element for RNA Polymerase

The cellular process of transcription depends on previously underappreciated sections of both the DNA promoter region and RNA polymerase, according to work done with *E. coli* and published in the June 16 issue of the journal *Cell*.

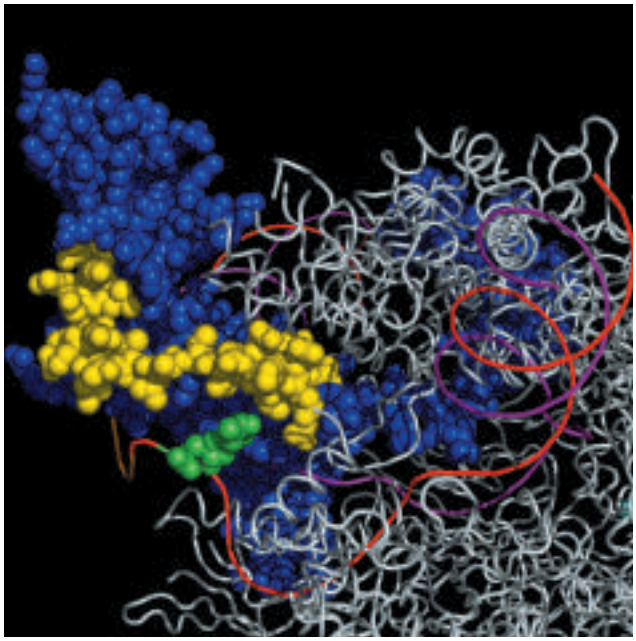
This fundamental research about a key step in RNA synthesis has important implications for the study of gene expression in other organisms, and adds to the wealth of knowledge about *E. coli*.

"The kinds of processes that we study in *E. coli* happen in a wide variety of bacteria of medical, environmental, and agricultural importance," notes Rick Gourse, of the University of Wisconsin-Madison, who published the *Cell* paper along with a team from his laboratory. "This knowledge can ultimately be put to use in systems that aren't so amenable to investigation, such as bacteria that cause cholera or lead to ulcers and stomach cancer."

Regulation of transcription initiation is generally attributable to activator/repressor proteins that bind to specific DNA sequences. However, regulators can also achieve specificity by binding directly to RNA polymerase and exploiting the kinetic variation intrinsic to different RNA polymerase-promoter complexes.

In the *Cell* paper, Gourse and his colleagues report that a previously unknown promoter interaction with *Escherichia coli* RNA polymerase defines additional recognition elements both in the promoter and in the RNA polymerase. They found a specific base in promoters that makes contact with a highly conserved, but previously underappreciated, segment of the sigma subunit of the enzyme. While this contact with sigma is very strong at promoters for

Continued on page 17



A model (modified from Haugen et al. (2006) Cell 125, 1069-1082 and Lawson et al. (2004) Curr. Opin. Struct. Biol. *14, 10-20) illustrating the newly identified contact between a segment of the sigma subunit of RNA polymerase (yellow spacefill) and a base in promoter DNA (green spacefill) in a bacterial transcription initiation complex.*

ASBMB member Richard L. Gourse is a Professor in the Department of Bacteriology at the University of Wisconsin, Madison. He received his A.B. in American Civilization, M.A.T. in Education, and Ph.D. in Cellular and Molecular Biology at Brown University in 1971, 1973 and 1980, respectively. Gourse did two post-doctoral fellowships, one at Brown University and one at the University of Wisconsin, Madison, and was an Assistant Professor in the Department of Genetics at the University of Georgia in Athens before becoming an Assistant Professor of Bacteriology at the University of Wisconsin in 1988.

Gourse has served on various national, university, and departmental committees, and has authored or co-authored over 100 publications, many with his wife and collaborator Wilma Ross. Currently, his laboratory studies bacterial gene expression, primarily at the level of transcription initiation, and has discovered new mechanisms governing promoter strength and regulation, providing new models for the mechanisms governing gene expression in all three kingdoms of life. His honors include a 1988 American Cancer Society Faculty Research Award and an NIH Research Career Development Award from 1988-1993. In 2002 he was elected to the American Academy of Microbiology and the American Association for the Advancement of Science.

Doctors Rick Gourse and Wilma Ross.

Scientists Learn How Epidermal

In a discovery that may help scientists design new cancer drugs, Howard Hughes Medical Institute researchers have provided scientists with the first definitive look at how the catalytic center of the epidermal growth factor receptor — a protein often implicated in cancer development — turns itself on to promote cell growth.

The epidermal growth factor receptor (EGFR) is overactive in many breast, lung, colon, and pancreatic cancers. Because of its key role in driving the proliferation of cells, EGFR is a target of several cancer drugs currently in development, as well as several approved therapies. The researchers said their findings offer fresh insight into how these drugs work, and clues for the design of the next generation of EGFR inhibitors.

The researchers, led by Howard Hughes Medical Institute (HHMI) investigator John Kuriyan, published their findings in the June 15 issue of the journal *Cell*. Xuewu Zhang, who is in Kuriyan's laboratory at the University of California, Berkeley, was the first author of the article. Other co-authors were from the Johns Hopkins University School of Medicine.

EGFR is a cell-surface receptor. When it is activated, it dimerizes, which then activates its tyrosine kinase domain. HHMI researchers have now learned that this dimerization causes a physical change in the shape of the kinase domain. This change of shape converts the normally inactive kinase into an active one, which then sends signals inside the cell that trigger cell growth.

"It had long been known that the EGFR ligand dimerizes the receptor and that this dimerization converts into an activation of the kinase domain; but it wasn't understood how that happens," said Kuriyan. "This paper provides for the first time a very specific and detailed molecular model for how the EGF receptor switches on at the level of the kinase domain."

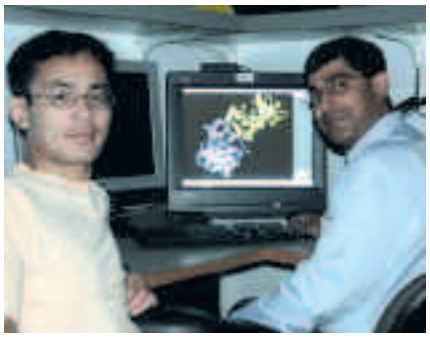
In their first set of experiments, the researchers demonstrated that the kinase domain of EGFR is normally maintained in the off state. They found that a particular mutation that activates EGFR in a large percentage of patients with lung cancer caused a 20-fold increase in the kinase domain's activity. And when Zhang forced kinase domains into close proximity to one another — as happens when the receptors dimerize — he found that the kinase switched on. This result suggests that the activation involves some kind of inter-molecular interaction.

The next step was to pinpoint how one EGFR kinase domain would switch on another. A clue came from earlier work by other researchers who were using x-ray crystallography to determine the structure of the kinase domain alone. In their structural studies, these scientists had found only the active conformation of EGFR in their protein crystals. "Those earlier findings made us realize that the crystals must hold the answer to how EGFR switches on," said Kuriyan.

Thus, Kuriyan and his colleagues performed detailed analyses of the active conformation of this crystal structure and their own new structures. These analyses revealed two types of dimers — a symmetric form, in which both units had the same relative position to each other, and an asymmetric form, in

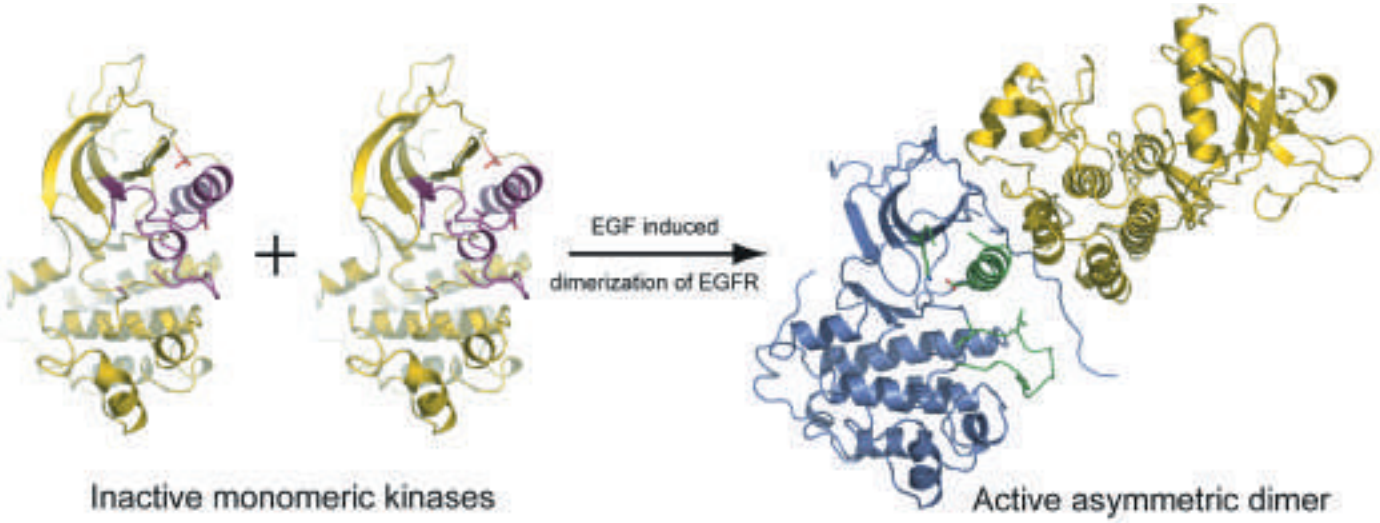
ASBMB member John Kuriyan is Chancellor's Professor at the University of California, Berkeley in the Department of Molecular and Cell Biology and the Department of Chemistry. He is also an Investigator at the Howard Hughes Medical Institute. Born in Mavelikera, India, Kuriyan began his undergraduate program in Chemistry at the University of Madras in India, and finished his B.S. degree at Juniata College in Huntingdon, Pennsylvania in 1981. He earned his Ph.D. from the Massachusetts Institute of Technology in 1986, whereupon he did a fellowship at Harvard University and worked with Gregory Petsko and Martin Karplus on the dynamics of proteins. In 1987, he began as Assistant Professor and University Fellow at the Rockefeller University in New York, New York and became Full Professor in 1997. From 1995 until 1997, he was Associate Dean of Graduate Studies at the Rockefeller University.

Kuriyan is also active as a consultant on several advisory boards internationally. He has authored or co-authored over 120 publications, many of which focus on DNA replication and the structure and mechanism of the enzymes and molecular switches that carry out cellular signal transduction. He is known for his innovative use of x-ray crystallography and resulting three-dimensional structures of proteins. His many honors include the 2005 Richard Lounsbery Award from the U.S. National Academy of Sciences.



Drs. Xuewu Zhang and John Kuriyan.

Growth Factor Receptor is Activated



Activation of the epidermal growth factor receptor tyrosine kinase domain.

which one unit took a different position relative to the other. Their subsequent experiments determined that the asymmetric conformation was important for activation.

Their studies also determined in structural detail how this activation takes place. They found that the asymmetric activation of one EGFR kinase domain by another is analogous to the activation of cyclin-dependent kinase (CDK) by cyclin, which is involved in regulating cell growth.

"Our model now is that EGFR normally sits in an inactive conformation, which we call Src/CDK-like. But when it is brought into high local concentration — that is, when it's dimerized — that overcomes the barrier for activation through an intermolecular interaction, and one EGFR molecule then pushes the active site of the other into the active state, and that switches it on," said Kuriyan.

Kuriyan said that the activation mechanism they discovered is more complex than might be expected, but for good evolutionary reason. "When the ligand arrives outside the cell, the receptor has to transmit that information to the inside of the cell. I suspect the way this worked when the first transmembrane receptors tyrosine kinase evolved was simply to make activation contingent on phosphorylation of one receptor by the other. My suspicion is that, as the EGF receptor evolved, it moved away from that primordial mechanism."

Evolution of the more specialized mechanism has ultimately enabled more specific and responsive control of the family of EGFRs. For example, this evolutionary fine-tuning has enabled different combinations of EGFR family members (including ErbB2/HER2, ErbB3/HER3 and ErbB4/HER4) to switch on one another and result in a wide spectrum of specific signals. This kind of specificity is critical to the cell, given the powerful role EGFRs play in cell proliferation, differentiation and migration, Kuriyan noted.

RNA Polymerase continued...

Continued from page 15

most genes, it is particularly weak at promoters for ribosomal RNA. Thus, the varying strength of this sequence-specific interaction affects the lifetime of the complex with RNA polymerase.

"In this case, regulation is achieved not because the promoter makes a special contact, but because it can't establish the contact," says Gourse. "This regulation system illustrates how sometimes less is more and could be one of the ancient mechanisms that arose early in evolution to regulate gene expression."

Since ribosomal RNA makes up the bulk of ribosomes, and much of the cell's energy is used to make ribosomes, control of ribosomal RNA transcription is particularly crucial to a cell's well-being.

"This work is basic to the growth of most or all bacteria," says Gourse. "By understanding transcription and control of ribosome synthesis in *E. coli*, we can understand more about these processes in bacterial species that we need to control, like those that cause disease or make toxins. *E. coli* is also the workhorse of the biotechnology industry. Understanding *E. coli* gene expression in detail allows us to harness these cells for producing products of biotechnological importance, like pharmaceuticals."

ASBMB Launches Honor Society For Outstanding Students

"The American Society for Biochemistry and Molecular Biology has launched an Honor Society for outstanding students in the Molecular Life Sciences. The Society, XΩΛ, will induct undergraduates in their Junior and Senior Years in recognition of their achievements and commitment to research and education in the molecular life sciences. The Honor Society builds from the concept of the Undergraduate Affiliates Network (UAN) started several years ago and will provide both recognition for outstanding students and a mentoring network as they progress from their undergraduate program through graduate or professional school and beyond. As part of the "network," XΩΛ inductees are expected to act as mentors for other students in the network. To initiate the program, the UAN Steering committee has inducted a number of "senior" members of the Society who have agreed to act as mentors to undergraduate inductees.One of the founding "senior" members, Karlett Parra-Belky is shown here with her students and ASBMB Education Award winner (also an inductee in the honor society) Tom Cech. A full list of these "senior" inductees as well as recently inducted undergraduates is available on the XΩΛ web page

As described in the Mission Statement, The Honor Society exists to recognize outstanding juniors and seniors interested in pursuing careers in the molecular life sciences and to provide a mentoring network to assist in the attainment of their goals.

Upon election to the society new members receive a free one-year membership in ASBMB, a travel award to attend the next annual meeting of the society, access to the mentoring activities of the Honor Society (all Honor Society members mentor other members), a certificate of membership in the Honor Society, and the Society lapel pin.

UAN Faculty Advisors may establish local chapters of the Honor Society provided they maintain a minimum of 10 student members of ASBMB. Chapter benefits include being able to request a XΩΛ Speaker, free access to the undergraduate program consulting services of ASBMB, and support from ASBMB and the UAN in hosting approved regional UAN-XΩΛ Scientific Fall Meetings.

The Honor Society maintains a list of members of the Society who are available, upon request to the Society, to travel to a campus to present a XΩΛ seminar at no cost other than any local housing or meal costs (XΩΛ speakers have agreed to travel free to regional campuses and refuse to accept honoraria).

XΩΛ local chapters may request the services of a consultant or team of consultants for program review purposes with no travel costs or consultation costs, any local accommodation or meal costs must be paid by the Chapter.

UAN chapters encourage students to engage in meaningful research activities, often as early as their first year in college. Students engaged in summer research often find that the stimulation

One of the founding "senior" members of the ASBMB Honor Society, Karlett Parra-Belky (on the right) is shown here with her students (Sara Sorrell, Sarah Bilbo, and Mark Finch) and Tom Cech, recipient of the ASBMB Education Award for Exemplary Contributions to Education and also an inducteee in the honor society.

Sarah Wacker, who will attend Graduate School at Rockerfeller University this Fall, is shown with other students talking with another "senior" inducteee, Nobelist Edmund Fischer at the recent ASBMB Meeting.

of presenting at a Fall meeting focuses their research and helps them, for example, to prepare an abstract for submission to the next Annual ASBMB meeting. To provide an avenue for such meetings on a regional basis, Honor Society Chapters are encouraged, in consultation with the regional UAN Director to organize a Fall meeting where students from the chapter and from other regional schools present the results of their research in either poster or oral presentations. Chapters sponsoring such a meeting will receive travel awards to be awarded for outstanding students, to help them attend the ASBMB National Meeting the following Spring: for example a number of chapters are organizing Fall regional meetings this October so that students can present their research and get feedback prior to the abstract submission deadline for the Spring 2007 ASBMB Meeting in Washington, DC. At each of these regional meetings several travel awards will be presented for "best posters" to assist the student in attending the Washington DC meeting. These awards are in addition to awards the UAN chapter may already qualify for.

ΧΩΛ has already inducted its first class of undergraduates, one of whom, Sarah Wacker, who will attend Graduate School at Rockerfeller University this Fall, is shown with other students talking with another "senior" inductee, Edmund Fischer at the recent ASBMB Meeting. A detailed feature on these students will appear in the September Issue of the UAN Newsletter, Enzymatic.

R. James Turner Receives IADR Salivary Research Award

R. James Turner, Chief of the Membrane Biology section at the National Institute of Dental and Craniofacial Research (NIDCR), is the recipient of the 2006 Salivary Research Award from the International Association for Dental Research (IADR). The award was designed to stimulate and recognize outstanding and innovative achievements that have contributed to the basic understanding of salivary gland structure, secretion, and function, or salivary composition and function.


Dr. R. James Turner

Since 1985, Turner has focused his research on salivary epithelial cells, and he is widely recognized for identifying and characterizing the ion transport systems responsible for fluid secretion by rat parotid and human labial gland acinar cells, including their regulation by secretory stimuli. Turner has published approximately 100 peer-reviewed research papers and has given numerous invited international lectures. He currently serves on the editorial board of the *Journal of Biological Chemistry*.

The IADR Salivary Research Award is supported by the William Wrigley, Jr. Company, and consists of a cash prize and a plaque. It is one of 15 Distinguished Scientist Awards conferred annually by the IADR, representing the highest honor the Association can bestow. Turner received his award in June during the Opening Ceremonies of the IADR's 84th General Session.

David E. Clapham Lauded By Bristol-Myers Squibb

HHMI investigator David E. Clapham, Aldo R. Castañeda Professor of Cardiovascular Research at Children's Hospital Boston and Professor of Neurobiology at Harvard Medical School, recently received the Bristol-Myers Squibb Foundation Freedom to Discover Distinguished Achievement Award in cardiovascular research.

Initiated in 1977, the Distinguished Achievement Awards are presented annually to individuals for outstanding contributions in the fields of cancer, cardiovascular, infectious diseases, metabolic diseases, neuroscience and nutrition. Award recipients in each field receive a $50,000 prize and a silver medallion.

The Award for Distinguished Achievement in Cardiovascular Research was first presented in 1991. Winners are selected by an independent peer-review selection committee whose members are grant administrators of current Bristol-Myers Squibb Unrestricted Cardiovascular Research Grants.


Dr. David Clapham

Past award recipients include Shaun R. Coughlin, Masashi Yanagisawa, Jonathan G. Seidman, and Michael A. Gimbrone, Jr.

Scott D. Emr to Lead Biology Institute at Cornell

ASBMB member Scott D. Emr has been selected as the Frank H. T. Rhodes Class of '56 Endowed Director of the new Institute of Cell and Molecular Biology at Cornell University.

The institute, which will eventually be located in Cornell's new Life Science Technology Building, will provide a bridge between different departments related to basic cell biology.


Dr. Scott D. Emr

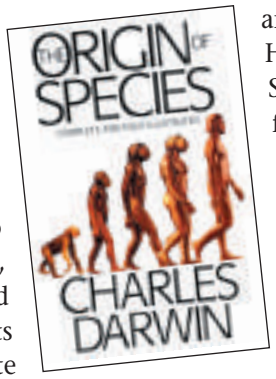
The institute is being planned as an interdisciplinary center that links cell biology and the physical sciences, in which physics, chemistry, applied engineering, chemical engineering, computational sciences and the newest technologies might be used to advance human understanding of the cell.

Emr, who is currently a Professor of Cellular and Molecular Medicine at the University of California-San Diego School of Medicine and an Investigator with the Howard Hughes Medical Institute, will begin his Cornell appointment in February 2007. The $158 million Life Science Technology Building is expected to open in early 2008.

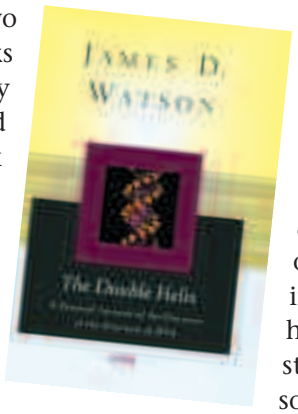
Popular Science Books – What to Recommend to Family and Friends

By The ASBMB Education and Professional Development Committee

One of the best ways to interest people in science, in general and in what we do in particular, is to get them to read about science and the way it is done. Fortunately, there is a lot of high quality popular science writing available to anyone who has access to a good library or bookseller. We, the members of the Educational and Professional Development Committee, wondered which of these popular science books to recommend to family, friends and, of course, interested students. We asked a group of about 60 scientists to recommend their favorite books. Thank you very much to everyone who sent in suggestions (the response was very gratifying) and our apologies for any omissions.



You can see the resulting list of over 70 books on the ASBMB website. They range in time from "The Origin of Species" to books that were first published last year. The subjects they cover run the gamut from general books such as "Guns, Germs and Steel" by Jared Diamond, through interesting historical treatments of the scientific endeavor, like "The Eighth Day of Creation" by Horace Freeland Judson to personal accounts, such as "The Double Helix" by James Watson and "What Mad Pursuit: A Personal View of Scientific Discovery" by Francis Crick, to books that cover topics that are very much in the news these days, including "The Proteus Effect: Stem Cells and Their Promise for Medicine" by Ann Parsons and "The Plausibility of Life: Resolving Darwin's Dilemma" by Marc Kirschner and Jon Gerheart. Stephen J. Gould's many books and essays were highly recommended by multiple people, as were two of Matt Ridley's books ("Genome: The Autobiography of a Species in 23 Chapters" and "The Red Queen: Sex and the Evolution of Human Nature"). Several people also found "The Billion Dollar Molecule: One Company's Quest for the Perfect Drug" by Barry Werth an exciting read.



The list is divided into very general topical groups including, among others, "About Science and Scientists" (by far the largest), "Biology" and "Physics." The Publisher, date and ISBN refer, where possible, to the original edition. Many of these, however, are also available in paperback editions or have been reissued, and all can be found on the online bookseller sites. This list is by no means comprehensive—there is an amazing amount of good science writing out there—but we hope it will provide a starting place and some ideas for what to recommend the next time someone asks about what you do, or shows an interest in science, as well as perhaps stimulate you to read a few good books you may have missed. In the future, we hope to provide book reviews for some of these books in upcoming issues of *ASBMB Today*.

Some New Faces at Our Journals

Recently, there have been some additions to the editors of our Journals. The *Journal of Lipid Research* has two new associate editors: Carol C. Shoulders, Medical Research Council Clinical Sciences Centre in London, and Robert C. Murphy, University of Colorado Health Sciences Center in Aurora, Colorado. *Molecular & Cellular Proteomics* has named Al Burlingame, University of California, San Francisco, co-editor with Ralph Bradshaw.

In addition, the *Journal of Biological Chemistry* has added 10 new Associate Editors: Dale John Benos, University of Alabama at Birmingham; George Carman, Rutgers University, New Brunswick, New Jersey; Martha Fedor, The Scripps Research Institute, La Jolla, California; Joel M. Gottesfeld, The Scripps Research Institute, La Jolla, California; Peter Guengerich, Vanderbilt University, Nashville, Tennessee; John Kyriakis, Tufts University School of Medicine, Boston, Massachusetts; Luke O'Neill, Trinity College, Dublin, Ireland; James N. Siedow, Duke University, Durham, North Carolina; Linda Spremulli, University of North Carolina at Chapel Hill; and Xiao-Fan Wang, Duke University Medical Center, Durham, North Carolina.

By Nicole Kresge, Science Editor

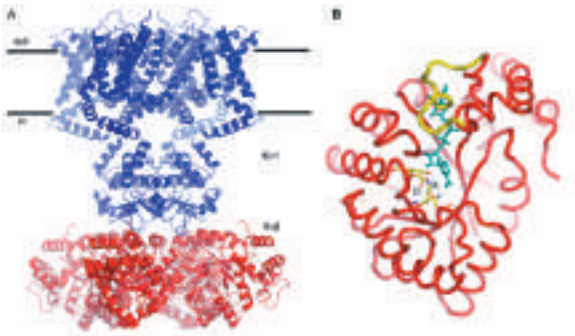
ASBMB Bio Bits

Modulation of Voltage-dependent Shaker Family Potassium Channels by an Aldo-Keto Reductase

Jun Weng, Yu Cao, Noah Moss, and Ming Zhou

J. Biol. Chem. 2006 281: 15194-15200

Aldo-keto reductases catalyze redox reactions using NADPH as a cofactor, turning aldehydes into alcohols. It has been known for some time that Kvβ, a subunit associated with Kv potassium channels, has structural elements characteristic of aldo-keto reductases, but whether it serves this enzymatic function has not previously been demonstrated. The authors of this paper identified several Kvβ substrates and demonstrated that Kvβ is a functional aldo-keto reductase. They also found that channel function is modulated when the Kvβ-bound NADPH is oxidized. This study is the first to show that Kvβ subunits have aldo-keto reductase activity and that this activity is responsible for the modulation of Kv channel gating properties by β subunits. More importantly, the aldo-keto reductase activity of β subunits represents the functional link between the redox state of the cell and potassium channel activity that regulates membrane excitability.



Structural features of Kvβ.

NMR Structure of the Full-length Linear Dimer of Stem-Loop-1 RNA in the HIV-1 Dimer Initiation Site

The structure of SL1.

Nikolai B. Ulyanov, Anwer Mujeeb, Zhihua Du, Marco Tonelli, Tristram G. Parslow, and Thomas L. James

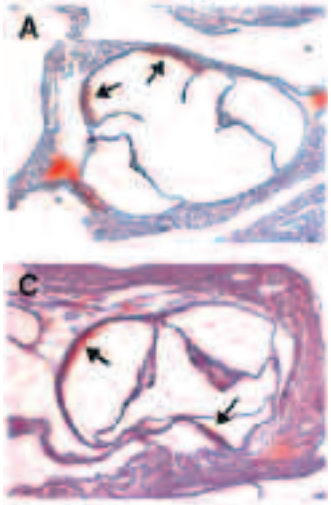
J. Biol. Chem. 2006 281: 16168-16177

During retrovirus assembly, two identical copies of genomic RNA are packaged into viral particles. This non-covalently linked dimer of RNA is important for various critical events in the viral life cycle, including reverse transcription, recombination, RNA packaging, and viral infectivity. The packaging signal for the RNA is located in the 5′-untranslated region of unspliced RNA, which contains the stem-loop structure SL1. This structure serves as the dimerization initiation site and spontaneously dimerizes via a palindromic hexanucleotide sequence in its apical loop. Several structures of short SL1 RNA constructs have been solved, but no model of the full-length SL1 RNA exists. In this paper the authors present the NMR structure of the full-length linear dimer of SL1 from HIV-1. The structure was refined using nuclear Overhauser effect and residual dipolar coupling data. Determination of this SL1 structure is important for understanding dimerization and packaging of retroviral RNA and is potentially valuable for structure-based development of therapeutic drugs that interfere with these processes in HIV-1.

Lack of the Antioxidant Glutathione Peroxidase-1 Does Not Increase Atherosclerosis in C57BL/J6 Mice Fed a High-Fat Diet

Judy B. de Haan, Paul K. Witting, Nada Stefanovic, Josefa Pete, Michael Daskalakis, Ismail Kola, Roland Stocker, and Joseph J. Smolich

J. Lipid Res. 2006 47: 1157-1167.



Atherosclerosis is a major cause of morbidity and mortality in Western societies. Oxidative stress is thought to contribute to the initiation and progression of the disease. To regulate the flux of reactive oxygen species and to limit oxidative damage, eukaryotic cells have evolved an extensive array of antioxidant defense systems, including intracellular antioxidant enzymes such as glutathione peroxidase-1 (Gpx1). Studies have suggested that the levels of these enzymes decline during atherogenesis, implying a link between reduced antioxidant capacity and increased disease. In this paper, the authors tested the impact of Gpx1 deficiency on atherosclerotic processes and antioxidant enzyme expression in mice fed a high-fat diet. Surprisingly they found that a specific deficiency in Gpx1 was not accompanied by an increase in markers of oxidative damage or increased atherosclerosis in their murine model of high-fat diet-induced atherogenesis.

Lipid deposition was not significantly different in control (A) and Gpx1-deficient mice (c) after 12 weeks of a high-fat diet.

Proteome Analysis of Halobacterium sp. NRC-1 Facilitated by the Biomodule Analysis Tool BMSorter

Rueichi R. Gan, Eugene C. Yi, Yulun Chiu, Hookeun Lee, Yu-chieh P. Kao, Timothy H. Wu, Ruedi Aebersold, David R. Goodlett, and Wailap Victor Ng

Mol. Cell. Proteomics 2006 5: 987-997.

Halobacterium species are halophilic microorganisms that have adapted to optimal growth under conditions of extremely high salinity—10 times that of sea water. The genomes of *Halobacterium* species are very unstable and are known for their large number of insertion elements. In this paper, the authors analyzed the soluble proteome of *Halobacterium* species NRC-1 by two-dimensional liquid chromatography coupled to electrospray ionization tandem mass spectrometry. They identified a total of 888 unique proteins with a ProteinProphet probability (*P*) between 0.9 and 1.0. To evaluate the biochemical activities of the organism, the proteomic data were subjected to a biological network analysis. The authors found that up to eight amino acids could be converted to oxaloacetate, fumarate, or oxoglutarate in the citrate cycle for energy production. In addition, glutamate and aspartate could be interconverted from other amino acids or synthesized from citrate cycle intermediates to meet the high demand for the acidic amino acids that are required to build the highly acidic proteome of the organism.

Interaction network of the enzymes, amino acids, and intermediates in 17 amino acid metabolic pathways and the citric acid cycle of Halobacterium

by John D. Thompson, Editor

Premiums Show Big Pharma Hungry for Little Biotechs

Pharmaceutical company Novartis AG's recent decision to acquire NeuTec Pharma PLC for £305 million (US $570 million) in cash adds two highly promising anti-infection drugs to its portfolio. Novartis' offer of a 109% percent stock premium is seen as evidence of just how hungry big pharma is for drugs discovered by small biotech companies

According to Reuters, large take-out premiums are becoming the norm in the sector as more drug makers decide that buying young rivals outright can make more sense than signing licensing deals, which would see sizeable future revenues spent on royalties. With licensing deals becoming increasingly expensive and the world market for biotech drugs growing at three times the rate of the conventional drug market, big pharma companies are showing greater willingness to acquire innovative smaller firms.

NeuTec, formed in 1997, specializes in developing medicines against hard-to-treat hospital-acquired infections known as "superbugs." The firm currently has two medicines in clinical development. Mycograb, used with antifungals to treat candida infections, is scheduled for submission to U.S. health authorities in 2009. Aurograb, used with antibacterials to treat staph infections, will be submitted in 2010.

"In clinical trials, Mycograb has been shown to significantly lower the mortality of patients with severe fungal infections," Vasella said. "Both Mycograb and Aurograb promise to dramatically improve the treatment possibilities in this area, and will also enable Novartis to strengthen its biologics pipeline and anti-infective drug portfolio."

"There is a very strong demand in large cap pharma to fish in the pond for quality biotech companies," said Alexis de Rosnay, Lehman Brothers' head of healthcare investment banking, who advised Novartis on the NeuTec deal. He told Reuters, "You'll find continued opportunistic M&A activity with Novartis, GSK and Pfizer—and with AstraZeneca potentially moving into the fray—but I don't think you'll see mega deals."

WTO Battle Looms over Patents

Developing countries led by India and Brazil are on a collision course with Washington by stepping up their campaign in the World Trade Organization to require that patent applicants disclose the origin of inventions using biological resources or traditional knowledge.

India, Brazil, Tanzania, Thailand, Peru, and Pakistan are pushing an amendment to the WTO's intellectual property agreement that would make such disclosure a condition of receiving a patent. In the event of failure to comply, existing patents would be revoked or made unenforceable.

The sponsors claim their proposal is needed to stop "bio-piracy," the exploitation of their genetic resources for drug development without a fair return to the host communities. However the pharmaceutical industry says existing rules are adequate and claims that draconian penalties for non-disclosure would stifle interest in developing new biomedicines.

The proposal, which is expected to attract support from many of the WTO's poorer members, was made as part of the Doha global trade round, and may be used as a bargaining chip with rich countries for other concessions in the negotiations. The WTO has set a deadline of July 31 to make progress on this issue and also on a European Union demand for the extension of rules protecting geographical names for products other than wines and spirits. However, Rufus Yerxa, WTO deputy director-general, who is in charge of consultations on these issues, said last month he did not expect agreement by the deadline.

The proposed amendment would require patent applicants to disclose both the country from which the resource was obtained and the country of origin of the resource. They would also have to show that they had complied with national laws on "prior informed consent" for access to the resource and on equitable benefit- sharing from its commercial development.

"Prior informed consent" and equitable benefit-sharing are required by the United Nations convention on biological diversity, but the convention leaves it to member countries to decide whether, and how, to put these concepts into national law. The U.S., as a non-signatory, is not bound by the convention.

Pharmaceutical companies say they already obey national laws, which normally require a contract with the government, and that only a handful of bio-piracy cases have been identified. But India and Brazil argue that without international rules, national laws can be easily evaded.

For Your Lab/For Your Lab/For Your Lab

The information in For Your Lab has been provided by manufacturers and suppliers of laboratory equipment. For further information about any of these products listed contacts are listed at the bottom of each panel. When contacting any of these companies, please mention that you saw their product in *ASBMB Today*. Please note that a listing in *ASBMB Today* does not imply an endorsement by the American Society for Biochemistry and Molecular Biology or by any of its members or staff.

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by John D. Thompson, Editor

GSK Planning New (S) $300 Million Vaccine Plant in Singapore

GlaxoSmithKline (GSK) will be strengthening its presence in Asia with the establishment of its first vaccine manufacturing plant in Singapore. The plant, due to be operational in 2010, will be Singapore's first primary vaccine facility and GSK's largest vaccine investment in Asia.

The company will spend more than (Singapore) $300 million over the next four years, in the first phase of development of the plant dedicated to the primary production of pediatric vaccines. Building work, which has already started, will be phased over a number of years with a view to ensuring maximum manufacturing flexibility. More than 200 jobs will be created to support this facility.

Speaking at the groundbreaking ceremony for the facility, Khaw Boon Wan, Singapore's Minister for Health, said, "This GSK facility will be our first vaccine manufacturing facility. This is significant for two reasons. First, it will add to our growing base of biologics manufacturing activities and reinforce our position as one strategic global manufacturing node for the biomedical sciences industry. Second, vaccines are important weapons in our battle against the spread of infectious diseases. By acquiring this capability to produce vaccines locally, we have further enhanced our preparedness against such outbreaks."

Since the early 1970s, Singapore has played a key role in the expansion of GSK's global network. Most recently, in 2005, GSK opened its Centre for Research in Cognitive and Neurodegenerative Disorders in Singapore's Biopolis, and also announced its plans to build a new research and development pilot plant at its Global Manufacturing Supply site in Jurong. With this primary vaccine facility, GSK's total investment in Singapore will exceed (S) $1.5 billion.

Patrick Florent, Senior Vice President, Global Industrial Operations, GSK Biologicals, said, "GSK has enjoyed a presence in Singapore since 1959, even before Singapore became an independent nation. We chose to develop our new vaccine plant—also our largest vaccine investment in Asia—in Singapore, due to its excellent infrastructure, highly-qualified workforce, superb geographical location and strong government commitment to the biomedical sciences sector. The new plant emphasizes our long-term commitment to Singapore and to the Asia-Pacific region, and Singapore remains an attractive location for any future investment for GSK."

Once operational, the new plant will be the centre of GSK's bulk polysaccharides and conjugates production worldwide, and will play a pivotal role in the production of pediatric vaccines to meet global demand. The new facility will manufacture GSK's innovative conjugate vaccine that provides protection against *Streptococcus pneumonia* and Non-typeable *Haemophilus influenza*, two pathogens responsible for serious illness among children. GSK's multiple combinations of new meningitis conjugate vaccines also will be produced at this facility.

The plant is expected to contribute significantly to the delivery of GSK's broad pipeline of innovative vaccines, and to the growth of the biomedical industry and other inter-related sectors in Singapore. Built on an 85,000 square meter plot, the new facility will include high-tech production buildings, as well as administration offices, meeting rooms, quality control laboratories, power plants and a warehouse. It is also designed to allow for future site expansion. GSK intends to boost employee skills by sending key personnel to Belgium, Germany, and Hungary for training in its manufacturing plants.

HHS Awards BioShield Contract for Botulism Antitoxin

The Department of Health and Human Services (HHS) has awarded a contract to the Cangene Corporation of Winnipeg, Canada in the amount of $362,641,105 for 200,000 doses of *Heptavalent Botulism Antitoxin*. The contract runs for five years, with product delivery to the Strategic National Stockpile scheduled to begin next year.

The number of doses being purchased under the new contract is based on the Department of Homeland Security's determination that botulinum toxins pose a threat to the U.S. population, and the interagency Weapons of Mass Destruction Medical Countermeasures Subcommittee's recommendation that heptavalent botulism antitoxin be acquired to improve the nation's biodefense preparedness and response capabilities and protect civilians from a potentially lethal exposure to botulinum toxin.

The botulinum neurotoxin disrupts nerve functions which may result in muscle paralysis within hours. Respiratory muscle paralysis can result in death unless assisted (mechanical) ventilation is provided; therefore, the need for rapid diagnosis, access to intensive medical care, and antitoxin is vital. Botulism antitoxin blocks the action of circulating neurotoxin in the bloodstream.

Career Opportunities

TENURE-TRACK POSITION IN BIOCHEMISTRY

University of Wisconsin—Madison

The Department of Biochemistry at the University of Wisconsin-Madison invites applications for a position in biochemistry at the Assistant Professor level. Applications in all areas of biochemistry will be considered. The University and Department provide an excellent environment for the development of an outstanding research program. The successful candidate will be expected to develop a vigorous, extramurally funded, independent research program, and to participate in the undergraduate and graduate teaching programs of the Department. They will also be expected to perform university and community service as appropriate. Applications should include your curriculum vitae, a list of publications, a brief summary of accomplishments and direction of future research and three letters of reference. Electronic applications are preferred and should be sent to: Professor Elizabeth Craig, chair@biochem.wisc.edu or send your application and supporting materials to the Department of Biochemistry, University of Wisconsin-Madison, 433 Babcock Drive, Madison, WI 53706-1544. Applications must be received by September 15, 2006 to ensure consideration. The University of Wisconsin is an Affirmative Action, Equal Opportunity Employer and encourages applications from women and minorities.

STAFF SCIENTIST

PDL BioPharma, Inc.

PDL BioPharma, Inc. is a biopharmaceutical company focused on discovering, developing and commercializing innovative therapies for severe or life-threatening illnesses. The company currently markets a portfolio of leading products in the acute-care hospital setting in the United States and Canada, and generates royalties through licensing agreements with top-tier biotechnology and pharmaceutical companies, based on its pioneering antibody humanization technology. Our product pipeline includes six investigational compounds in Phase 2 or Phase 3 clinical development for hepatorenal syndrome, inflammatory and autoimmune diseases, cardiovascular disorders and cancer. We currently have the following opportunity in our Fremont, CA location:

Staff Scientist (4106)
Reporting to the Director of Analytical Sciences, the successful candidate will manage a group that oversees projects involving the characterization of protein therapeutics including monoclonal antibodies and the development of new analytical methods. Other responsibilities include preparing/defending regulatory submissions, developing and executing comparability plans/protocols, working with external partners, writing technical reports, and transferring methods to Quality Control and other external groups. Will also investigate new analytical methodologies and coordinate analytical activities within and outside of Process Development.

Requirements:

- BS/MS/PhD in Biochemistry, Pharmaceutical Chemistry, Chemistry or related field.
- 5-15 years of relevant biotechnology experience.
- A background in antibody/protein and glycoprotein chemistry with a clear understanding of the CMC regulatory guidance as well as hands-on experience with IND and/or BLA filings.
- Ability to design scientific studies in response to or anticipation of regulatory issues and technical challenges.
- The ideal candidate will have a proven track record of managing a technical/scientific function as well as exceptional organizational, communication and interpersonal skills.

PDL BioPharma is proud to offer a comprehensive benefits package, including medical, dental, vision, 401k and life insurance. Please apply online at www.PDL.com Reference # 4106. We are an Equal Opportunity Employer.

Calendar of Scientific Meetings

AUGUST 2006

20th Annual Symposium of the Protein Society

August 5–9 • San Diego, CA
E-mail: cyablonski@proteinsociety.org; www.proteinsociety.org
Ph: 301-634-7277

ISMB 2006: Intelligent Systems for Molecular Biology

August 6–10 • Fortaleza, Brazil
E-mail: admin@iscb.org; ismb_2006.cbi.cnptia.embrapa.br//
Ph: 858-822-0852 .

9th Annual Scientific Forum of the Southeast Lipid Association

August 11–13 • Amelia Island, FL
www.lipid.org/chapters/sela
Email: ssheridan@lipid.org

Kern Aspen Lipid Conference

August 19–22 • Aspen, CO
www.uchsc.edu/kernconference/
Email: Julie.morris@uchsc.edu

ISPMB 2006 — 8th International Congress of Plant Molecular Biology

August 20–25 • Adelaide Convention Centre, South Australia
Abstract and Early Registration Deadline: Friday, March 3.
Online registration and abstract submission pages:
www.sallyjayconferences.com.au/ispmb2006/registration.htm
www.sallyjayconferences.com.au/ispmb2006/abstract.htm
Abstracts cannot be accepted without registration and payment. All abstracts must be submitted online, abstracts sent as attachments will not be accepted.
www.sallyjayconferences.com.au/ispmb2006/program.htm

1st FECS European Chemistry Conference

August 27–31 • Budapest, Hungary
E-mail: narasza@para.chem.elte.edu
www.fecs-budapest2006.hu/

17th International Mass Spectrometry Conference

August 27–September 1 • Prague, Czech Republic
www.imsc2006.org; E-mail: info@imsc2006.org
Ph: 420-241-062-645

SEPTEMBER 2006

7th Siena Meeting from Genome to Proteome: Back to the Future

September 3–7 • Siena, Italy
www.unisi.it/eventi/proteome/

29th European Peptide Symposium

September 3–8 • Gdansk, Poland
www.29eps.univ.gda.pl; E-mail: 29eps@chem.univ.gda.pl
Ph: 48-58-3450363

47th International Conference on the Bioscience of Lipids — ICBL-ELIFE-ILPS Joint Meeting

September 5-10 • Pécs, Hungary
For information contact:
www.cbi12006icbl2006.hu/

5th European Conference on Computational Biology

September 10–13 • Eliat, Israel
www.eccb06.org/; E-mail: eccb06@diesenhaus.com
Ph: 972-3-5651313

American Chemical Society National Meeting and Expo

September 10-14 • San Francisco
For Information: Department of Meetings & Expositions Services; Kathleen Thompson, Assistant Director, Melissa Redd, Assistant
Fx: 202-872-6128; Ph: 202-872-6061
E-mail: k_thompson@acs.org; E-mail: m_redd@acs.org

5th European Congress of Biogerontology

September 16-20 • Istanbul, Turkey
Ph: +90 216 347 35 35 Pbx; Fax: +90 216 347 78 50
Email: okarabel@symcon.com.tr; Website: www.symcon.com.tr
Congress President Prof. Serif Akman, Etlik, Ankara , Turkey
Ph: +90 312 304 3306; Fax: +90 312 304 3300
E-mail: sakman@gata.edu.tr

The 33rd Annual Conference of the Federation of Analytical Chemistry and Spectroscopy Societies (FACSS)

September 24–28 • Disney's Contemporary Resort, Lake Buena Vista, FL
Contact: FACSS, PO Box 24379, Santa Fe, NM 87502
Phone: 505-820-1648; Fax: 505-989-1073
Email: facss@facss.org; www.facss.org

2nd International Conference: Metzincin Metalloproteases in Health and Disease

September 24-29 • Monte Verità, Ascona, Switzerland
Information, registration and abstract submission: www.metz-incin.unibe.ch
Organizers: Erwin Sterchi, Judith Bond, Walter Stoecker
Contact: erwin.sterchi@mci.unibe.ch

OCTOBER 2006

4th Euro Fed Lipid Congress

October 1–4 • Madrid, Spain
www.eurofedlipid.org/meetings/madrid/index.htm
Email: amoneit@eurofedlipid.org

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; www.bcii2006.org

3rd Annual Scientific Forum of the Midwest Lipid Association

October 20–22 • Kansas City, MO
www.lipid.org/chapters/mwla; Email: ssheridan@lipid.org

Asilomar Conference on Mass Spectrometry

October 20-24 • Asilomar Conference Center, Pacific Grove, CA
Fundamentals of Gas Phase Ion Chemistry: Experiment and Theory
Program Chairs: Frantisek Turecek and Thomas Morton
For information contact: ASMS
Ph: 505-989-4517; Email: asms@asms.org; www.asms.org

FEBS Special Meeting: European Lipidomics Initiative

October 21–25 • Noordwijkerhout, The Netherlands
www.febslipid2006.chem.uu.nl/

4th International Conference on Structural Genomics

October 22–26 • Beijing, China
Website: www.sino-meetings.com/icsg2006/

NHUPO 5th Annual World Congress

October 28–November 1 • Long Beach, CA
www.hupo2006.com; E-mail: Wehbeh.Barghachie@mcgill.ca
Ph: 514-398-5063

The Liver Meeting 2006— 57th Annual Meeting of the American Association for the Study of Liver Disease

October 27–31 • Boston, MA
www.aasld.org/eweb/DynamicPage.aspx?webcode=2006_AnnualMeeting

NOVEMBER 2006

Transcriptional Regulation by Chromatin and RNA Polymerase I I

November 2–6 • Kiawah Island, South Carolina
Organizer: Ali Shilatifard, Saint Louis, University School of Medicine, Email: shilatia@slu.edu

43rd Japanese Peptide Symposium/4th Peptide Engineering Meeting

November 5–8 • Yokohama, Japan
www.peptide-soc.jp/43JPS4PEM.html
E-mail: hmihara@bio.titech.ac.jp

Fall Workshop: The Present and Future of Quadrupole Ion Trap Mass Spectrometry

November 9-10 • Catamaran Resort, San Diego
Program Chairs: Victor Ryzhov and Richard Vachet
For information contact: ASMS
505-989-4517; asms@asms.org; www.asms.org

Annual meeting of the Society for Glycobiology

November 15-18 • Los Angeles
Contacts: Linda Baum, President; lbaum@mednet.ucla.edu
Kelley Moremen, Secretary; moremen@uga.edu
Website: www.glycobiology.org

The 19th Annual Tandem Mass Spectrometry Workshop

November 29–December 2 • Lake Louise, Alberta, Canada
www.csms.inter.ab.ca/louise.htm
E-mail: mnlouise@telusplanet.net; Ph: 403-335-3707

DECEMBER 2006

Second ISN Special Neurochemistry Conference: Neural Glycoproteins and Glycolipids

December 1-5 • Antigua, West Indies
For information contact:www.isnantigua2006.org/

19th World Diabetes Congress

December 3–7 • Cape Town, South Africa
www.idf2006.org/

American Society for Cell Biology 46th Annual Meeting

December 9-13 • San Diego
Ph: 301-347-9300; Email: ascbinfo@ascb.org
Website: www.ascb.org

APRIL 2007

American Society for Biochemistry and Molecular Biology Annual Meeting in Conjunction with EB2007

April 28 – May 2 • Washington, DC
Contact: ASBMB 2007, 9650 Rockville Pike, Bethesda, MD 20814-3008
Ph: 301-634-7145
Email: meetings@asbmb.org
Website: www.asbmb.org/meetings

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