SEE WHAT YOU DID OR WHAT YOU MISSED

ASBMB today

June 2007

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exhibits

THE 2007 ASBMB MEETING

hill visits

symposia

American Society for Biochemistry and Molecular Biology

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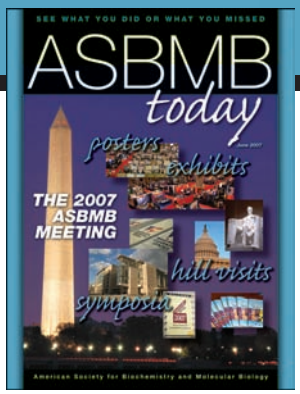
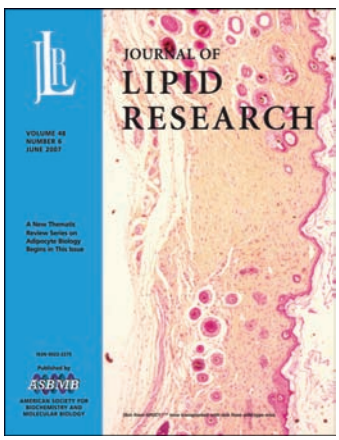
JUNE 2007



ON THE COVER:
The 2007 ASBMB Annual Meeting is over, but you can read highlights from the meeting throughout this issue of *ASBMB Today*.



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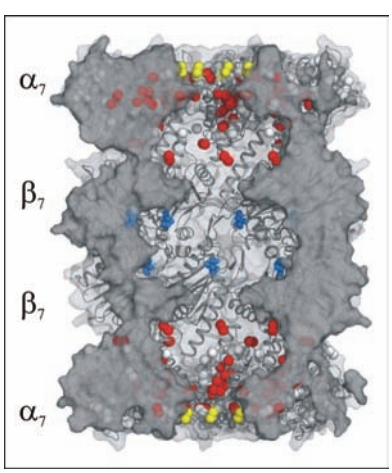

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letters to the editor

RESPONSE

Medical Biochemistry

Upon reading the "Letter to the Editor" on page 2 of the April issue of *ASBMB Today*, I was impressed by the abstract from Manuel João Costa, in Portugal, decrying the deficiency of integration of medical information, especially in biochemistry.

Having taught medical biochemistry (with special focus on endocrinology) from 1952 until 2006 in various frameworks and having thus found and written of my findings, I decided to share those which seemed relevant with you and your readership in hope that they might be helpful.

Herewith are enclosed two brief reprints from *The Scientist*, a paper published in the *Journal of the American Osteopathic Association* ((1991) **91,** 1005–1018) when I was chairing the Biochemistry Department at the Chicago College of Osteopathic Medicine, and a short, unpublished note I wrote to the Dean of Medical Education at Northwestern University School of Medicine when I was teaching there.

Wells E. Farnsworth
Schaumburg, Illinois

Editor's note: In the interest of space, we cannot reprint Farnsworth's articles. However, the citation information for the articles is as follows, and readers are encouraged to access the articles themselves:

- *Farnsworth, W. E. In Teaching Science, Let the Textbook Support the Classwork, Not Vice Versa. The Scientist (1992)* ***6,*** *12*
- *Farnsworth, W. E. Government Research Support. The Scientist (1996)* ***10,*** *12*
- *Farnsworth, W. E. Training Physicians to Be Doctors–Teachers and Healers, Problem-solvers and Decision-makers. Journal of the American Osteopathic Association (1991)* ***91,*** *1005–1018*

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president's message

Science Is Changing—A New Refrain?

HEIDI HAMM, PRESIDENT

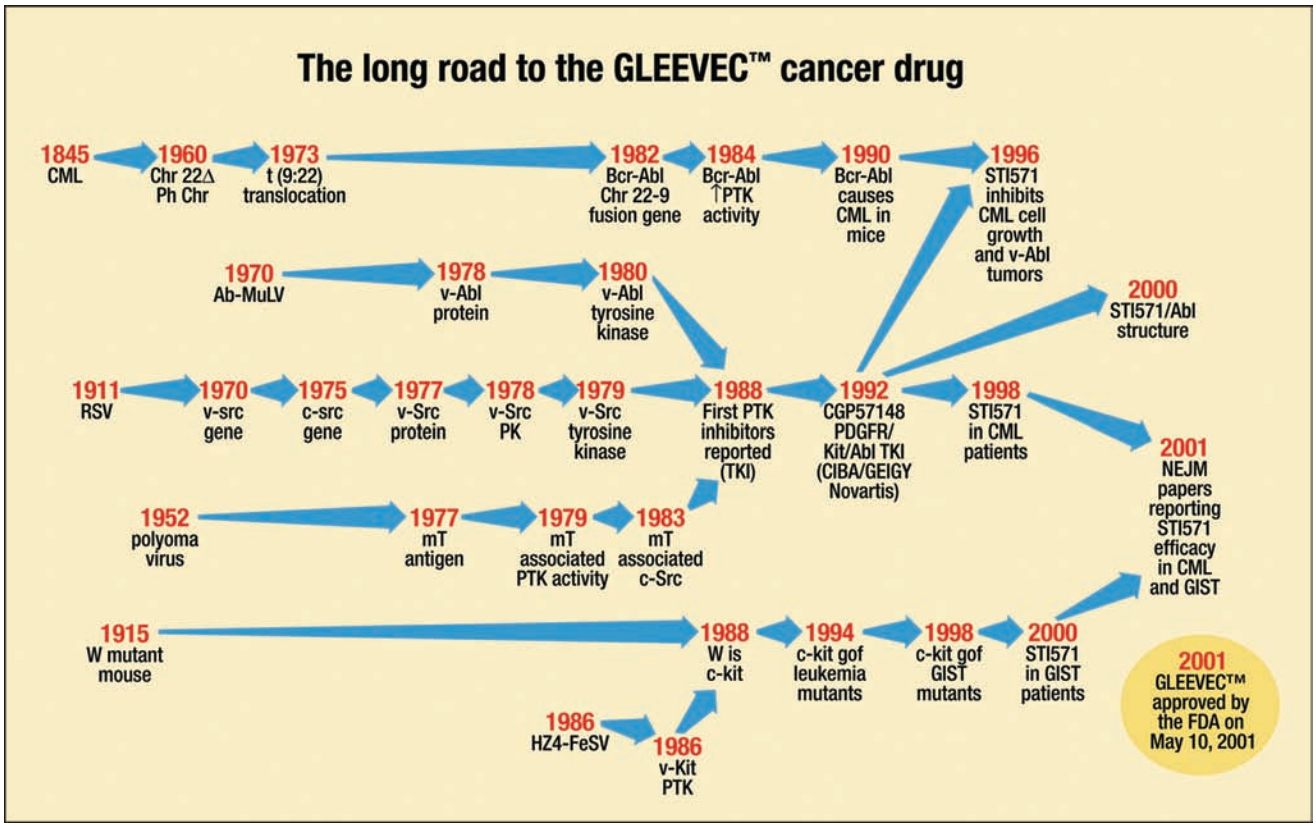
We are beginning to hear talk, both within National Institutes of Health (NIH) and outside in the broader biomedical research community, about how "science is changing." Twice in recent private conversations, this phrase has been used to explain why the amount of resources going to unsolicited, investigator-initiated R01 grants is declining as a percentage of total NIH dollars. National Cancer Institute Director John Niederhuber used a variant of the phrase in an April 20 *Science* article about the difficulty in getting an NIH grant.

So, is science changing? To some extent, it probably is; science, like any large, complex system, evolves slowly over time. In many ways, science is clearly different from what it was even 20 years ago. The pace of discovery is quickening, for one thing. But change is not necessarily a good thing; there are changes that can occur that are very damaging.

One such change that we must continue to fight is the slow devaluation of the investigator-initiated grant, which we have discussed repeatedly in this space over the past year. This change must be halted before it goes any further. The reason is that these grants have a proven track record of creating knowledge of enormous value. Let's take a look at some of the basic research that went into just one new class of drug—the protein kinase inhibitors now used to treat cancers, of which Gleevec™ is the best known.

Tony Hunter of the Salk Institute is one-half of the duo who gave the Herbert Tabor *Journal of Biological Chemistry* Lecture at this year's ASBMB Annual Meeting. He hit a nerve with me and many others in the audience with his remarks about the nature of progress in science. He showed a slide (a simplified version of which appears on this page) that illustrates the many discoveries from several disparate fields that came together over the years to bring to fruition the first of a completely novel series of cancer drugs, the first to market of which is Gleevec. He made the extremely important point that breakthroughs in science are built on the many prior discoveries needed to lay a foundation for current knowledge.

It took a century and a half, and several completely independent fields merging, for an understanding of the role of tyrosine kinases in growth control and cancer to mature to the point that biotech companies began to make ATP analog inhibitors to tyrosine kinases. (This is a much abbreviated account of this story; the complete story by Tony Hunter will appear in the August 1 issue of the *Journal of Clinical Investigation*). The independent developments began with the discovery in 1845 of chronic myelogenous leukemia (CML) followed by the discovery in 1960 that



A timeline of the many different avenues of research that came together and led to the successful development of imatinib mesylate (Gleevec) as a treatment for CML. Most of these disparate research efforts were started through a desire to understand the mechanisms underlying cancer and ultimately develop therapies.

the genetic basis of the disease was a chromosomal abnormality resulting from a deletion at the end of chromosome 22. In 1973, Janet Rowley showed that this was due to a reciprocal translocation with chromosome 9. In the '80s, this was reported by a large number of investigators including Jon Groffen, Gerard Grosveld, Eli Canaani, Owen Witte, and David Baltimore to result in a Bcr-Abl fusion that had increased protein tyrosine kinase activity.

This work depended on the knowledge of the Abl tyrosine kinase, whose activity was shown in 1980 to be essential for transformation by the Abelson murine leukemia virus. The sequence of the viral Abl gene product showed significant sequence homology to v-src, which thus connects with the Rous chicken sarcoma virus (RSV) line of investigation. In 1975, this v-src gene was shown to be a captured cellular gene, c-src, by Dominique Stehelin, Mike Bishop, and Harold Varmus, and in 1979 the v-Src protein was discovered to be a tyrosine kinase. Another thread comes through the W mutant mouse, and Hardy-Zuckerman feline sarcoma virus, where both genes were shown to encode yet another tyrosine kinase, c-Kit. Yukihiko Kitamura's group showed in 1994 that rare mast cell leukemias have gain-of-function mutations in c-KIT, as did many gastrointestinal stromal tumors (GISTs).

The recognition in the 1980s that activated tyrosine kinases could have a causal role in cancer engendered a serious interest in the development of small molecule inhibitors, first in academia, notably the laboratory of Alex Levitzki, and then Alex Matter and many others at Ciba-Geigy, working with Brian Druker, showed efficacy of the compound, called Gleevec, in CML, in 2001. Subsequently, George Demetri showed efficacy in GIST, whose activated c-Kit kinase, is also inhibited by Gleevec. This is the first molecularly-based cancer treatment, and it has surprisingly few side effects. Unfortunately, resistance develops, and thus newer drugs are needed to overcome resistant tumors. But the Gleevec story has opened the doors to tyrosine kinases as valid drug targets, and by 2007 seven more protein kinase inhibitors have been approved, with many, many more in the pipeline.

This is only one of the many stories that could be told of the long time lines and independence of different areas of research that can finally merge into breakthroughs. This highlights the need for many dedicated researchers, who with creativity and passion push their fields forward, and finally, with much serendipity and unexpected connections, put

together multiple threads of research that lead to breakthroughs.

As this brief review shows, discovery happens incrementally over many years. The chain of discovery leading to Gleevec is a classic example of how science is done, and one has to ask a number of questions. First, do we really want to "change" this process? Or, could we change it even if we wanted to? Furthermore, how would one try to manage the process of discovery over a century and a half of hard work by numerous scientists working in many different areas? Is it true that this is "just basic research," and therefore not as important as more targeted clinical research—as some disease advocates have been stating?

It seems to me that the biomedical research community has not done a very good job of teaching the public about the nature of science, how multiple threads of investigations over the long term lead to insights, and how long it takes to get to medical breakthroughs or new therapeutics.

I think the scientific community needs to embark on a pervasive education campaign to make this point. You can help make a difference in this effort. Try to get invited to speak at civic association meetings, church discussion groups, and other such events in your home town. Get involved in your local community; tell people you are a scientist and mention the important work you do.

Our Schachman Public Service Award recipient this year, Mary Woolley, president of Research!America, talked about what you should say when, on a long airplane trip, your seatmate asks you what you do. She said we should all answer with the sentence, "Well, I work for you." And then follow the conversation to where it leads. It is an enormous privilege to be entrusted with taxpayer dollars to follow your intellectual curiosity, and we must never forget that. But for this to continue, the public must be informed of its value.

The bottom line is that scientific progress comes in fits and starts. It is messy and not easily managed. It is a creative act. This process is not one that should be "changed"; rather, it is essential to continued progress in biomedical research.

Hundreds Turn Out to Hear Zerhouni, Porter Talks at EB

BY PETER FARNHAM

An April 30 symposium at the 2007 Experimental Biology meeting featuring National Institutes of Health (NIH) Director Elias Zerhouni and former Rep. John Porter attracted over 500 attendees to hear these two veterans of biomedical research policy wars discuss the symposium topic, *"NIH at the Crossroads: How Diminished Funds Will Impact Biomedical Research and What Scientists Can Do about It."*

The Seven Rules

Porter's comments were characteristically brief and to the point—he focused on the need to increase medical research funding and on what scientists should do. His rules were simple:

- Be a public citizen, beyond simply voting in elections.
- Invite your Representatives and Senators to your lab to see the work you do, and invite their staff to accompany them.
- Make an appointment to go see them when they are in the state or district. During the meeting, thank them for their service, show your passion, tell them what you want them to do, and be brief.
- Respond to alerts from Research!America and your professional society.
- Take your message to the public. Ask to speak at service club events, church groups, civic association meetings, and the like. Also, send letters to the editor or op-ed pieces to your local paper.
- Work with patient advocacy groups in your community, like the American Heart Association, American Cancer Society, Juvenile Diabetes Research Foundation, and others.
- Get involved in the 2008 elections. Attend candidate forums and debates, and ask questions about medical research and NIH funding.

"Be proud of what you do, and share it broadly with the American people and their representatives," Porter said. "Reach out to them. Educate them. Inspire them. Make a difference as a public citizen of this great country for the things you believe in. . . We must all be leaders in this vital cause."

Elias Zerhouni, Leo Furcht, and Rep. John Porter.

A Perfect Storm

Zerhouni focused his remarks on the state of funding at NIH and what the agency's current plans are. He characterized the current situation as a "perfect storm" involving a 12% reduction in purchasing power since 2003—the end of the doubling—and an increase in applications, which are expected to exceed 51,000 in 2008. This has reduced overall success rates for grant applications from about 30% in 2003 to about 20% this year. Other factors include a building boom on college campuses, as well as what Zerhouni called "budget cycling," in which grants have to go through a 4–5-year cycle before funds are freed up when some of them are not renewed.

To cope with this situation, NIH has adopted a strategy of allowing no inflationary adjustments for non-competing renewal grants in 2007. The agency will also try to increase the number of grants available in 2007 as well as protect "at-risk" investigators such as new investigators, first grant renewals, and senior investigators with no additional support.

Zerhouni's PowerPoint slide show will be available on the ASBMB Web site under the "What's New" column through the end of June.

Biochemists Visit Capitol Hill during EB

BY PETER FARNHAM

More than 40 ASBMB members visited their U.S. representatives and senators in late April during the Experimental Biology 2007 meeting held in Washington. Their message was simple: please support a $2 billion increase in NIH appropriations in Fiscal Year 2008.

This message was mostly well received; all but one of the after-meeting reports we have received were very positive. A few sample comments:

"We had a great conversation. . . Rep. [Pete] DeFazio is a big supporter of the NIH and is very much in favor of the 6.7% increase in the NIH budget. . . . thank you for arranging the meeting."

"My meeting with Rep. John Linder's staff went very well. He informed me that [Linder] is in support of having NIH well funded and would most definitely support the 6.7% increase in the NIH budget. . . Thank you for setting up the meeting for me and for the extremely useful advice. . . "

"We had a great meeting with Rep. McNulty's chief of staff. . . [McNulty] is in our court on the NIH and NSF budgets. One of our current goals is to have Rep. McNulty and Rep. Gillibrand come on a visit to see biomedical research in action. What we need is to have more scientists outraged at the situation and writing letters, visiting their representatives' offices at home and writing letters to the local newspaper. Further, we need to start looking into how the NIH (and NSF) allocates funds away from. . . investigator-driven research. . . I hope I can be of continued service in these efforts. Thanks for setting up the meeting. . . very much worth the effort!"

The ASBMB visits were arranged as part of an EB-wide Capitol Hill Day program organized by the public affairs staff of the participating societies. By all accounts, the event went well, with approximately 75 meeting attendees making visits.

Training DVD

Most of the attendees were new to the experience of visiting with a member of Congress, so a number of training events were set up to help them understand what was likely to occur during such meetings. One such training event was the debut of a new DVD produced for ASBMB by Bayou City Productions, a Houston-based media company, called "*Meeting with Your Congressman: A Guide for the Grass Roots Advocate*."

The ASBMB Public Affairs Advisory Committee sponsored the production of the DVD in response to numerous requests for information on how to conduct Hill visits.

The 19-minute DVD shows two meetings between a group of ASBMB members and a fictitious member of Congress. The first meeting shows what *not* to do; the visitors make just about every mistake that can be made during such a visit, including showing up late, interrupting, not having a clear message, and being argumentative.

After a review of the many mistakes made at this meeting—all of which have occurred in such meetings although thankfully not in the same meeting—the same meeting is shown with the visitors making none of the mistakes made in the first. The visitors do a lot of other things right in the meeting as well.

The DVD is available for review on the ASBMB Web site under the "What's New" column. Feel free to download it and share it with your colleagues. An article about making the DVD will also appear this summer in *Associations Now*, the magazine of the American Society of Association Executives. We will link to this article on the ASBMB site once it is published.

Volunteers Needed for Local Advocacy

ASBMB is continuing to build its grass-roots network of local advocates in various congressional districts around the United States. If you are interested in participating in this network, we would like to hear from you! Please send us your name, postal address (with 9-digit zip code, if possible), and e-mail address. If you know who your member of Congress is, please send that information along as well. (We can ascertain this if you don't know—that's why we want your 9-digit zip code.) The network consists of almost 300 ASBMB members at the moment, but we would very much like to expand it if possible. Please send your information to Peter Farnham, ASBMB Public Affairs Officer, at pfarnham@asbmb.org.

Peter Farnham, CAE, is ASBMB's public affairs officer.

FASEB

Harmful Amendments Attacking Peer Review Defeated in NSF Reauthorization Bill: *The FASEB Take on Latest Salvo in Worrisome Trend*

BY CARRIE D. WOLINETZ

Reps. Scott Garrett (R-NJ) and John Campbell (R-CA) introduced two amendments to the National Science Foundation (NSF) reauthorization bill (H.R. 1867) that posed a grave threat to the peer review system. The amendments would have blocked funding from specific research proposals that had already passed through the peer review system, based on the perception that their titles characterized the grants as "silly" or wasteful. The proposals targeted by the amendments were primarily social science projects and included cognitive studies, investigations related to reproduction and aging, and historical anthropology projects. However, the implications of such an amendment reach well beyond the grants cited, assaulting the very core of NSF's funding program, the peer review system.

FASEB responded swiftly to the attack on peer review, sending a letter to every member of the House of Representatives, urging them to defeat the amendments, and alerting FASEB societies. "Judging a project by its title is inadvisable and inappropriate; scientific discoveries arise from unpredictable pathways and interfering based on inadequate information could cause loss of crucial breakthroughs," wrote FASEB President Leo Furcht. He quoted House Appropriations Chairman David Obey (D-WI) who had said during a previous debate, "the day that we politicize. . . research, the day we decide which grants will be approved. . . that is the day that we ruin science research." Fortunately, although the debate on the NSF reauthorization bill lasted well into the night, the amendments were ultimately defeated. Reps. Brian Baird (D-WA), himself a psychologist, and Vernon Ehlers (R-MI), a member of the House Science and Technology Committee, were particularly eloquent in their defense of the peer review system.

This is not the first attempt at congressional micromanagement of the peer review system. The National Institutes of Health (NIH) has been a frequent target in the past few years of amendments that circumvent the peer review system through blocking funds to specific research grants. Former Rep. Pat Toomey (R-PA) tried to halt NIH funding of grants related to sexually transmitted diseases and sexual behavior. This amendment was narrowly defeated, losing by only two votes, and began a trend of proposed amendments to NIH appropriations bills in order to stop the funding of grants that were disliked by members of Congress, a trend most recently supported by Rep. Randy Neugebauer (R-TX). Included among the targeted grants have been basic research studies using animal models or molecular investigations. Such amendments hearken back to the days of the late Sen. William Proxmire (D-WI), who would give out "Golden Fleece Awards" to government research projects he considered examples of wasteful spending.

Although FASEB and our partners in the scientific community have been successful in forestalling such efforts, their continued appearance is a stark reminder of the poor understanding of the peer review system among policymakers, as well as the lack of comprehension of the importance of basic research. To that end, FASEB continues to produce materials, such as our *Breakthroughs in Bioscience* and brochures like "Science Fortune: How Unpredictable Research Advances Have Saved Millions of Lives," aimed at conveying to lawmakers and the public how science is done. The most recent *Breakthroughs in Bioscience* article, "Science, Serotonin and Sadness: The Biology of Antidepressants," examines the fundamental scientific discoveries that led to our modern treatments for depression and is now available on our Web site, opa.faseb.org. Along those same lines, among the positive amendments adopted by the House in conjunction with the NSF reauthorization was an adaptation of the Science Communications Act, recently introduced by Rep. Doris Matsui (D-CA). FASEB supported this bill, and also the subsequent amendment, which would begin an NSF-funded communications initiative for science graduate students.

Carrie D. Wolinetz is with the FASEB Office of Public Affairs.

Research!America Honored at EB

BY PETER FARNHAM

Research!America, the nation's largest non-profit public education and advocacy alliance working to make research to improve health a higher national priority, was honored by receiving ASBMB's 2007 Howard K. Schachman Award for Public Service, the first organization so honored since the award's founding in 2001. Mary Woolley, Research!America's president, accepted the award on behalf of the organization at a ceremony on May 1.

Woolley's Schachman Award lecture, entitled "Public Policy and Biomedical Research," was a wide ranging discussion of public attitudes toward biomedical research and what scientists can and should do to improve the public's understanding of their profession.

Public attitudes toward and understanding of biomedical research are mixed. Scientists and biomedical research receive high marks for trust and importance from the public. But few understand exactly how—or even where—medical research is actually done.

Consider the following facts from Research!America polling data:

1. When Americans are asked what U.S. institutions they have the most confidence in, the scientific community is ranked third at 89%, behind only the medical community at 92% and the military at 90%. By contrast, the media ranks 55%.
2. Scientists hold the most prestigious job, with 87% of respondents saying the job has a great deal or considerable prestige. This contrasts with "Congressman," where the value is 58%.
3. 74% of respondents were unable to name a living scientist.
4. When asked to name the federal agency that supports most biomedical research in the United States paid for with taxpayer dollars, only 5% named the National Institutes of Health. 8% believed it was the Food and Drug Administration; 73% of respondents did not know.
5. Approximately half the public is unable to name a location where biomedical research is conducted, including in states such as California, Texas, Massachusetts, and Illinois.

The lack of understanding extends both ways. Most researchers do not understand how to approach the public or Congress about the value of medical research. For example, many scientists think the way to win over the public is to explain technical details about their work. As last year's Schachman awardee, former Rep. Sherwood Boehlert said Congressmen "don't have time for tutorials." Instead, scientists should get right to the point and explain why research is important, why it should be funded first, and what it means for society.

Howard Schachman, Mary Woolley, and Bill Brinkley.

Woolley's message was simple—here is what researchers can do to advance the cause of medical research:

- Know the positions of your elected officials regarding medical research
- Build and support "research champions," that is, members of Congress and other decision makers who will actively advocate for research
- Use public opinion poll data to make the case for research as a high priority
- Understand the importance and influence of the media
- Master communicating in three sentences or less
- Use messages that work (no long technical explanations)
- Put a human face on research—yours!

For a look at much of this fascinating polling data, we have posted Woolley's slide presentation on the ASBMB Web site (www.asbmb.org) under the "What's New" column. This will be available for viewing through the end of June.

2007 annual meeting

Highlights from the 2007

Tony Pawson discusses his work at the Meet the Speaker Series.

Meeting attendees were treated to refreshments and music at the ASBMB Opening Reception.

The Career and Regular Research Grants Workshop provided a chance for attendees to network.

Posters and exhibits filled the exhibition hall at the Washington DC Convention Center.

Thousands of scientists gathered in Washington, D.C., from Saturday, April 28, to Tuesday, May 2, for the 2007 ASBMB Annual Meeting. Once again, the meeting contained several smaller thematic meetings within the larger meeting. The thematic meetings, which covered topics from chemical biology to organelle dynamics, were organized to allow scientists within a field to interact with each other more effectively. These interactions were also facilitated by several Scientific Thematic Receptions that were held at the end of the day. Summaries of some of the scientific talks can be found in the Science Focus articles in this issue of *ASBMB Today*.

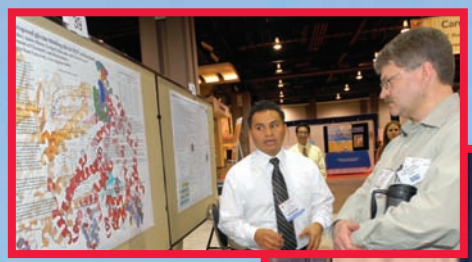
In addition to the scientific symposia, there were 10 award lectures on topics ranging from the causes and con-

ASBMB Annual Meeting

BY NICOLE KRESGE

Audience members listen to a panel discussion at the Women Scientists Mentoring and Networking Session.

Scientists discuss career options and minority issues at the Minority Scientists Networking Mixer.



Undergraduates present their research at the 11th Annual Undergraduate Student Research Achievement Poster Award Competition.

sequences of aneuploidy to the relationship between PPAR and obesity. The awardees included Anthony Hunter and Anthony Pawson, co-recipients of the Herbert Tabor/Journal of Biological Chemistry Lectureship; Scott D. Emr, winner of the Avanti Award in Lipids; Sarah C. R. Elgin, recipient of the ASBMB Award for Exemplary Contributions to Education; Judith P. Klinman, Avanti Award in Lipids recipient; Christopher B. Burge, winner of the Schering-Plough Research Institute Award; Mary Woolley, who accepted the Howard K. Schachman Public Service Award on behalf of Research!America; Angelika Amon, recipient of the ASBMB-Amgen Award; Susan S. Taylor, winner of the William C. Rose Award; and Ronald M. Evans, who gave the Fritz Lipmann Lectureship. Meeting attendees were able to talk with several of the award recipients during the ASBMB Meet the Speakers Series.

The meeting also had several events geared towards students and younger scientists. These included the Graduate/Postdoctoral and Graduate Minority Travel Award Program, which for the first time included a morning career development session featuring four speakers, representing industry, academia, patent law, and science writing. The morning session was followed by a poster session and presentations from travel award winners. Undergraduate scientists got a chance to present their work at the 11th Annual Undergraduate Student Research Achievement Award Poster Competition. The winners of the competition were announced the following day during the Exemplary Contributions to Education award lecture. There were also two lunchtime workshops geared towards younger scientists interested in publishing in the *JBC*. The workshops, which were held at the La Tasca restaurant in downtown D.C., were run by *JBC* Associate Editor William Smith, who explained the manuscript review process and urged the young scientists to read the *JBC* Instructions to

continued on next page

Ken Chen of Amgen presents the ASBMB Amgen Award to Angelika Amon.

Judith P. Klinman accepts the ASBMB Merck Award from Keith Rickert of Merck Research Laboratories.

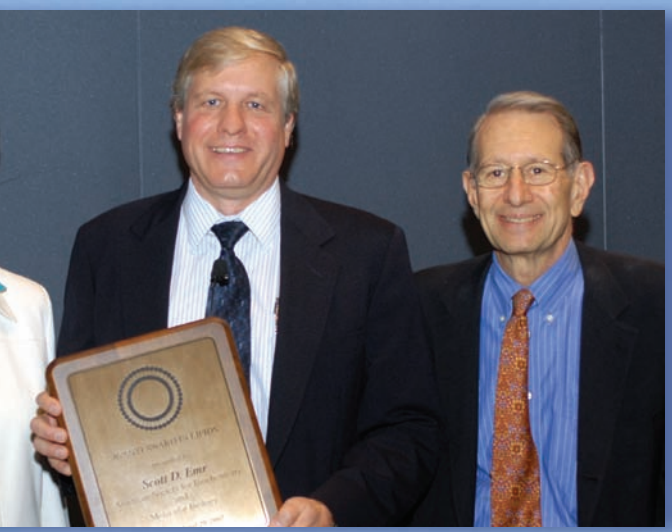
ASBMB President Heidi Hamm presents the William C. Rose Award to Susan S. Taylor.

Sarah C. R. Elgin receives the ASBMB Award for Exemplary Contributions to Education from Craig Cameron of Pennsylvania State University.

Authors before submitting their papers. *JBC* Editor Herbert Tabor as well as several *JBC* associate editors, including Richard Hanson, Martha Fedor, and Kenneth Neet, also attended the event.

Networking, which is a big part of every meeting, was facilitated by several organized events. The ASBMB Opening Reception, held immediately after the Opening Lecture, was a chance for meeting attendees to enjoy light refreshments and live jazz while interacting with their colleagues. Both the PUI Grantwriting Workshop and the Career and Regular Research Grants Workshop held networking receptions after their programs. The lunchtime Minority Scientists Networking Mixer brought PIs, industry professionals, and educators together with young investigators and students to discuss career opportunities, mentoring options, and issues facing minority scientists. And finally, there was the Women Scientists Mentoring and Networking Session & Reception, which provided a panel discussion by women at the early stages of their careers and a chance to talk to several successful women scientists, including ASBMB Past-President Judith Bond.

If you missed this year's events, slides from several of the award lectures and other presentations will be posted on the ASBMB website in the coming months. And don't forget to save the date for next year's meeting in San Diego from April 5 to 8.



The Avanti Award in Lipids was presented to Scott D. Emr. Pictured above are ASBMB Past-President Judith S. Bond, Scott D. Emr, and *JLR* Editor Ed Dennis.

At the presentation of the Schering-Plough Research Institute Award were Judith S. Bond, award recipient Christopher B. Burge, and Eric Gustafson of the Schering-Plough Research Institute.

Seen at the Herbert Tabor/*Journal of Biological Chemistry* Lectureship award presentation are (left to right) John Grinnell of Cadmus Communications (sponsor of the award), Tony Pawson, Tony Hunter, and Heidi Hamm.

At the presentation of the Fritz Lipmann Lectureship were Heidi Hamm, award recipient Ronald M. Evans, and meeting organizer Benjamin Cravatt.

ASBMB congratulates the following 2007 Best Poster Awardees:

Sarah Bissonnette
MIT

Michael Davies
UNIVERSITY OF MINNESOTA

Elysa Goldberg
CORNELL UNIVERSITY

Michael Patrick Housley
JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE

Patrick Ryan Potts
UT SOUTHWESTERN MEDICAL CENTER

Evan Nilda Rodriguez-Cruz
UNIVERSITY OF PUERTO RICO, RIO PIEDRAS

Sean Patrick Ryder
UNIVERSITY OF MASSACHUSETTS MEDICAL SCHOOL

Alfica Sehgal
THE JOHNS HOPKINS UNIVERSITY

Olivier Soubias
NIAAA, LMBB, NIH

Yong Tian
ST. JUDE CHILDREN'S RESEARCH HOSPITAL

Dong Wang
STANFORD UNIVERSITY SCHOOL OF MEDICINE

Undergraduates Participate in Annual Poster Competition

BY NEENA GROVER

The Washington Convention Center Hall C was the venue for an enthusiastic, energetic gathering of over 100 undergraduate students and their mentors at the 11th Annual ASBMB Undergraduate Research Achievement Award Poster Competition held on April 28, just prior to the official start of the ASBMB 2007 Annual Meeting. Although the students would also present their posters during the general meeting, the "undergraduates-only" poster session provided students with the opportunity to meet fellow attendees and make important contacts before the meeting began. The poster competition was jointly sponsored by the Educational and Professional Development Committee and the Minority Affairs Committee. Generous financial support was provided by Springer. This year's event was chaired by Kathleen Cornely, Providence College; Philip Ortiz, Empire State College; and Joe Provost and Mark Wallert, both of Minnesota State University Moorhead.

Victor Fedorov, Sarah Elgin, Heidi Hamm, Sadie Barholomew, Akiko Doi, and Paloma Maria Guzzardo.

More than 50 judges evaluated the 100-plus poster presentations and chose four grand prize winners. Each winner received a framed certificate and a $500 prize. The award winners were announced at the beginning of the ASBMB Award for Exemplary Contributions to Education lecture given by Sarah Elgin.

The following four students were this year's grand prize winners:

"Expression of PAT-1/MLDP increases triacylglycerol stores and promotes changes in lipid drop morphology in a CHO cell model" Sadie Bartholomew, Otterbein College.

"N-terminal ubiquitination of the encephalomyocarditis virus 3C protease" Akiko Doi, Bates College.

"Is scanning downstream of the premature termination event required to trigger nonsense-mediated mRNA decay?" Paloma Maria Guzzardo, University of Puerto Rico-Rio Piedras.

"Role of extracellular HSP90 in MMP2 activation in glioma cell lines." Victor Fedorov, University of Richmond.

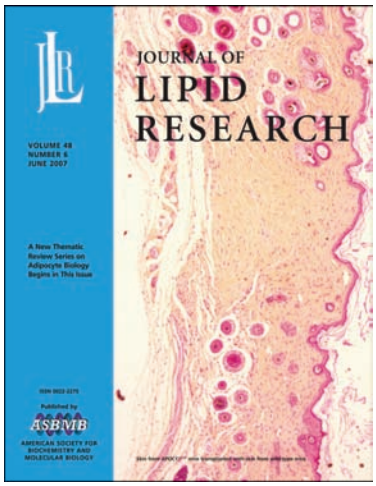
Other students who received awards (framed certificates) were: Caitlin Rice, Alyssa Johnson and Charles G. Sierzant, Hope College; Angela M. Bopra and Brent Hehl, Grand Valley State University; Sebastian Brown and Carolyn Scheel, University of Richmond; Kenneth Maksimchuk, Pennsylvania State University; David Scott Booth and Byran Denison Eason, Colorado College; Jessian Muñoz, University of Puerto Rico at Cayey; Christopher James Pelham, Northwest Missouri State University; Lindsay Morgan Higdon and Wen Allen Tseng, University of Delaware; and Callie Nguyen and Jennifer Taves, Minnesota State University Moorhead.

Many students participating in the poster competition received travel awards through Undergraduate Affiliate Network (UAN) chapters at their institutions. ASBMB awards a travel grant in the amount of $400 to each UAN chapter. Twenty UAN chapters received travel awards to support a student's attendance at this year's meeting. An additional 20 students earned travel awards through competitions at regional meetings held prior to the national meeting. Undergraduate faculty mentors who are interested in founding a UAN chapter at their institutions can find additional information at www.faseb.org/asbmb/epd/UAN.html.

Undergraduate poster session attendees also had the opportunity to find out information about a number of graduate schools. Representatives from several graduate schools set up tables at the poster session to answer student questions and distribute information about their programs.

The involvement of undergraduates at ASBMB annual meetings has increased in recent years. The meeting provides undergraduates with an opportunity to present their own research, to find out what others are doing, and to learn about new and exciting developments in the field.

New Adipocyte Biology Series in *JLR*



The June issue of the *Journal of Lipid Research* (*JLR*) marks the beginning of a new Thematic Review Series for the journal. The series, coordinated by *JLR* Associate Editor Alan D. Attie of the University of Wisconsin-Madison, will look at adipocyte biology. It will run from June through November and feature six articles on different aspects of adipocyte science. The first article of the series appears in the June issue along with an editorial by Attie.

"This past decade has been very good to the adipocyte," Attie explained. "For many years, the adipocyte was only recognized for its role as a fat storage cell and, in the case of brown adipose, for thermogenesis. But adipocyte science now describes a far more complex tissue, an endocrine organ that exerts a profound influence on other tissues and the whole animal. Therefore, we are pleased to bring you a thematic review series on Adipocyte Biology, and several experts in the field were invited to contribute."

Adipocyte science now describes a far more complex tissue, an endocrine organ that exerts a profound influence on other tissues and the whole animal

Adipose tissue is important for the storage of triglyceride, and excess amounts of this lipid in the tissue are associated with obesity and insulin resistance. The first article in the series, by Antonio Vidal-Puig, will explore the partitioning of lipid between adipose tissue and other tissues.

Lipodystrophy, the absence or paucity of adipose tissue, leads to many metabolic abnormalities, including diabetes mellitus. In the second article of the series, Robert Hegele will review the genetic basis for mutations that cause human partial lipodystrophy syndromes as well as the chemical and biochemical phenotypes associated with these disorders, the diversity of clinical phenotypes observed in afflicted patients, and potential treatment strategies.

Adipose tissue is in constant communication with the central nervous system. In his review article, Timothy Bartness will discuss the relationship between photoperiod and obesity and what it teaches us about the neural circuits to adipose tissue.

In recent years, studies have shown that obesity is accompanied by an inflammatory response in adipose tissue. This, in turn, affects adipocyte insulin signaling and hormone release. Gokhan Hotamisligil will review this topic as well as some of the therapeutic implications of these new insights.

In the penultimate article of the series, Dawn Brasaemle will look at the proteins associated with lipid droplets and describe some of their structural and regulatory roles.

Closing out the series, Paul Pilch will review the possible functions of caveolae, the small invaginations found in the plasma membrane of adipocytes.

A Taste of What's to Come: The 2008 Annual Meeting

BY KEN BLUMER AND ANNA MARIE PYLE

The 2008 annual meeting of the American Society for Biochemistry and Molecular Biology (ASBMB) will be held in San Diego April 5–8, 2008, as part of the FASEB Experimental Biology meeting. The ASBMB meeting attracts thousands of scientists—from undergraduates to senior investigators—who work on molecular mechanisms that underpin all of biology. The meeting offers an extraordinary opportunity to explore the depth and breadth of biology, to renew or establish relationships within the scientific community, and to educate the public and policymakers about the excitement of biological research and its impact on human health and well being.

Ken Blumer

Anna Marie Pyle

In planning the 2008 meeting, the co-chairs, Ken Blumer (Washington University) and Anna Marie Pyle (Yale University), and ASBMB leadership endeavored to: 1) use the thematic approach employed successfully in recent years; 2) develop an exciting and comprehensive program that highlights cutting edge research in core fields of ASBMB, draws attention to the expanding field of RNA biology, and illustrates how single molecule-, chemistry- and systems-driven approaches are changing the ways that biological problems are conceived, studied, and solved; 3) offer greater opportunity for undergraduate, graduate, and postdoctoral students to present their research in platform sessions and receive career guidance; 4) augment the scope of the meeting and encourage relationships between investigators in allied fields by cosponsoring programs with other FASEB societies; and 5) honor seminal achievements in biochemistry and molecular biology by conferring to eminent scientists the Herbert Tabor/*JBC* Award, the ASBMB Amgen Award, and the FASEB Excellence in Science Award.

To whet your appetite, here is an overview of the scientific program for the 2008 meeting:

DNA/RNA Biology Cluster

Genome Dynamics: Replication, Recombination, and Damage Response, co-organized by Peter Burgers and Tom Ellenberger (both at Washington University, St. Louis), will include symposia focusing on DNA replication mechanisms, DNA damage response and the cell cycle, DNA repair mechanisms, and double-stranded breaks and DNA recombination mechanisms.
Dynamic Chromatin, co-chaired by Brad Cairns (University of Utah, Salt Lake City) and Danesh Moazed (Harvard University), will consist of platform sessions on non-coding RNAs in gene regulation and chromosome structure, chromatin changes in development and stem cell regulation, chromatin structure in gene activation, and chromatin regulation of DNA repair, recombination, and genome stability.
RNA-mediated Gene Expression, co-organized by Lynn Maquat (University of Rochester) and William Marzluff (University of North Carolina), will include sessions on regulation of nuclear RNA processing and metabolism, ribonucleoproteins, RNA transport and localization, and RNA turnover.
Small RNAs and Dynamic RNA Elements, co-organized by Frank Slack (Yale University) and Robert Batey (University of Colorado, Boulder), will include symposia focusing on regulatory RNAs, roles for small non-coding RNAs, riboswitches, and other dynamic RNA structures.

Molecular Structure and Dynamics Group

Form and Function of Molecular Machines, co-organized by Steve Block (Stanford University) and Lemeor Joshua-Tor (Cold Spring Harbor Laboratory), will focus on single molecule and structural analysis of protein assemblies in four areas: DNA replication, DNA unwinding and translocation, cytoskeletal motors and filament dynamics, and gene expression.
Biomolecular Catalysis, Folding, and Design, co-organized by Susan Marqusee (University of California, Berkeley) and Vern Schramm (Albert Einstein College of Medicine, New York) will include sessions focusing on recent advances in understanding protein interactions in catalysis, enzymes as drug targets, protein/RNA folding and functional dynamics, and protein design.
Protein Synthesis, Turnover, and Misfolding, co-chaired by Mark Hochstrasser (Yale University) and Rachel

Green (Johns Hopkins University), includes sessions focusing on protein turnover and quality control, protein turnover in cell regulation, protein synthesis mechanisms, and protein-assisted folding and misfolding.

Cell Systems and Metabolism Cluster

Metabolism, organized by Mark Johnson (Washington University, St. Louis), will highlight new understanding of metabolic control mechanisms in cancer, diabetes, and neurodegeneration and illustrate new ways of identifying and studying complex metabolic systems and networks.
Systems Biology, co-chaired by Brenda Andrews (University of Toronto) and Fritz Roth (Harvard University), will highlight progress toward four key goals of systems biology: identifying components of systems, finding relationships between system components, studying the dynamics of system components and their relationships, and dissecting and simulating networks and their subsystems.
Cell and Organelle Dynamics, co-organized by Matt Welch (University of California, Berkeley) and Lois Weisman (University of Michigan), will consist of sessions highlighting mechanisms of cell division, organelle dynamics, cell migration, and pathogen exploitation of host machinery.

Signaling Transduction Group

Signal Transduction, organized by Kun-liang Guan (University of Michigan), consists of sessions on cell growth regulation and survival, G protein and protein kinase signaling, post-translational modifications in cancer, microbial pathogenesis and progeria, and therapeutic targeting of signaling pathways in human disease.
Lipid Signaling and Metabolism is co-chaired by James Ntambi (University of Wisconsin-Madison) and Suzanne Jackowski (St. Jude Children's Research Hospital, Memphis). This program features sessions on tissue-specific regulation of lipid metabolism, lipid-mediated control of gene expression, stress regulation of lipid metabolism and membrane biogenesis, and lipid metabolism and signaling in atherosclerosis and inflammation.

Chemical Biology Cluster

Chemical Biology, co-organized by Laura Kiessling (University of Wisconsin-Madison) and Anna Mapp (University of Michigan), will consist of sessions focusing on new strategies for imaging protein localization and dynamics, small molecule control of protein folding and assembly, chemical probes and their use in identifying new therapeutic targets, and chemical perspectives in neurobiology.
Drug Discovery will consist of a platform session and panel discussion organized by Jeff Conn (Vanderbilt University) that highlight the roles of academic institutions in the drug discovery process and a symposium organized by Steve Projan (Wyeth Pharmaceuticals) that focuses on challenges and successes in target-based drug discovery.

Education and Professional Development

This theme, organized by Ellis Bell (University of Richmond), will include the following components: 1) an undergraduate research poster session and competition, 2) platform presentations in scientific sessions described above by selected undergraduates and faculty from undergraduate-focused institutions, 3) workshops for faculty teaching at undergraduate-focused institutions, and 4) a graduate school fair to build relationships between graduate programs and students and faculty from undergraduate-serving institutions.

Minority Affairs

George Hill (Vanderbilt University) has organized a theme focusing on mental health, which will include sessions on Alzheimer disease, depression and anxiety disorders, drug abuse, and technology development.

Partnerships with Other FASEB Societies

G Protein Colloquium, featuring talks by Lee Limbird (Meharry Medical College, Nashville), Robert Lefkowitz (Duke University), Heidi Hamm (Vanderbilt University and ASBMB president), and Alfred Gilman (University of Texas Southwestern Medical Center, Dallas), will be co-sponsored by ASBMB and the American Society for Pharmacology and Experimental Therapeutics (ASPET).
Signal Transduction Platforms from the ASPET program focusing on cardiovascular and cancer signaling mechanisms by G12/13 (organized by Sandra Siehler, Novartis Institutes for Biomedical Research) and on nicotinic receptor structure and function (organized by Palmer Taylor, University of California, San Diego) will be co-sponsored by ASBMB.
Signal Transduction Colloquium, co-organized by Susan Taylor and Alexandra Newton (both at University of California, San Diego) and co-sponsored by ASBMB and ASPET, will focus on spatial and temporal sensors of second messenger signaling and structural mechanisms of macromolecular complexes in protein kinase signaling.
Immunohistochemistry Course, co-organized by Denis Baskin and William Stahl (both at the University of Washington, Seattle), will be co-sponsored by ASBMB and the Histochemistry Society.

For further details, we invite you to watch for upcoming issues of *ASBMB Today* that will include full-length articles about each scientific theme and information about special events planned for the 2008 meeting. See you in San Diego!

9 ASBMB Members Elected to National Academy

Nine ASBMB members have been elected to the National Academy of Sciences. They are among 72 new members and 18 foreign associates elected in early May in recognition of their distinguished and continuing achievements in original research. Election to the academy is considered one of the most prestigious honors bestowed upon American scientists.

Newly elected ASBMB members and their affiliations at the time of election are:

Michael B. Brenner, Theodore Bevier Bayles Professor of Medicine, Harvard Medical School, Boston, Massachusetts


Michael B. Brenner

Scott D. Emr, investigator, Howard Hughes Medical Institute, and director, Institute of Cell and Molecular Biology, Cornell University, Ithaca, New York


Scott D. Emr

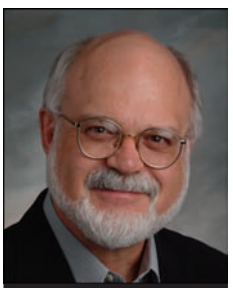
David Ginsburg, investigator, Howard Hughes Medical Institute, and James V. Neel Distinguished University Professor, University of Michigan Medical School, Ann Arbor


David Ginsburg

Angela M. Gronenborn, professor of pharmacology, and director, Structural Biology Program, University of Pittsburgh, Pittsburgh, Pennsylvania


Angela M. Gronenborn

John G. Hildebrand, Regents Professor and professor of neurobiology, biochemistry and molecular biophysics, entomology, and molecular and cellular biology, and director, Arizona Research Laboratories Division of Neurobiology, University of Arizona, Tucson


John G. Hildebrand

Laura L. Kiessling, professor of chemistry and biochemistry, University of Wisconsin, Madison


Laura L. Kiessling

Stephen C. Kowalczykowski, distinguished professor of microbiology and of molecular and cellular biology, and director, Center for Genetics and Development, University of California, Davis


Stephen C. Kowalczykowski

Vern L. Schramm, professor and chair, department of biochemistry, Albert Einstein College of Medicine of Yeshiva University, Bronx, New York


Gerald I. Shulman

Gerald I. Shulman, investigator, Howard Hughes Medical Institute, and professor of medicine and cellular and molecular physiology, Yale University School of Medicine, New Haven, Connecticut


Vern L. Schramm

Reaching Out at the National Meeting

BY NEENA GROVER

The ASBMB national meeting in Washington, D.C., was packed with activities for scientists interested in outreach. The outreach efforts—which actually started before the meeting—began with the launch of a new Education and Professional Development Web site (www.faseb.org/asbmb/epd/epd.html). The new site has a place for building a resource for various types of outreach activities for which we are now soliciting material from all of you.

A morning pre-meeting workshop on April 27 titled "Outreach in Action" was the official start of the outreach activities in Washington, D.C. This outreach workshop was sponsored by the Education and Professional Development Committee and was run by Neena Grover of the Colorado College, Colorado Springs.

Scientists at the Minority Scientists Networking Mixer.

A wide range of students and faculty attended the workshop, which started out by defining outreach as all those activities that communicate science to a wider audience. It was quickly apparent that most scientists are involved in outreach work, whether or not they themselves recognize it as such. Many of the attendees were just beginning to formalize their outreach efforts. For those interested in developing carefully planned outreach activities, either for the broader impact portion of their grants or to improve the quality of science education, various levels of organization were provided to ensure successful outcomes.

The Minority Affairs Committee sponsored a Minority Scientists Networking Mixer on May 1. In this informal, packed lunchtime session, faculty discussed collaborative research projects, met with grants officers, and interacted with bright and energetic students. There were also several other Minority Affairs Committee-sponsored scientific sessions on research activities in genetic and infectious diseases, some of which are covered in the Science Focus section of this magazine.

A well attended Women Scientists Mentoring and Networking Session and Reception was held on May 1. A panel organized by Adele Wolfson of Wellesley College provided a forum in which the success of women scientists at academic institutions was discussed. This annual event has served as a forum for issues that are not normally discussed and shared among colleagues. A new subsection on Women in Science and Engineering is being created for the Society's outreach Web site. All those who have materials or advise women students and scientists are encouraged to share these materials with the larger community.

As the meeting was in Washington D.C., several scientists met with their congressional representatives to discuss science-related issues.

Overall, those who attended the various outreach sessions at the meeting are likely to have a wider perspective on the role of national meetings. Sessions such as these provide hope for the future of the scientific community.

Adele Wolfson and panel members at the Women Scientists Mentoring and Networking Session.

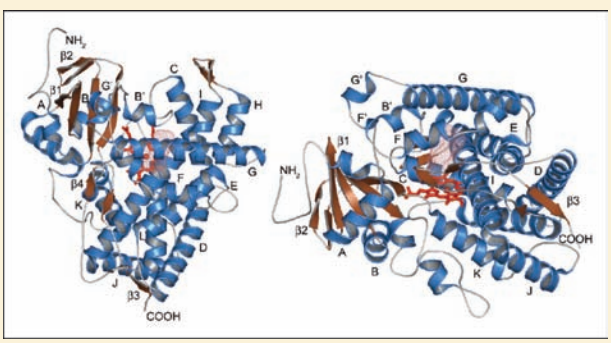
biobits asbmb journal science

J. Biol. Chem. 2007 282: 14348–14355

Adaptations for the Oxidation of Polycyclic Aromatic Hydrocarbons Exhibited by the Structure of Human P450 1A2

Stefaan Sansen, Jason K. Yano, Rosamund L. Reynald, Guillaume A. Schoch, Keith J. Griffin, C. David Stout, and Eric F. Johnson

Enzymes in the cytochrome P450 superfamily play a significant role in the detoxication of foreign compounds and the biosynthesis of several endogenous compounds, including steroid hormones, bile acids, and cholesterol. P450 1A2 is the principal cytochrome family 1 enzyme. It is expressed in the human liver and participates extensively in the hepatic oxidation of a wide range of drugs. In this article, the authors present the crystal structure of human P450 1A2 in complex with the inhibitor α-naphthoflavone at a resolution of 1.95 Å. Their structure reveals a compact, closed active site cavity that is highly adapted for the positioning and oxidation of relatively large, planar substrates. The topology is distinct from the known active site structures of P450 enzymes from other families and demonstrates how P450 family 1 enzymes have evolved to efficiently catalyze the oxidation of polycyclic aromatic hydrocarbons.



Two views of the structure of P450 1A2.

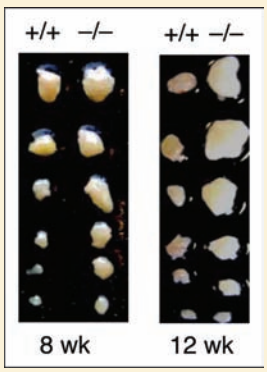
jbc

J. Biol. Chem. 2007 282:15884–15893

Deubiquitinating Enzyme CYLD Regulates the Peripheral Development and Naive Phenotype Maintenance of B Cells

Wei Jin, William R. Reiley, Andrew Joon Lee, Ato Wright, Xuefeng Wu, Minying Zhang, and Shao-Cong Sun

Deubiquitinating enzymes (DUBs) form a family of cysteine proteases that digest ubiquitin chains and reverse the process of protein ubiquitination. Despite the identification of a large number of DUBs, their physiological functions remain poorly defined. In this article, the authors provide new and important information on the DUB enzyme CYLD and its role in NF-κB regulation and maintenance of the B cell phenotype. They found that CYLD-deficient B cells are hyperproliferative when stimulated *in vitro* and display elevated levels of antigen responses *in vivo*. The cells also exhibit constitutive activation of the transcription factor NF-κB. In addition, CYLD$^{-/-}$ mice develop B-cell hyperplasia and lymphoid organ abnormalities. These findings establish CYLD as a key regulator of B-cell activation and development and reveal a physiological function for CYLD in NF-κB regulation.



CYLD-deficient mice develop lymphoid organ abnormalities.

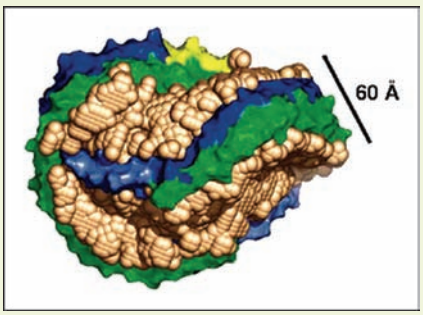
jbc

J. Lipid Res. 2007 48: 1035–1044

Apolipoprotein E·dipalmitoylphosphatidylcholine particles are ellipsoidal in solution

Clare A. Peters-Libeu, Yvonne Newhouse, Steven C. Hall, H. Ewa Witkowska, and Karl H. Weisgraber

Apolipoproteins are amphipathic lipid-binding proteins that serve as enzyme co-factors, receptor ligands, and lipid transfer carriers. Thus far, two structural models of lipoprotein particles have been proposed. In one, the phospholipid is arranged in a micelle-like shape, with the protein partially submerged in the micelle surface. In the second, the discoidal model, the phospholipid is arranged as in a bilayer with the protein wrapped around the edge of the disk, covering the exposed hydrophobic tails of the phospholipid. The discoidal model has been widely accepted for apolipoprotein A-I-phospholipid complexes. In this paper, the authors used small-angle X-ray scattering to show that particles of apolipoprotein E bound to dipalmitoylphosphatidylcholine (DPPC) are ellipsoidal and that the shape of the phospholipid core is compatible with a twisted-bilayer model. The results demonstrate that the interactions of apolipoprotein A-I and apolipoprotein E with phospholipids are distinctly different.



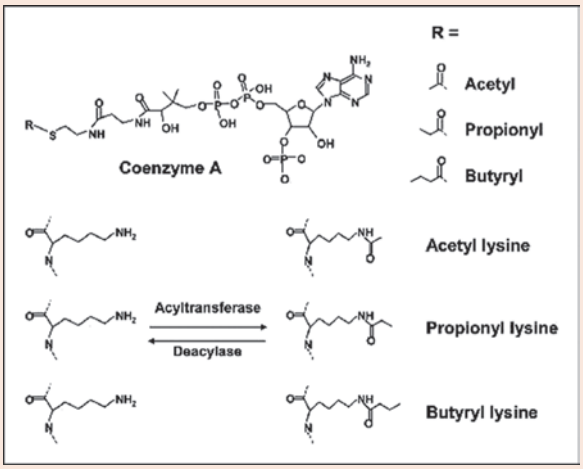
A twisted-bilayer model of apoE·DPPC.

Mol. Cell. Proteomics 2007 6: 812–819

Lysine Propionylation and Butyrylation Are Novel Post-translational Modifications in Histones

Yue Chen, Robert Sprung, Yi Tang, Haydn Ball, Bhavani Sangras, Sung Chan Kim, John R. Falck, Junmin Peng, Wei Gu, and Yingming Zhao

Lysine acetylation is an abundant, reversible, and highly regulated post-translational modification that plays important roles in cellular processes such as apoptosis, metabolism, transcription, and the stress response. Acetyltransferases carry out the acetylation reaction using acetyl-CoA. However, it is unknown whether cells can use other short-chain CoAs, such as propionyl- and butyryl-CoA, to carry out similar post-translational modifications of lysine. The authors of this paper report the discovery of two novel, *in vivo* lysine modifications in histones, lysine propionylation and butyrylation. Their unbiased global screening procedure involved exhaustive peptide identification by nano-HPLC/MS/MS analysis, protein sequence database search, and manual verification. The authors also identified two previously known acetyltransferases, p300 and cAMP-response element-binding protein-binding protein, that could catalyze lysine propionylation and lysine butyrylation in histones.

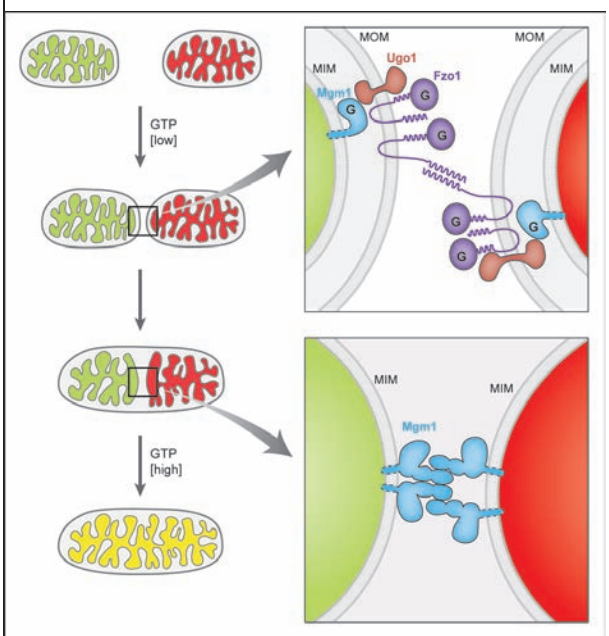


Structures of three short-chain CoAs and the three modified lysines.

How Mitochondria Fuse with Each Other

BY PAT PAGES

Mitochondria are known as the powerhouses of cells, generating energy in the form of adenosine triphosphate (ATP) by oxidizing the major products of glycolysis, but they are also dynamic entities that divide and fuse with each other, probably to help them work more efficiently. How these division and fusion processes occur and the benefits they offer to mitochondria are still not clear, but recent research is shedding new light on these mechanisms.



Model of the mechanism of mitochondrial fusion showing the sequential interaction of the outer and inner mitochondrial membranes (*top* to *bottom*).

At ASBMB's 2007 annual meeting, Jodi Nunnari, professor of Molecular and Cellular Biology at the University of California, Davis, presented the latest findings about mitochondrial fusion. Although many questions still remain as to why this process occurs, how it happens is better understood.

"Mitochondrial fusion is unique and complex," Nunnari says. "Its main role is to allow mitochondria to share their products and DNA among one another. The importance of this process is emphasized by the fact that mutations in mitochondrial fusion proteins in humans cause neurodegenerative diseases."

Nunnari and her colleagues looked at proteins that are involved in mitochondrial fusion in yeast cells (1). The first thing the scientists noticed was that the outer and inner membranes fused separately and successively—the outer membranes fusing first—and that different proteins were involved in each case.

When the outer membranes of two mitochondria get close to each other, complexes of proteins located on each membrane combine, driving the membranes closer and ultimately fusing them. The complexes are made of a protein called Fzo1, which contains several domains, including a guanosine triphosphatase (GTPase) and helical regions. Current evidence shows that two Fzo1 complexes tether with each other through the helical regions of the proteins.

When outer membrane fusion is completed, the matrices from both mitochondria—surrounded by their respective inner membranes—align with each other, and a new fusion process occurs, this time between the parts of the inner membranes that are closest (see figure). Complexes of a protein called Mgm1, located on each opposing membrane, bind to each other to tether the membranes and ultimately to fuse them, allowing the contents of both matrices to mix.

Nunnari's team noticed that Mgm1 may also help in the formation and maintenance of infoldings of the inner membrane called cristae. When cells contained nonfunctional forms of Mgm1, the cristae became disorganized.

Nunnari and her colleagues also showed that outer and inner membrane fusion events are coordinated. While looking at mitochondrial fusion in fungi, they noticed a protein complex made of Fzo1, Mgm1, and a protein called Ugo1 that seems to act as a "bridge" between the two other proteins. The role of this complex is unknown, but it is likely that it coordinates outer and inner membrane fusion events, Nunnari says.

These results show that mitochondria are more dynamic than previously thought and may offer new ways to treat diseases in which mitochondria are defective.

"When mitochondrial fusion goes wrong, mitochondrial DNA is either completely or partially lost from a subset of mitochondria," Nunnari says. "The exact mechanism of this DNA loss has not yet been determined, but our results should help in that direction and hopefully lead to a better understanding of mitochondrial diseases."

REFERENCE

1. Hoppins, S., Lackner, L., and Nunnari, J. (2007) The Machines That Divide and Fuse Mitochondria. *Annu. Rev. Biochem.* **76,** 33.1–33.30

New Insight into Cholesterol Regulation

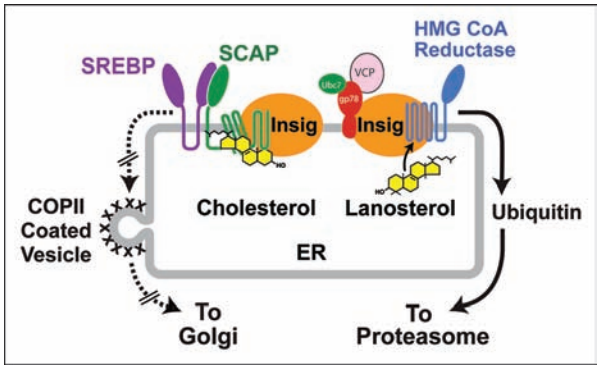
BY PAT PAGES

At ASBMB's 2007 annual meeting, Russell DeBose-Boyd, assistant professor of Biophysics and Molecular Genetics at the University of Texas Southwestern Medical Center, Dallas, presented the latest findings on the most important proteins involved in cholesterol regulation, including a newly discovered one called Insig.

Two well known proteins, called Scap and 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG CoA reductase), regulate cholesterol through separate mechanisms. These proteins are present in the membrane of the endoplasmic reticulum (ER), where cholesterol is synthesized from acetyl coenzyme A. The newly characterized Insig protein is another key component that is bringing new light on cholesterol regulation in both mechanisms.

In the first mechanism, Scap regulates the amount of cholesterol in the ER by either triggering a signaling pathway that activates cholesterol-producing genes or blocking the pathway. When the amount of cholesterol in the ER is low, a protein complex in which Scap binds to a protein called sterol regulatory element-binding protein (SREBP) exits the ER in a vesicle called Coat protein II (COPII) that transports them to the Golgi apparatus. Once in the Golgi, the SREBPs are broken down, and the resulting fragments enter the nucleus where they activate the genes coding for cholesterol.

When cholesterol builds up in the ER, it binds to the Scap/SREBP complex, preventing it from exiting the cell. DeBose-Boyd presented recent results (1) from the laboratory of Joseph Goldstein and Michael Brown, both at the University of Texas Southwestern Medical Center, showing that cholesterol also triggers a change of conformation of the Scap/SREBP complex that allows it to bind to Insig and prevents Scap from binding to COPII proteins. To further explain Insig's role in this process, the scientists suggest that, when in the nucleus, the SREBP components also turn on the gene for Insig, which increase the amount of Insig in the ER, so that enough of it is available when cholesterol levels go up.



Insigs regulate ER-to-Golgi transport of Scap/SREBP in a process that is inhibited by cholesterol. Insigs also regulate the ubiquitin-mediated degradation of HMG CoA reductase in a process that is stimulated by lanosterol.

The second mechanism regulates the amount of lanosterol, one of the key intermediates in cholesterol synthesis. HMG CoA reductase, the main protein in this mechanism, is one of more than 20 enzymes required for cholesterol synthesis. When too much lanosterol is made—indicating that too much cholesterol is produced as well—the reductase is destroyed by a proteasome.

DeBose-Boyd showed that Insig was key in the breakdown of HMG CoA reductase. The protein first binds to a complex made of Insig, a ubiquitin ligase called gp78, an enzyme called ubiquitin-conjugating 7 (Ubc7), and a protein called valosin-containing protein (VCP). Then gp78 attaches ubiquitin proteins on the surface of the reductase, which is extracted from the membrane by VCP and delivered to a proteasome for degradation.

Both mechanisms share similarities—sterols trigger the binding of a protein to Insigs—but also display major differences. The Scap/Insig interaction blocks the binding of COPII proteins to Scap, allowing Scap/SREBP to remain in the ER in a stable complex with Insigs. On the other hand, the reductase binds to an Insig-containing complex, which leads to the degradation of the reductase.

These results show that cholesterol regulation has not yet revealed all its secrets, but a clearer picture of the processes involved is now emerging that could help devise new treatments against cholesterol-related disorders.

REFERENCE

1. Goldstein, J. L., DeBose-Boyd, R. A., and Brown, M. S. (2006) Protein Sensors for Membrane Sterols. *Cell* **124,** 35–46

How RNA Enzymes Work

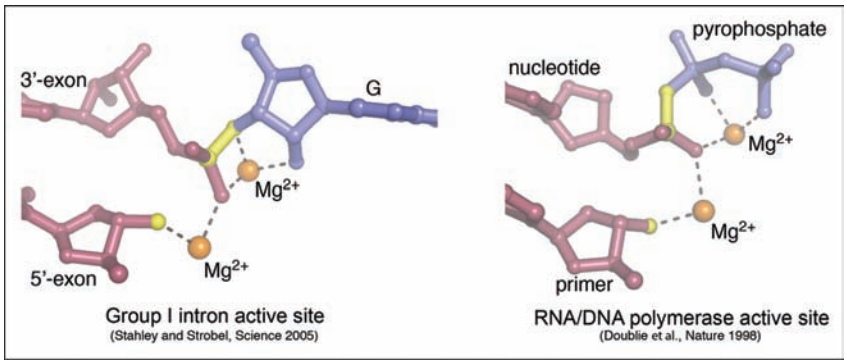
BY PAT PAGES

Since their discovery in the early 1980s, RNA enzymes—or ribozymes—have generated increasing interest from scientists. At first a biological curiosity, these molecules have been shown to be part of important cellular processes, and their ability to recognize and cut specific RNA molecules is making them potentially useful for human therapy. However, their mechanism of action is still the subject of intense research.

At ASBMB's 2007 annual meeting, Scott Strobel, professor of Molecular Biophysics and Biochemistry at Yale University, New Haven, Connecticut, showed that ribozymes can act by very different mechanisms depending on whether they perform RNA splicing or translation or regulate gene expression.

The first process studied by Strobel's team is RNA's role in a splicing mechanism in which introns are removed from an RNA molecule (1). In the case of mRNA, this process is often conducted by a ribonucleoprotein—a complex made of RNA and proteins called the spliceosome. But, in some cases, the intron itself can act as a spliceosome, removing itself and joining the ends of the remaining RNA pieces, or exons.

Strobel and his team provided a detailed description of how one such intron, called a group I intron, works. He showed that the intron's action mechanism shares many similarities with that of a DNA or RNA polymerase—an enzyme assisting in DNA replication and transcription, respectively. In particular, both the intron and the polymerase use two metal ions and promote their reactions through similar mechanisms (see figure).



Comparison of the active site of a group I intron (*left*) and an RNA or DNA polymerase (*right*), showing how two magnesium ions are used in both cases.

The scientists also looked at RNA's catalytic role within the ribosome, which binds to two substrates—an aminoacyl transfer RNA and a peptidyl transfer RNA—and catalyzes the formation of a peptide bond that, through many cycles, leads to a protein.

Strobel's team, in collaboration with Tom Steitz's group, also at Yale, determined a series of structures of a ribosome while the two tRNAs are bound together (2) and showed that the catalytic reaction does not involve metal ions—as in the RNA splicing process—but a water molecule and a hydroxyl (−OH) group at the end of the peptidyl tRNA.

"These findings revealed a second mechanism by which RNA enzymes work, which was not what we were expecting," Strobel says.

RNA enzymes can also control gene expression. A special type of RNA called a riboswitch can be found before the coding region of an mRNA molecule, where it regulates the production or activity of the coding region by binding to a small molecule.

Strobel presented the structure of a riboswitch called GlmS that is located upstream of the gene encoding glucosamine 6-phosphate (GlcN6P) synthetase, a protein that makes GlcN6P, a precursor to cell wall biosynthesis in bacteria (3). The riboswitch regulates the production of GlcN6P synthetase by binding to GlcN6P.

Unlike other riboswitches identified thus far, GlmS does not appear to undergo any structural rearrangement upon binding to GlcN6P, but instead functions as a ribozyme that uses GlcN6P as a chemical cofactor.

Stimulated by these surprising findings, Strobel and his team continue to explore RNA enzymes in various cellular processes. They look forward to discovering still unknown catalytic processes used by RNA enzymes.

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How Proteins Move

BY PAT PAGES

A technique developed over half a century ago by physicists to explore the properties of matter is now being used to study the internal movements of proteins. At ASBMB's 2007 annual meeting, Lewis Kay, professor of Chemical Physics at the University of Toronto, Canada, presented the latest applications of this technique, called nuclear magnetic resonance (NMR) spectroscopy, to study protein folding and the inner workings of a key protein that removes damaged proteins from cells.

The technique relies on the fact that the chemical, structural, and dynamic properties of a molecule can be determined by a set of experiments that use pulses of magnetic fields. When such fields are applied briefly to a protein, small magnets in the molecules that are inside the protein are perturbed—as if jumping from an electric shock—and then return to their original positions. While doing so, the molecules emit signals that can be recorded and that reveal the chemical nature and position of the atoms making up the molecules.

"The atoms act like small radio stations, each characterized by a different frequency that tells us a lot about their motion and the atomic structure surrounding them," Kay says. "This information can be combined with that obtained from many other experiments to determine the positions of atoms in a protein and how these positions change over time."

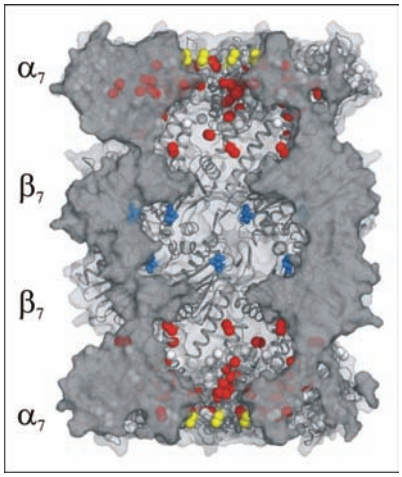
NMR spectroscopy allowed Kay's team to describe what happens to a protein evolving from an unfolded to a folded state in much more detail than with other techniques (1). The NMR technique was applied to a domain from Fyn tyrosine kinase—a protein involved in the coating of nerve cells with myelin—and showed which parts of the protein folded first and which ones folded later.

Kay and his colleagues also showed that NMR spectroscopy can be used to study large molecular complexes (2). They provided new insight into the inner workings of the proteasome (see figure), which is known to remove damaged and misfolded proteins from cells. The protein is made of an entrance channel, two antechambers where damaged proteins are stored before degradation, and a catalytic chamber where the proteins are degraded.

Until now, scientists had not been able to apply NMR spectroscopy in a quantitative way to such a large molecule because only very weak signals are created. Kay and his colleagues perfected their technique to increase the lifetime of the NMR signals, thus improving the quality of the signals emitted by the atoms.

Kay's team noticed that the amino acids in the entrance channel and those inside the antechambers moved in a concerted manner, suggesting a potential mechanism for the transport of misfolded proteins from the entrance channel to the catalytic chamber.

"NMR spectroscopy can now provide valuable information about the internal dynamics of proteins," Kay says. "When combined with data from x-ray diffraction and electron microscopy, NMR spectroscopy promises to significantly improve our understanding of how proteins work at the molecular level."



Cross-section of the side view of the proteasome. Residues undergoing concerted motion are shown in *red* and *yellow*. The active sites are shown in *blue*.

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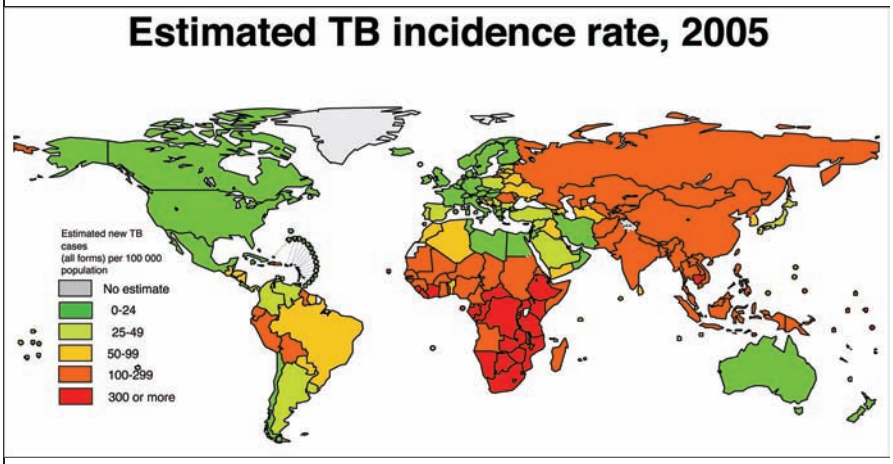
Finding New Ways to Fight Tuberculosis

BY PAT PAGES

Tuberculosis (TB) is a major global disease infecting one-third of the world population—2 billion people—and killing 2 million people each year. This situation is aggravated by the fact that new strains of drug-resistant TB bacteria have developed, forcing infected people to take at least four drugs for a period lasting usually between 6 and 18 months. No new drug has been introduced into this regimen since the mid-1970s, stimulating renewed research to find new and more powerful drugs.



ASBMB's Minority Affairs Committee sponsored a symposium at the Society's 2007 annual meeting to look at the latest research results on the mechanisms of action of new anti-TB drugs and possible novel ways to fight the disease.

The symposium was part of a series of four sessions that focused on health issues affecting minorities and underserved populations and included presentations by Ujjini Manjunatha, a researcher at the National Institutes of Health's (NIH) National Institute of Allergy and Infectious Diseases, Bethesda, Maryland; Bavesh Kana, a researcher at the University of the Witwatersrand, Johannesburg, South Africa; and Jamaine Davis, a postdoctoral fellow at NIH's National Cancer Institute, Frederick, Maryland.

Manjunatha discussed the mechanism of action of a compound currently tested against tuberculosis. The compound, PA-824, is part of a family of compounds called nitroimidazoles and is active not only against drug-resistant TB bacteria but also dormant ones.

Manjunatha and NIH researcher Clifton Barry studied how TB bacteria might become resistant to PA-824 and uncovered biochemical pathways showing how drug resistance arises from this class of compounds.

The scientists discovered mutations in Rv3547, a protein that allows bacteria to be resistant not only to PA-824 but to many similar drugs as well. With the discovery of the specific protein that activates PA-824, the researchers could develop an improved version of PA-824 and accelerate the pace of new TB drug development.

In the second presentation, Kana reported research on ways to prevent TB bacteria from reactivating after lying dormant in human hosts. TB bacteria lie dormant in about 90% of infected people and can be reactivated at any time to cause disease. This reactivation could be caused in part by proteins called resuscitation-promoting factors (Rpfs), which may form the basis of novel anti-TB drugs.

Kana and his colleagues discovered that when the five known versions of Rpf were mutated, TB bacteria did not reactivate in culture and did not cause significant disease in infected mice. The scientists also mutated four of the five Rpfs in the TB bacterium and found that the resulting strains behaved differently in culture and in mice.

These observations showed that the five Rpfs may perform specialized, discrete functions and suggest that understanding the roles of each version of Rpf and its biochemical activities may help in the design of novel anti-TB drugs.

Davis presented the structure of part of a TB bacterium protein that plays a central role in DNA biosynthesis. Called ribonucleotide reductase (RNR), the protein catalyzes the reduction of all four ribonucleotides to their corresponding deoxyribonucleotides.

An active RNR complex is made of two subunits called R1 and R2, so scientists have considered devising drugs that prevent these subunits from binding to each other. Davis and his colleagues have resolved the structure of R2, but the structure of R1 has not been determined yet. To understand how a drug would prevent association between R1 and R2, scientists would need to elucidate the structure of the entire RNR complex.

Aneuploidy Can Cause Cancer

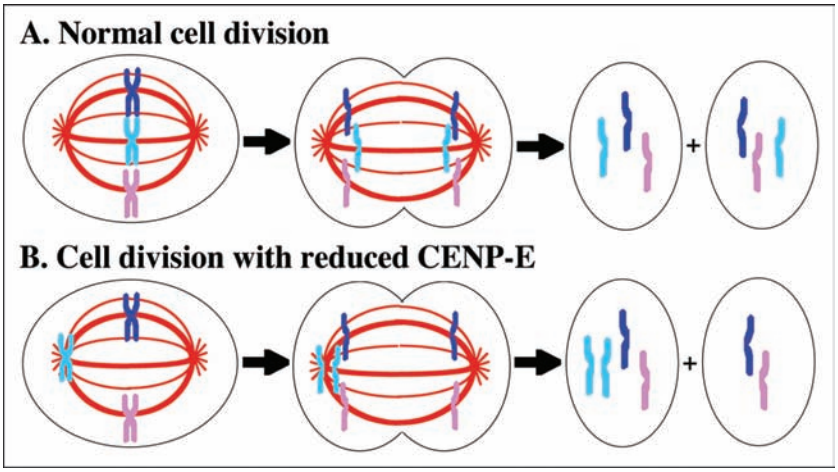
BY PAT PAGES

When cell division goes wrong, cells can end up with an abnormal number of chromosomes—a condition called aneuploidy and a cause of genetic disorders such as Down syndrome and various birth defects. Aneuploidy is also linked to most human solid cancers—cancers occurring in "solid" organs, such as the breast or prostate, as opposed to blood cancers—although whether aneuploidy causes cancer or results from it has not been well established—until now.

At ASBMB's 2007 annual meeting, Don Cleveland, professor of Medicine, Neuroscience and Cellular and Molecular Medicine at the University of California in San Diego, presented evidence in mice that aneuploidy results in the formation of tumors in aged animals (1). Unexpectedly, the scientists also reveal that, in certain circumstances, aneuploidy can also inhibit tumor formation.

The hypothesis that aneuploidy causes cancer was made nearly 100 years ago by a German biologist named Theodor Boveri, but the evidence accumulated so far had been inconclusive. Cleveland and his colleagues provided new insight into Boveri's hypothesis by studying mice with reduced level of a protein called centromere-associated protein E (CENP-E) that causes random missegregation of one or a few chromosomes.

CENP-E is a motor protein involved in aligning chromosomes during mitosis and in delaying mitosis to prevent errors in chromosome segregation. Previous studies had already examined mutations in genes encoding proteins with similar functions—such as Mad2, Bub3, and BubR1—but these proteins had other functions, so that the mutations caused defects other than those related to aneuploidy. Unlike these proteins, however, CENP-E is known only to generate high rates of aneuploidy, which makes it a more ideal candidate to test Boveri's theory.



A, in normal cell division, all chromosomes are equally segregated to give rise to two genetically identical daughter cells. *B*, reduction in CENP-E results in the misalignment of one—or a few—chromosomes (*turquoise* chromosome). Chromosomes are ultimately missegregated to produce an aneuploid progeny.

Cleveland's team found that mice with reduced levels of CENP-E did indeed develop cancer, but it affected mainly old mice. Ten percent of the mice developed spleen cancer, and they were three times more likely to develop lung tumors than normal mice.

Surprisingly, the scientists also found that high aneuploidy rates from low levels of CENP-E could sometimes have the opposite effect of delaying tumor onset. All mice that lacked a tumor suppressor gene called p19/ARF developed fatal tumors. But, in these mice, increased aneuploidy from reduced CENP-E sharply slowed tumor development. A possible explanation is that aneuploidy can increase the loss of mutations that drive cell growth—a hallmark of cancer—or trigger cell death, say, from loss of an essential chromosome.

Cleveland explains that this situation is similar to genetic instability caused by DNA damage. Cells sustain low levels of DNA damage on a regular basis, but this is normally countered by repair mechanisms. Higher levels of DNA damage due to mutations result in viable cells but are associated with cancers. Chemotherapeutic drugs—such as cisplatin—produce even higher levels of DNA damage, causing cellular death and tumor regression.

"These results show for the first time that aneuploidy can both cause cancer—as Boveri had initially proposed—and inhibit it, depending on the level of genomic damage that is present," Cleveland says.

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The Inner Workings and Promises of Skin Stem Cells

BY PAT PAGES

Skin cells continually renew themselves to repair wounds, replace old cells, and regrow hair. Scientists have shown that the renewing cells are stem cells present in the skin, but how they work is not completely understood.

At ASBMB's 2007 annual meeting, Elaine Fuchs, Howard Hughes Medical Investigator and Rebecca C. Lancefield Professor of Mammalian Cell Biology and Development at Rockefeller University, New York, reviewed the latest research on skin stem cells and presented the various biochemical pathways leading to skin or hair renewal.

"The skin is a rich source of readily accessible stem cells that are used to regenerate the surface of our skin and may one day be used to generate other tissues," Fuchs says. "Although we still don't know all the biochemical pathways involved, recent studies are providing a wealth of new information that could be valuable for clinical applications."

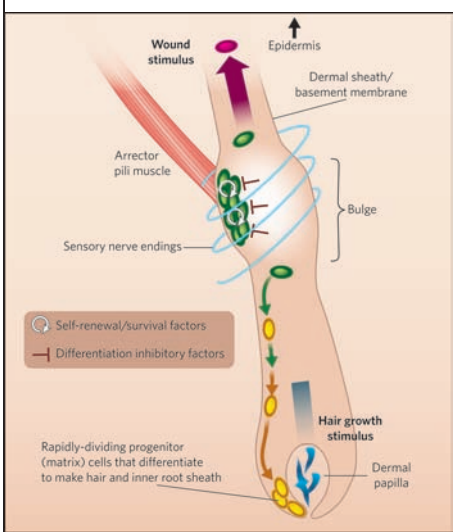

Diagram of a hair follicle. The stem cells (*green*), located in an area called the bulge, can genarate a new hair follicle and repair the epidermis on injury. *Reprinted by permission from Macmillan Publishers Ltd: Nature Vol. 445, p. 838, copyright 2007. www.nature.com/nature/index.html.*

Skin stem cells are located in small reservoirs that can be found in three different areas of the skin: the epidermis, which is a series of stratified layers on the surface of the skin; the hair follicle, which is a narrow tube with cells that produce hair; and the sebaceous gland, located near the hair follicle and the source of an oily substance that lubricates hair and protects it from bacterial infections.

Fuchs and her colleagues (1) developed a clever method to label and monitor the hair follicle's stem cells, which are located in an area that forms a bulge within its shaft (see figure). The hair follicle undergoes constant bouts of growth and shedding. At the start of new growth, a protein called β-catenin accumulates and partners with two other proteins called lymphoid enhancer-binding factor 1 (LEF1) and transcription factor 3 (TCF3). This switches on new genes and prompts the stem cells to proliferate and grow downward to generate the new hair follicle. Then the follicle begins to grow a new hair, which moves upward and appears at the skin surface.

Fuchs's research, extending back to the 1990s, revealed that the critical protein involved in initiating new rounds of hair growth is β-catenin, which can be generated in response to a signaling pathway called the Wnt pathway. Fuchs showed at the presentation that β-catenin can also be stabilized by inhibiting a second pathway, the bone morphogenetic protein (BMP) pathway. Together, these two signaling pathways help to generate new hair.

The epidermis also contains stem cells in its innermost layers. But when these stem cells are damaged, the hair follicle's stem cells receive biochemical signals telling them to divide and move upward to replenish the stem cells in the epidermis and repair the injury.

Recently, Fuchs's team discovered stem cells at the base of the sebaceous gland. Again, when these stem cells are damaged, hair follicle stem cells appear to be able to replenish them.

Better understanding of these three sources of skin stem cells may provide new ways to use them to treat skin and hair disorders.

"Our recent studies—in collaboration with Peter Mombaerts's lab at Rockefeller—suggest that skin stem cell nuclei from adult mice can be reprogrammed when placed in an enucleated, unfertilized oocyte," Fuchs says. "We have generated healthy mice from these skin stem cell nuclei. Hence, if current ethical and technical hurdles can be overcome to permit cloning of human hybrid embryonic stem cells from unfertilized oocytes and adult skin nuclei, it might be possible to harness their potential for broader uses in regenerative medicine in the future."

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OCTOBER 11–13, 2007
BOSTON MARRIOT, NEWTON, MA
This scientific meeting will bring together national and international leaders as well as researchers in the clinical practice of the syndrome
E-mail: insulinresistance@pacbell.net or metabolicinst@pacbell.net
Tel.: 818-342-1889
Fax: 818-342-1538

Protein Misfolding and Neurological Disorders Meeting
OCTOBER 17–19, 2007
DUNK ISLAND, NORTH QUEENSLAND, AUSTRALIA
www.proteinmisfolding.org

4th International & 2nd Asia-Pacific Peptide Symposium
OCTOBER 21–26, 2007
CAIRNS, QUEENSLAND, AUSTRALIA
www.peptideoz.org
E-mail: mibel.aguilar@med.monash.edu.au
Tel.: 613-9905-3723

NOVEMBER 2007

The Liver Meeting 2007
Annual Meeting of the American Association for the Study of Liver Diseases
NOVEMBER 2–6, 2007
BOSTON, MA
www.aasld.org/eweb/DynamicPage.aspx?webcode=07am

44th Japanese Peptide Symposium
NOVEMBER 7–9, 2007
TOYAMA, JAPAN
peptide-soc.jp/english/engindex.html
E-mail: jps@peptide.co.jp

APRIL 2008

International Conference on Cellular and Molecular Biology
A satellite meeting of the 4th World Congress on Cellular and Molecular Biology
APRIL 6–8, 2008
INDORE, INDIA
PLEASE SUBMIT YOUR CV AND PROPOSAL TO:
ak_sbt@yahoo.com

AUGUST 2008

HUPO 7th Annual World Congress
AUGUST 16–21, 2008
AMSTERDAM, THE NETHERLANDS
www.hupo2008.com
E-mail: Wehbeh.Barghachie@mcgill.ca
Tel.: 514-398-5063

30th European Peptide Society Symposium
AUGUST 31–SEPTEMBER 5, 2008
HELSINKI, FINLAND
www.30eps.fi/
E-mail: 30eps@congrex.fi
Tel.: 358-(0)9-5607500