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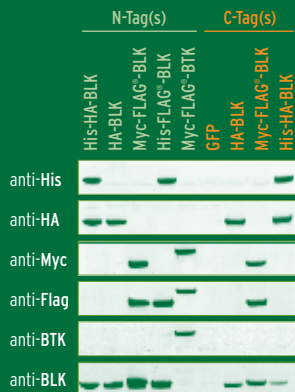
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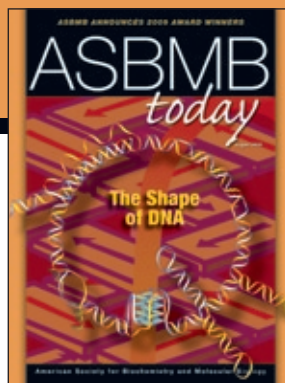


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ON THE COVER:
Karen Vasquez unwinds the mysteries of unusual DNA structural variants that contribute to genome instability, recombination, and gene expression.

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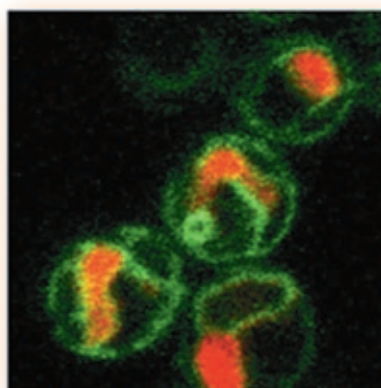
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ASBMB today

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from the editor

Focus on DNA

BY NICOLE KRESGE

This issue of *ASBMB Today* is chock full of DNA-related content. We have four articles that look at what's in store for attendees of the 2009 ASBMB Annual Meeting in New Orleans who are interested in DNA and nuclear research. First, Ronen Marmorstein and Trevor Archer tell us all about what we can expect at the Chromatin Regulation theme symposia in their article on p. 14. Some of the highlights include lectures on genomic approaches to studying the structure and function of chromatin and a look at the proteins that target chromatin via histone modifications. Then, Seth Darst and Jesper Svejstrup give an overview of the Gene Regulation symposia on p. 16. These talks include a lecture on RNA polymerase by Nobel Laureate Roger Kornberg of Stanford University. On p. 18, Traci Hall and Ben Blencowe summarize the talks that will be held under the RNA: Processing, Transport, and Regulatory Mechanisms theme. ASBMB member Joan Steitz, who was recently awarded the Albany Medical Center Prize (the nation's richest prize in medicine and biomedical research; p. 8), will be giving a talk titled *RNPs: Versatile Regulators of Gene Expression in Mammalian Cells*. And finally, on p. 20, Wei Yang and Anindya Dutta tell us what we can expect in the Genome Dynamics theme, including sessions on genetic approaches to studying replication and initiation, and the mechanisms of DNA replication, recombination, and repair.

In addition to these four articles, our Science Focus this month on p. 30 profiles Karen Vasquez, an associate professor in the Department of Carcinogenesis at the University of Texas M.D. Anderson Cancer Center. Vasquez looks at mechanisms of DNA damage and repair from the perspective of how DNA secondary structures can influence these events. She hopes that she can exploit her findings to create new strategies for targeted therapies, such as inducing recombination events in specific regions of DNA.

We are also pleased to announce that *ASBMB Today* recently received a 2008 APEX Award for Publication Excellence in the category of Most Improved Magazines and Journals. We couldn't have done this without our excellent writers, staff, and designer, and of course, suggestions from you, our readers. So keep sending those thoughts and comments to asbmbtoday@asbmb.org. 



It Is Alive*

BY GREGORY A. PETSKO

They're at it again. Armed with another new idea from the Discovery Institute, that bastion of ignorance, right-wing political ideology, and pseudo-scientific claptrap, the creationist movement has mounted yet another assault on science. This time it comes in two flavors, propaganda and legislative.

The propaganda is in the form of a poorly written, badly acted movie produced by Ben Stein, an attorney and entertainment figure who once served as a speechwriter for U.S. Presidents Gerald Ford and Richard Nixon. As if working for Nixon didn't do enough to demonstrate his faulty judgment, he has become an ardent critic of evolution and an advocate for 'intelligent design,' which is creationism poorly disguised as 'science.' He co-wrote and stars in the film *Expelled: No Intelligence Allowed*, which attempts to link evolution to the eugenics movement in Nazi Germany and to the Holocaust, and portrays advocates of intelligent design as champions of academic freedom and victims of discrimination by the scientific community. The famous evolutionary biologist and atheist Richard Dawkins has a spirited attack on the film on his web site (<http://richarddawkins.net/>).

Fortunately, the film is sinking faster than the *Lusitania*. As far as I can discover, it has done less than \$8 million in ticket sales to date, far less than its cost, and is playing to virtually empty houses in the few theaters that are still showing it. Whether this is because people recognize it as rubbish or because it is simply a bad movie, I don't know. So we can probably ignore it, as it so richly deserves to be. But the legislative attack is much more serious.

On June 11, 2008, the Louisiana House of Representatives voted 94-3 in favor of a bill that would promote 'critical thinking' by students on topics such as evolution, the origins of life, global warming, and human cloning. The Louisiana Senate had already passed a similar bill, Senate Bill 733, by a vote of 35-0, but an amendment adopted by the House, which would allow the state Board of Elementary and Secondary Education to prohibit supplemental materials it deems inappropriate, meant that the Senate had to pass the bill again. It did. The bill was then sent to Louisiana Governor Bobby Jindal, at age 36 the youngest governor in the United States and the first Indian-American to serve as the head of a state government. A former Hindu who converted to Catholicism in high school, Jindal attended Oxford on a Rhodes scholarship. Jindal was a biology major at Brown University, so he



understands the science at stake here, but he opposes stem cell research and has publicly supported the teaching of "intelligent design" in public schools. A fascinating subtext to this story is that Jindal is reportedly under consideration by Republican presidential nominee John McCain as a possible vice-presidential nominee. Unfortunately, Jindal signed the bill on Monday, June 23. He also did so with no public announcement; in fact, no one in the state knew he'd done it until several days later.

The bill is cleverly worded: it states in Section 1C that it "shall not be construed to promote any religious doctrine, promote discrimination for or against a particular set of religious beliefs, or promote discrimination for or against religion or nonreligion." In an interview with the conservative newspaper the *Washington Times* (June 12, 2008), Jason Stern, vice president of the Louisiana Family Forum, insisted "It's not about a certain viewpoint. It's allowing [teachers] to teach the controversy."

Let me say this as clearly as possible, so there can be no mistake about what I mean: there is no controversy. Just because a few misguided so-called scientists question the validity of the concept of evolution doesn't mean there is a controversy. There are still some people who believe the earth is flat (there's even a "Flat Earth Society"), but that doesn't mean that a grade school science teacher should teach his or her students that the earth might be flat. The fact that some people believe nonsense does not give that nonsense scientific credibility. A challenge to existing scientific principles must be based on evidence, not on belief, and there isn't a shred of evidence to support either creationism or intelligent design. Those ideas belong in a religion or philosophy class, not in a science class.

(By the way, speaking of religion class, if we accept the creationists' own rationale for this bill, then shouldn't right-wing fundamentalist Christian schools be forced to "teach the controversy" about religion? It's a much more controversial subject than science. Shouldn't their students be forced to consider the possibility that there is no God, or that the Muslim faith, or Hindu faith, or Jewish faith, might be the true one? Or that there are so many different translations and versions of the Bible that there is no way of knowing which one is the "word of God"? You can see how quickly their argument breaks down.)

What about the academic freedom argument? If someone wants to teach creationism in a science class, shouldn't they have the right to do so? Certainly—if they want to get fired. Because if they do that they deserve to get fired. It has nothing to do with academic freedom; it's about basic competence.


Consider, for example, a science teacher who taught that the sun revolves around the earth. Even the intelligent design advocates would probably have to admit that such a science teacher was incompetent and ought to be dismissed. That teacher might counter with a claim that his or her academic freedom was being infringed, but no court would uphold it, any more than a court would uphold a similar claim from a history teacher who taught that the Allies lost World War II or that Napoleon Bonaparte was King of Japan. Science, and history, may welcome speculation but the speculation must be based on facts, and when it isn't, then it doesn't belong in that subject. Any "science" teacher who teaches that the earth might have been created about 6,000 years ago and that all the material evidence that it's billions of years old is controversial is simply incompetent. If the state of Louisiana wants its children taught by such people then they deserve the kind of workforce and citizenry they are going to get.

It's worth pointing out that in 1987, in the case of *Edwards v. Aguillard*, the U.S. Supreme Court ruled as unconstitutional the idea of equal time for creation science and evolution in biology classes. That precedent will almost certainly be used as the basis for a constitutional challenge to the Louisiana law. Also, in the state of Pennsylvania, the *Kitzmiller v. Dover Area School District* case in 2005 put to rest the idea of intelligent design as an alternative to evolution being taught in biology classes. Although not a Supreme Court case, this decision was strong enough to cause creation science advocates to switch tactics to arguments about academic freedom, the focus of the current legislation at issue in Louisiana.

Lest you think this is merely some Bible Belt aberration, let me assure you that the creationists are marshalling this argument in other states as well. In Michigan, Senate Bill 1361, introduced in the Michigan Senate on June 3, 2008, and referred to the Senate Committee on Education, is yet another "academic freedom" bill aimed squarely at the teaching of evolution. Identical to Michigan House Bill 6027, which is still in the House Committee on Education, SB 1361 would, if enacted, require state and local administrators "to create an environment within public elementary and secondary schools that encourages pupils to explore scientific questions, learn about scientific evidence, develop critical thinking skills, and respond appropriately and respectfully to differences of opinion about controversial issues" and "to assist teachers to find more effective ways to present the science curriculum in instances where that curriculum addresses scientific controversies" by allowing them "to help

pupils understand, analyze, critique, and review in an objective manner the scientific strengths and scientific weaknesses of existing scientific theories pertinent to the course being taught." And in Texas (why is it not a shock that the state that gave us George W. Bush would also give us this), the Texas State Board of Education is again considering mandating a science curriculum that teaches the "strengths and weaknesses" of evolution. On June 7, 2008, the *Houston Chronicle* wrote that "strengths and weaknesses" language is "a 'teach the controversy' approach, whereby religion is propounded under the guise of scientific inquiry." The editorial went on to say: "What students really need is to be able to study science from materials that have not been hijacked by creationists whose personal agenda includes muddying the science curriculum. Creationism is not a 'system of science'."

As scientists we need to join such protests with our feet and wallets. The ASBMB Annual Meeting is scheduled to take place in New Orleans in April 2009. We have longstanding contractual obligations that require us to meet in Louisiana next spring. But I think we need to see to it that no future meeting of our society will take place in Louisiana as long as that law stands, nor should we hold it in any other state (are you listening, Michigan and Texas?) that passes a similar law. And I call upon the presidents of the American Chemical Society, the American Association of Immunologists, the Society for Neuroscience, and all the other scientific societies around the U.S. and the world, to join me in this action and make clear to the state legislators in Louisiana, the governor of the state, and the mayor and business bureau of New Orleans that this will be the consequence. You can do the same. Governor Jindal can be reached through his website (www.bobbyjindal.com/) and so can Mayor Ray Nagin (www.cityofno.com/Portals/Portal35/portal.aspx).

In its ability to rise again just when we think we've got it licked, creationism is like Frankenstein's monster. "Come see, villagers! It is alive!" We'll never be rid of it by being silent and doing nothing, so it is important to force governments that fall prey to this monster to pay for their folly by denying them our business. In addition, we must all arm ourselves with the one weapon we have that in the end the monster cannot overcome: the truth. All of us need to familiarize ourselves with the facts of evolution so that we can mount a spirited defense against the forces of ignorance and the charlatans who would exploit human insecurity and need for certainty. Carl Sagan memorably called science "a candle in the dark." Well, the darkness is always around us, closer than you think sometimes. Yes, it is alive. It's alive because some of our fellow men and women keep it alive. In the dark. 

*Reprinted with permission from *Genome Biol.* (2008) 9, 106 with minor updates.

FASEB Holds Its Fourth Annual Hill Day

BY JENNIFER A. HOBIN

Sixteen members of FASEB's Board and Science Policy Committee (SPC), including ASBMB members Robert Palazzo and Kenneth Mann, participated in FASEB's fourth annual Hill Day on June 3. Joined by FASEB-society staff, participants visited 13 Congressional offices on both sides of the aisle, including the Senate Committee on Health, Education, Labor, and Pensions and the Senate Subcommittee on Labor, Health, and Human Services (LHHS) Appropriations. The group also visited the offices of Senators Lamar Alexander (R-TN), Sherrod Brown (D-OH), Hillary Clinton (D-NY), Robert Menendez (D-NJ), Patty Murray (D-WA), Barack Obama (D-IL), Bernard Sanders (I-VT), Richard Shelby (R-AL), and Arlen Specter (R-PA), as well as those of Representatives Cliff Stearns (R-FL) and Jim Cooper (D-TN).


The meetings provided FASEB society scientists with a chance to talk with their members of Congress about their research, the contributions biomedical research funding makes to their states, and the negative impact that flat science funding is having on the research enterprise. In addition, with both the House and Senate negotiating major spending bills, participants took the opportunity to thank those Representatives who have championed biomedical research funding and to encourage others to do the same. FASEB leaders were particularly grateful to the Senators who supported the fiscal year (FY) 2008 emergency spending supplemental appropriations bill. With a vote on the bill pending in the House, they encouraged their Representatives to back the legislation as well.

Seen as the last opportunity to increase FY 2008 funding for the National Institutes of Health (NIH), National Science Foundation (NSF), and Department of Energy (DOE), passage of the supplemental bill had been a high priority for FASEB. In May, with the Senate poised to vote on the bill, FASEB President Robert Palazzo sent letters to every Senator asking them to support the supplemental and "the lifeline it provides to scientific research." FASEB also issued an e-action alert calling on scientists across the country to contact their Senators in support of the legislation. The same two-pronged advocacy strategy was adopted in the days before the House voted on, and ultimately approved,

its version of the bill. Together, these efforts generated over 3,300 emails, letters, and telephone calls and sent a strong message to Congress that biomedical research should be a national priority.

This push for additional science funding proved to be a success: on June 19, after months of negotiation, the Senate approved the House version of the bill by an overwhelming vote of 92 to 6. The final legislation, which was signed into law by President Bush four days later, provided an additional \$150 million for NIH, \$62.5 million each for NSF and DOE, and \$150 million for the Food and Drug Administration.

While FY 2008 appropriations were wrapping up at the time FASEB met with Congress, budget negotiations for FY 2009 were just beginning. Hill Day participants took the opportunity to ask their Members to support a \$59.7 billion FY 2009 budget resolution for Function 550, the budget account that finances Public Health Service agencies, including NIH, Centers for Disease Control, and the Health Resources and Services Administration. Participants also asked Congress to provide \$31.1 billion for NIH in next year's LHHS appropriations bill. Although there is a long way to go in the FY 2009 budget process, there has been a strong show of support for science funding so far. On June 26, the Senate Appropriations Committee approved an LHHS package that includes \$30.3 billion for NIH, a 3.5% increase over the FY 2008 funding level. The House Appropriations Committee has yet to approve its own version of the bill, although in its present form it includes \$30.4 billion for NIH.

Although science funding was a priority issue during FASEB's Hill visits, it was not the only topic on the agenda. Participants also took the time to thank Members who voted for the passage of the Genetic Information Non-Discrimination Act (GINA). This legislation, which protects individuals against the misuse of their genetic information in health and employment decisions, passed unanimously in the Senate and was signed into law on May 21. 

Jennifer A. Hobin is a Senior Science Policy Analyst for the Office of Public Affairs at the Federation of American Societies for Experimental Biology (FASEB). She can be reached at jhobin@faseb.org.



Finally, Some Good News on Appropriations

BY PETER FARNHAM

A 2008 supplemental appropriations bill with some science funding, and increases in other science agency budgets as 2009 appropriations bills begin to move, bodes well for science funding in the waning days of the Bush Administration. The bad news is that it is very much an open question as to whether the increases will occur before next spring.

Supplemental Signed

President Bush signed the so-called “war supplemental” funding bill on June 30. This bill contains \$162 billion in funding for the Iraq/Afghanistan conflicts, as well as about \$350 million in funding for several science agencies, including the National Institutes of Health (\$150 million) and the National Science Foundation (\$62.5 million). The Department of Energy’s Office of Science and NASA also received \$62.5 million each.

ASBMB (on its own and as part of various coalitions) contacted its 2,000-strong Local Activists Network who contacted their own Members of Congress and senators in turn. We have been told by informed members of the congressional staff that without a push from scientists, the science funding would never have been included in the bill. We encourage any ASBMB member who is not a member of the LAN to contact the ASBMB Public Affairs Office and become one.

2009 Appropriations Bills— Net Pluses for Science Funding

The good news for science funding continued into late June as the FY 2009 appropriations bills began progressing through the Congress. NIH, NSF, and VA medical research all saw increases early on.

Regarding NIH, the Senate Appropriations Subcommittee on Labor/HHS and Education marked up its bill on June 24 and approved \$154 billion for FY 2009. \$1 billion would go to the NIH, approximately a 3% increase over FY 2008. Total funding for NIH would thus rise to \$30.2 billion. Subcommittee chair Tom Harkin (D-IA) said the increase was needed to keep up with biomedical inflation and also to help keep young researchers in science. Ranking minority member Arlen Specter (R-PA) welcomed the increase and said it was the best they could do, but

also said “I don’t think it’s a good bill.” Overall, the bill is \$7.2 billion more than the President indicated he would accept. The full appropriations committee approved the bill on June 26.

Conflict of Interest Addressed in Senate Report Language

An interesting side note in the Senate bill is rather opaque report language that seems to focus on conflict of interest in biomedical research funding. The HHS Secretary is required to seek public comment on draft regulations “strengthening federal oversight and identifying enhancements of policies, including requirements for financial disclosure to institutions, governing financial conflicts of interest among extramural investigators receiving grant support” from NIH.

We are not sure what this means but will keep you informed as the regulations are developed.

On June 19 the House L/HHS Subcommittee approved a slightly larger increase for NIH (\$1.150 billion, about 3.9%) than the Senate, but during full committee markup on June 26 partisan wrangling broke out over the Interior appropriations bill (also being considered during the same markup session), and Chairman Dave Obey (D-WI) abruptly adjourned the hearing. Obey, famously bad-tempered, then threatened to halt the entire appropriations process, implying that he would resort to use of a continuing resolution to fund the government through the fall elections and into 2009. Regardless of whether Obey makes good on the threat, the bill will not be considered until mid-July.

A continuing resolution was already a real possibility before Obey threatened one. Informed observers believe that it is unlikely that the L/HHS bill will go to the President for his signature before the November election, thus mandating a continuing resolution at least into the new year and possibly until March, when a new Congress and President will be in office. The only way this can be avoided is if the President has lost enough support in the House and Senate to allow vetoes to be overridden. With the conventional wisdom calling for Republican losses in

continued on page 15

ASBMB Announces 2009 Award Winners

The American Society for Biochemistry and Molecular Biology (ASBMB) has announced the recipients of its annual awards competition. Seven scientists were singled out for their outstanding achievements and contributions to science. The awards will officially be presented at the Experimental Biology 2009 Meeting, April 18-22, in New Orleans.

David Davies of the NIDDK, National Institutes of Health, will give the Herbert Tabor/*Journal of Biological Chemistry* Lecture. The award was established to recognize the many contributions of Dr. Herbert Tabor to the *Journal of Biological Chemistry* and the Society. Davies studies the structure and mechanism of action of the Toll-like receptors of the innate immune system as well as other proteins such as anti-anthrax lyase.

John Kuriyan, Howard Hughes Medical Institute Investigator and Chancellor's Professor at the University of California, Berkeley, will be honored with the ASBMB Merck Award for his exceptional achievements in and contributions to structural biology. Kuriyan is one of the world's leading researchers on the structure and function of protein kinases, and his studies of c-Src, c-Abl, and CaMKII have provided exciting new insights into the structure and function of molecular systems that are similar to those found in many other biological contexts.


Sarah Spiegel of the Virginia Commonwealth University School of Medicine will be presented with the Avanti Award in Lipids. This award honors outstanding scientists whose research interests are in the field of lipids. Spiegel is one of the founders of the paradigm that sphingolipid metabolites serve as signaling molecules, and the sphingolipid signal that she discovered, sphingosine 1-phosphate (S1P), is now the most thoroughly characterized mediator in this field.

Douglas Rees, a Howard Hughes Medical Institute Investigator and Professor of Chemistry at the California Institute of Technology, will give the Fritz Lipmann Lecture. This lecture, which is awarded every 2 years, recognizes investigators who make conceptual advances in biochemistry, bioenergetics, and molecular biology. Rees has made pivotal contributions to understanding the structure of integral membrane proteins, membrane transport mechanisms, and metalloenzyme structure and mechanism.

The Schering-Plough Research Institute Award will be presented to **Phillip Zamore**, Howard Hughes Medical Institute Investigator and Professor at the University of Massachusetts Medical School. The Schering Plough Award was established to recognize young investigators for outstanding research at an early stage of their careers. A pioneer in the study of RNA silencing in eukaryotes, Zamore's laboratory has played a role in nearly all of the major breakthroughs in the study of RNA silencing.

Sandra Schmid, an investigator at the Scripps Research Institute, will be honored with the William C. Rose Award. The award recognizes outstanding contributions to biochemical and molecular biological research and a demonstrated commitment to the training of younger scientists. Schmid is an internationally recognized biochemist who has been a pioneer in our understanding of the molecular basis of receptor-mediated endocytosis.

The ASBMB Award for Exemplary Contributions to Education will be presented to **Rochelle Schwartz-Bloom** of the Duke University Medical Center. The award, administered annually by the ASBMB Education & Professional Development Committee, is given to a scientist who encourages effective teaching and learning of biochemistry and molecular biology through his or her own teaching, leadership in education, writing, educational research, mentoring, or public enlightenment. Schwartz-Bloom's past research looked at novel pharmacologic approaches to preventing neuronal death caused by cerebral ischemia associated with cardiac arrest and stroke. Her current research program, which she started in 1996, focuses exclusively on science education.

FASEB has also tapped ASBMB member **Susan Lindquist**, Howard Hughes Medical Institute Investigator, member of the Whitehead Institute for Biomedical Research and Professor at the Massachusetts Institute of Technology, for its Excellence in Science Award. The award, given annually by FASEB, recognizes outstanding achievement by women in the biological sciences. Lindquist is a pioneer in the study of protein folding and has shown that changes in protein folding can have profound and unexpected influences in fields as wide-ranging as human disease, evolution, and nanotechnology. 

Lindquist Honored with Otto Warburg Medal and Stein and Moore Award




Susan Lindquist of the Whitehead Institute for Biomedical Research was selected to receive the Protein Society's 2008 Stein and Moore Award as well as the German Society for Biochemistry and Molecular Biology's Otto Warburg Medal.

The Stein and Moore Award, sponsored by The Merck Company Foundation, was presented to Lindquist in July at the Protein

Society's annual meeting. Lindquist is being honored for her groundbreaking discoveries in understanding the wide array of biological processes governed by protein folding.

The Otto Warburg Medal has been awarded by the German Society for Biochemistry and Molecular Biology (Gesellschaft für Biochemie und Molekularbiologie, GBM) since 1963. It honors and encourages pioneering achievements in fundamental biochemical and molecular biological research. The Medal is regarded as the highest award for biochemists and molecular biologists in Germany.


Lindquist has resolved a variety of difficult problems in biology, ranging from delineating cellular responses to stress to uncovering genetic variation in evolution. Her work on prions has provided the molecular framework for an extraordinary new form of protein-based inheritance. 

Hendrix to Serve on NIH Council of Councils



Mary J. C. Hendrix, Northwestern University Feinberg School of Medicine, has been selected to serve as the National Cancer Institute's representative to the NIH Council of Councils. Hendrix, a former FASEB President, also serves ASBMB as chair of its Public Affairs Advisory Committee.

The NIH Council of Councils is made up of 27 members selected from the NIH Institute and Center (IC) advisory councils and advisory committees to the NIH Office of the Director. The Council advises the NIH Director on cutting-edge trans-NIH priorities and matters related to the policies and activities of the Division of Program Coordination, Planning, and Strategic Initiatives, established by the NIH Reform Act 2006, and the Office of Portfolio Analysis and Strategic Initiatives. The Council also acts as an external advisory panel to the IC Directors during the concept approval stage of the review process for trans-NIH initiatives.

"My charge to the Council is to be bold and define experiments that engage the community that NIH can do and fund reasonably," said NIH Director Elias A. Zerhouni, M.D. "The Council should foster incubation of new ideas and build resources as needed, all driven by analysis of the science." 

Steitz Wins Albany Medical Center Prize




ASBMB Council member Joan Steitz, Sterling Professor of Molecular Biophysics and Biochemistry at Yale University, has been awarded the Albany Medical Center Prize, the nation's richest prize in medicine and biomedical research. Steitz shares the honor with Elizabeth Blackburn for work that has improved disease treatments and may lead to new ones for degenerative and

other age-related disorders.

Steitz and Blackburn are the first women ever to receive the 8-year-old Albany Medical Center Prize. They will share the \$500,000 award, which ranks second only to the \$1.4 million Nobel Prize among medical prizes.

Steitz is known for research that has improved the diagnosis and treatment of certain autoimmune diseases, including lupus, scleroderma, and some forms of arthritis. She discovered the function of small ribonucleoproteins that play a vital role in producing proteins for the body's most basic biological processes.

The Albany Medical Center Prize in Medicine and Biomedical Research was established in the fall of 2000 when the late Morris "Marty" Silverman announced a gift of \$50 million from the Marty and Dorothy Silverman Foundation to Albany Medical Center to establish the prize to be given annually for 100 years. 

Wells Honored at Research Symposium




This past April, Robert D. Wells was honored at a research symposium entitled, "DNA Structure, Mutagenesis, and Human Disease." Wells, who is currently Director of the Center for Genome Research at the Institute of Biosciences and Technology, Texas A&M University, Texas Medical Center in Houston, was honored for his contributions to science, the Institute of Biosciences

and Technology, and national scientific societies.

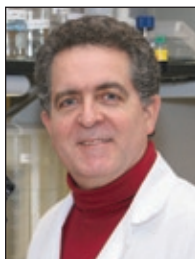
Wells is also a past president of the American Society for Biochemistry and Molecular Biology and of the Federation of American Societies for Experimental Biology (FASEB).

The event was attended by between 175 and 250 scientists and participants, including Wells' past graduate students and postdoctoral fellows as well as his friends, collaborators, and other associates.

After the symposium, a dinner was also held for approximately 115 people. After dinner remarks were provided by Robert J. Schwartz (IBT), Jacquelynn E. Larson (Wells' technician for 40 years), Lorrie Adams (IBT), Julian Davies (University of British Columbia), William R. Brinkley (Baylor College of Medicine), Peter Farnham (ASBMB), Bettie Sue Masters (University of Texas, San Antonio), and John Blaho (MDL Corporation). Following the remarks, Wells recited a poem that he had composed for the occasion. 




Franceschi Given Biological Mineralization Award



Renny Franceschi was given the 2008 Biological Mineralization Award at the International Association for Dental Research (IADR) 86th General Session & Exhibition in Toronto, Ontario, Canada this past July.

Franceschi is a Professor at the University of Michigan School of Dentistry in Ann Arbor. He has served as Associate Dean for Research at the University of Michigan

and as president of the IADR Mineralized Tissue Group. He has published approximately 100 peer-reviewed scientific articles and is particularly well known for scientific contributions to the field of mineralized tissue research.

The Biological Mineralization Award, which is supported by Unilever Oral Care, is one of 16 IADR Distinguished Scientist Awards, and it is one of the highest honors bestowed by the IADR. The award consists of a cash prize and a plaque and is designed to stimulate, encourage, and recognize basic research in the field of biological mineralization. 


Pawson Honored with Kyoto Prize



Anthony J. Pawson, a University of Toronto professor and a world-renowned cell biologist with the Samuel Lunenfeld Research Institute at Toronto's Mount Sinai Hospital, was honored with the 2008 Kyoto Prize in Basic Science. He will receive a gold medal and a cash gift of approximately \$460,000 at a ceremony in Kyoto, Japan, in November.

According to the Inamori Foundation, which administers the prize, Pawson received the award for "his proposal and proof of the concept of adapter molecules, which has established one of the basic paradigms in intracellular signal transduction and contributed significantly to the subsequent development of the life sciences."

Pawson is best known for his 1986 discovery of the Src homology 2 (SH2) domain which binds phosphorylated tyrosine (pTyr) residues and is essential in cell proliferation, metabolism, and cell-cell communication. This discovery was not only the first identification of what would become the largest class of known pTyr-recognition domains, it also heralded a new era in protein science by confirming that proteins were composed of distinct modules with specific functions.


The Kyoto Prize, given annually, honors people who have contributed significantly to the scientific, cultural, and spiritual betterment of mankind in the areas of advanced technology, basic sciences, and arts and philosophy. 

Marnett to Receive Founders' Award



Lawrence J. Marnett, director of the Vanderbilt Institute of Chemical Biology and Mary Geddes Stahlman Professor of Cancer Research at Vanderbilt University, will receive the first Founders' Award from the American Chemical Society's Division of Toxicology. The award will be presented to Marnett during the fall ACS meeting in Philadelphia.

Marnett's research focuses on the role of the enzyme cyclooxygenase-2 in cancer and inflammation. He uses structure-based approaches and medicinal chemistry to design selective cyclooxygenase-2 inhibitors as potential anti-inflammatory, cancer-preventative, and antiangiogenic agents. Marnett also studies the contribution of normal metabolism to the generation of DNA damage and mutation.

The annual award is given to a member of the division whose scientific activities have emphasized innovative research in the general field of chemical toxicology. The award was established to honor the vision and contributions of individuals who worked to get the division started in the mid-1990s. 


IN MEMORIAM: Rune L. Stjernholm



Rune L. Stjernholm, Professor Emeritus of Biochemistry, Tulane University School of Medicine, died peacefully on March 6, 2008 in Huntington Beach, California. He was 84 years old.

Stjernholm was the Biochemistry Chair at Tulane from 1971 to 1990 and continued serving the department as a professor for another 13 years. He was an outstanding educator who received numerous teaching awards, and his scientific career was underscored by a prolific record of important discoveries in intermediary metabolism and cancer biochemistry.

Stjernholm was born in Stockholm, Sweden, in 1924. He received his Ph.D. in 1958 from Case Western Reserve working with Harlan G. Wood. He then continued on as a faculty member at Case Western until 1971, when he moved to New Orleans to assume the Biochemistry Chair at Tulane.

During his years in Cleveland and later in New Orleans, he made several important contributions to our understanding of the general metabolism of human cells, especially in relation to cancer. At Tulane, he built a strong department that distinguished itself as a cornerstone of medical education and biomedical science at this institution. In addition, he served on a number of community-directed organizations that fostered support and excellence in cancer research in the New Orleans area. 

Academic Freedom Is

BY ANGELA HVITVED

Most of you probably read ASBMB President Greg Petsko's article on p. 3 about the "Academic Freedom" legislation in Louisiana and the subsequent concern over its potential effects on science education. In case you didn't, Governor Bobby Jindal signed the "Louisiana Science Education Act" on June 23 after it overwhelmingly passed both houses of the Louisiana legislature.

Although the many groups that sounded the early alarm on this legislation are credible proponents of sound science education, some members have reasonably asked, what is problematic about protecting academic freedom? On the surface, it would seem that those devoted to rigorous critical analysis—as most scientists are—would be in favor of legislation protecting the rights of educators to discuss controversial or unpopular ideas in their classrooms. Unfortunately, things aren't always what they seem.

The "Louisiana Science Education Act" (SB 733) is one of several "Academic Freedom" bills introduced in state legislatures this year that trace their lineage to an unsuccessful amendment proposed by former Pennsylvania Sen. Rick Santorum to the original "No Child Left Behind" legislation. The Santorum Amendment, as it was called, was drafted with the aid of the Discovery Institute, a pro-intelligent design/creationism think tank, as part of their "Teach the Controversy" strategy. The goal of this campaign was to provide a legally protected space for teaching the "controversies" of evolution by discussing "unresolved issues" and the "scientific weaknesses of evolutionary theory" in the science classroom. Critics countered that there is no controversy as to whether evolution has occurred. Although you can still find reference to the "Teach the Controversy" campaign on the Discovery Institute's website, it appears to have been supplanted by a newer strategy, "Free Speech on Evolution" (which ties in nicely with the theme of Ben Stein's movie *Expelled* and the proposed legislation in various states). Regardless of the strategy du jour, there is a well established link between the Discovery Institute's Center for Science and Culture and the push for

...at best, these bills are unnecessary and do not provide any additional legitimate protection

this particular strain of anti-evolution legislation.

"Academic Freedom" bills had been introduced in several state legislatures in the intervening years since the Santorum Amendment, but had not made it into law until Governor Jindal signed Louisiana's at the end of June. This year alone, bills were introduced in Florida, Louisiana, Alabama, Missouri, South Carolina, and Michigan. As of this writing, all have died except Louisiana's and Michigan's. The outcome of Louisiana's is now clear; Michigan still has twin bills working through both chambers.

Proponents argue the aim of these bills is to protect the rights of teachers and students to question and critically analyze certain scientific theories; evolution is given as an example of one such theory. Supporters claim legal protections are necessary to allow educators the freedom to criticize and discuss scientific issues and encourage "critical thinking skills, logical analysis, and open and objective discussion of scientific theories being studied."

This year, several of the bills included the phrase "strengths and weaknesses," which set off alarms for some and, in the case of Louisiana, was removed before final passage. Regardless of the exact wording, most science education groups agree that, at best, these bills are unnecessary and do not provide any additional legitimate protection and, at worst, provide cover for introducing intelligent design and other nonscientific topics into the science classroom. Barbara Forrest, a critic of intelligent design and expert witness in *Kitzmiller v. Dover Area School District*, is also a professor of philosophy at Southeastern Louisiana University. She helped organize a grassroots group, the Louisiana Coalition for Science, publicly opposed to passage of SB 733 and has posted an excellent deconstruction of the bill on their website (see box).

a Good Thing, Right?

and, at worst, provide cover for introducing intelligent design and other nonscientific topics into the science classroom.


Louisiana's bill was introduced by State Senator Bill Nevers on behalf of the Louisiana Family Forum, a group associated with James Dobson's Focus on the Family and the Family Research Council. Nevers, who chairs the Senate's education committee, is on the record as stating "scientific data related to creationism should be discussed when dealing with Darwin's theory." (*Hammond Daily Star*, April 6, 2008.) In addition to the "protections" outlined above, SB 733 also provides for the use of supplemental materials when discussing the scientific theories listed. These materials could be, but are not required to be, reviewed by the Board of Elementary and Secondary Education, although the criteria for review are not stated.

On June 11, Louisiana's House passed SB 733 by a vote of 94 to 3. The Senate had requested two amendments, specifying the scientific theories covered and requiring that educators present material from the standard text prior to introducing supplemental materials, forcing it back to the Senate where it passed on June 16 by a vote of 36 to 0.

After the bill passed both chambers, there were essentially three options for Governor Jindal: sign it into law, veto it, or wait 20 days after which it would automatically become law. Governor Jindal, who has a bachelor's degree in biology from Brown, did not announce his intentions when the legislation came to his desk, but past statements about creationism and intelligent design were cause for concern. On June 15, he appeared on CBS's *Face the Nation* stating: "I personally think that life, human life and the world we live in, wasn't created accidentally. I do think that there's a creator... I do think that God played a role in creating not only earth but mankind. Now, the way that he did it, I'd certainly want my kids to be exposed to the very

best science. I don't want them to be—I don't want any facts or theories or explanations to be withheld from them because of political correctness."

In a somewhat surprising move,

Governor Jindal signed the bill into law on June 23 without a public announcement. It was not known until a June 26 press release from his office listed it as one of 75 bills that the Governor had recently signed into law. It seems an odd tactic to take; waiting the 20 days would have accomplished the same objective, without actively taking a role in its passage. As of this writing, there had been no public comments by the Governor's office other than a one-sentence summary in their press release. Civil liberties and science education groups have vowed to monitor the implementation of this legislation very closely. Most agree that discussion concerning Louisiana's new "academic freedom" law has only just begun. 

Angela Hvitved is currently the ASBMB science policy fellow and can be reached at ahvitved@asbmb.org.

Resources

Like many policy issues, the context and implications of "academic freedom" legislation are complicated. Below are several links to additional resources for those who wish to read more.

- Full text of Louisiana's bill (SB 733): www.legis.state.la.us/billdata/streamdocument.asp?did=482728
- Barbara Forrest's analysis of SB 733: www.lasciencecoalition.org/docs/Forrest_UpdatedAnalysis_SB_733_6.5.08.pdf
- The National Center for Science Education: www.ncseweb.org/
- Wikipedia entry on Academic Freedom Bills: en.wikipedia.org/wiki/Academic_Freedom_bill

Hungry for Your Data to Tell the Story? Come to the Table!

This article is sixth in a series on publishing your research in the *Journal of Biological Chemistry*. The series will address a variety of issues that authors may have when writing and submitting articles to the *JBC*. The articles are written by Cadmus Communications, a Cenveo company, which is responsible for the editing, production, and printing of *JBC* articles.

If a picture is worth a thousand words, then surely a table is worth at least half that. When should you add a table to your manuscript? Tables should be used to present data that cannot be conveyed concisely in text or a figure. Tabular material is often preferable if you want to compare and contrast data. If you have large amounts of data or precise numeric values, these may be presented more clearly in a table. Data that will likely be calculated (for example, adding the column of percentages to equal

FIGURE ONE

TABLE 2
Intracellular ¹³C amino acid enrichments
ND, not detectable; n = 3; G, glucose.

	G5		G25		G25/M50		G25/VGB	
	SUR1 ^{-/-}	SUR1 ^{+/+}	SUR1 ^{-/-}	SUR1 ^{+/+}	SUR1 ^{-/-}	SUR1 ^{+/+}	SUR1 ^{-/-}	SUR1 ^{+/+}
Alanine								
M-2	21 ± 1 ^{ab}	9 ± 1 ^a	26 ± 2 ^a	26 ± 1 ^{ab}	31 ± 1 ^b	29 ± 2 ^a	25 ± 1 ^{ab}	20 ± 1 ^a
M-3	3 ± 1 ^b	2 ± 0	7 ± 1	8 ± 0	9 ± 1	10 ± 1	7 ± 1	8 ± 0
Aspartate								
M-2	14 ± 2	10 ± 2	17 ± 0 ^c	16 ± 2 ^b	16 ± 1 ^{bc}	15 ± 1 ^c	14 ± 1 ^c	16 ± 0 ^c
M-3	18 ± 1	19 ± 1	37 ± 0 ^c	30 ± 3 ^b	31 ± 1 ^a	38 ± 1	30 ± 0	30 ± 1
M-4	14 ± 1	15 ± 2	29 ± 0 ^c	33 ± 3 ^b	36 ± 0 ^{ab}	43 ± 1 ^b	39 ± 0	33 ± 1
GABA								
M-2	7 ± 2 ^a	14 ± 1 ^b	8 ± 1 ^a	21 ± 0 ^b	8 ± 2 ^{ab}	15 ± 2 ^c	13 ± 1 ^{bc}	25 ± 0 ^c
M-3	5 ± 1 ^a	13 ± 1	4 ± 2 ^a	21 ± 0 ^b	7 ± 2 ^a	31 ± 0	13 ± 0 ^{bc}	24 ± 1 ^b
M-4	1 ± 0 ^a	10 ± 1	8 ± 2 ^a	30 ± 1 ^b	16 ± 2 ^{bc}	42 ± 5	19 ± 1 ^{bc}	33 ± 0
Glutamate								
M-2	16 ± 0	15 ± 1	15 ± 1 ^c	16 ± 0 ^c	16 ± 1 ^c	17 ± 1 ^c	15 ± 0 ^c	16 ± 0 ^c
M-3	19 ± 1	15 ± 1	18 ± 0	20 ± 0 ^c	22 ± 1	24 ± 1	19 ± 1	20 ± 1
M-4	21 ± 2	17 ± 1	21 ± 1	27 ± 0	30 ± 2	38 ± 1 ^b	25 ± 1	28 ± 1
M-5	15 ± 1	12 ± 1	22 ± 0 ^c	29 ± 0 ^b	32 ± 1 ^{ab}	45 ± 1 ^b	33 ± 0 ^a	33 ± 0
Glucosamine								
M-1	2 ± 1 ^b	9 ± 1	4 ± 0 ^b	9 ± 0 ^c	ND	ND	4 ± 1 ^b	9 ± 0 ^c
M-3	4 ± 1	9 ± 1	5 ± 2	13 ± 0 ^c			6 ± 2	13 ± 0
M-4	7 ± 1	9 ± 0	11 ± 1 ^a	20 ± 0 ^c			11 ± 1	19 ± 1
M-5	4 ± 0 ^c	7 ± 0	13 ± 0 ^c	14 ± 1 ^b			12 ± 1	18 ± 1

^a p < 0.05 vs. SUR1^{-/-}.
^b p < 0.05 (for alanine only) vs. M-3.
^c p < 0.01 vs. G5.
^d p < 0.05 vs. SUR1^{-/-}.
^e p < 0.05 vs. G25.
^f p < 0.01 vs. M-3.
^g p < 0.05 (only compared M-2) vs. M-4.
^h p < 0.01 vs. G25.
ⁱ p < 0.05 vs. G5.

FIGURE TWO

TABLE 1

Expression levels of PAF-AH activity in freshly isolated plasma samples from various species

Plasma source	PAF-AH activity	
	<i>nmol/min/ml</i>	<i>nmol/min/mg</i>
Bovine	47.7 ± 0.6	0.33 ± 0.01
Human	73.2 ± 6.8	1.23 ± 0.23
Dog	61.4 ± 2.0	2.32 ± 0.15
Rat	183.1 ± 3.1	3.89 ± 0.13
Guinea pig	234.1 ± 9.5	10.78 ± 0.88
Mouse	630.0 ± 5.2	15.72 ± 0.26

100%) are often best presented in a tabular format. All data should be presented in an organized, easy to read format. The table should be kept as simple as possible: the more complex the table, the greater the need for logical organization. The *JBC* avoids dividing tables into parts A and B. Please number as Tables 1 and 2, using Arabic (not Roman) numerals.

Tables may be prepared by authors in a variety of ways, but using the table feature in Microsoft Word is probably the best way. Many alignment problems are resolved by using Word's table creation feature. Don't want to use Word's table feature? That's okay, but remember that consistency is the key to a well formatted table. If you use the space bar in one column, then the tab key in a second column, and then a comma to separate data in the third column, the alignment of the information in the finished table may not come out as you expected. Extra or blank rows and columns may also throw off the alignment of your data within the table. Tables created in Excel will be converted to Word before copyediting. Again, avoid extra or blank rows and columns. Think of your table as a grid. Include only one piece of information in each cell. Alignment of information can make a huge difference in the reader's understanding (or misunderstanding!) of your message.

The table title should be a short phrase. If necessary, a

If a picture is worth a thousand words, then surely a table is worth at least half that.

short explanatory legend may precede the table. Column headings (boxheads) should refer to the data immediately below in the column. Straddle headings span two or more columns and can only be used if there are at least two sub-headings (Figure 1). Units of measure should be displayed under the rule and directly above the numeric values (Figure 2).

For the stub column (leftmost column of table) the terms used refer to values read horizontally across the table. If there are subentries, then the main entries are boldface (see Figure 1). If no information is available for certain cells, it is preferable to leave the space blank; a dash may be used, but please explain it in a footnote.

Footnotes are indicated by superscript letters and are permitted for clarity of information not already provided in the table. Non-standard abbreviations that are used in the table only

(not already defined in the text) must be defined in a footnote. Your table should be uploaded to Cadmus as part of the Word text document.

Large tables containing complicated information may best be suited to be presented as supplemental material. You will find this particularly useful for those tables that are more than one page in length. The supplemental data appear in the on-line version of the *JBC*, not the print version. A link within the PDF of your article will take the reader to the cited supplemental material. If the editor agrees during the review process that a table can be supplemental, it is not necessary to upload it to Cadmus. The supplemental material will be posted online by the *JBC* Office exactly as you have submitted it. ☺

Chromatin Regulation

BY RONEN MARMORSTEIN AND TREVOR ARCHER

The eukaryotic genetic information is packaged into a compact form called chromatin, which contains nucleosome core particles with DNA wrapped around two copies of each of the four histone proteins, H2A, H2B, H3, and H4. Because of this tight association between DNA and histone proteins, all DNA-mediated activities, including transcription, replication, recombination, and repair, occur in the context of chromatin; nature has evolved an elaborate and coordinated system to mediate such DNA transactions.

Chromatin regulatory proteins can be grouped into three broad categories as follows: ATP-dependent chromatin remodeling enzymes that physically move the histone proteins about the DNA; post-translational modification enzymes that covalently modify histones, chromatin-targeting proteins, or modules that recruit proteins to the DNA, histones, or modified histones; and histone chaperone proteins that assemble and disassemble histones as well as replace variant histones in chromatin. The “Chromatin Regulation” theme will cover these diverse chromatin regulatory proteins with a focus on how they coordinate their distinct activities to modulate varied biological processes, including their misregulation in many human diseases.

The “Histone Modifications” session will look at the enzymes that post-translationally modify the histone proteins. Ray Trievel (University of Michigan Medical School) will describe studies on the structure and mechanism of the protein-lysine methyltransferases as well as the demethylase enzymes. Shelley Berger (The Wistar Institute) will discuss biochemical and cellular studies to probe how different histone and non-histone protein modifications work in coordination to regulate normal processes within the nucleus, such as transcription. Ronen Marmorstein (The Wistar Institute) will explain the structure and chemistry of histone acetyltransferases (HATs). Interestingly, although these enzymes were the first histone modifiers to be biochemically characterized well over a decade ago, current studies of these enzymes are still revealing new secrets about the diversity of HAT function.

The “Chromatin Recognition and Assembly” session will address the proteins that target chromatin through native and modified histone targets and the histone chaperone

proteins that ensure the proper assembly of the histone proteins within chromatin. Ming-Ming Zhou (Mount Sinai School of Medicine) will explain studies on the structure and biochemistry of histone targeting modules, including the acetyl-lysine recognizing bromodomain and domains associated with E3 ligase activity. Sepideh Khorasanizadeh (University of Virginia) will describe structural studies on the chromodomains that target lysine-methylated histone tails as well as nucleic acids within chromatin. Paul Kaufman (University of Massachusetts Medical School) will discuss biochemical and cellular studies on the histone chaperone proteins and how their functions are coordinated with other chromatin regulatory activities such as histone acetylation.

The “Chromatin Remodeling” session will explore the enzymes and mechanisms that disrupt histone-DNA contacts and change the architecture of chromatin. Jerry Workman (Stowers Institute of Medical Research) will look at the functions of histone-modifying complexes (HATs, histone deacetylases, histone methyltransferases, and histone demethylases) in the processes of chromatin remodeling for preinitiation complex formation at promoters as well as during transcription elongation. Geeta Narlikar (University of California, San Francisco) will detail biophysical and structural approaches to understand how chromatin remodeling machines couple the energy of ATP to alter nucleosome structure. Finally, Trevor Archer (NIEHS, National Institutes of Health) will explore the ability of chromatin remodeling complexes to function in concert with transcription factors within chromatin. Collectively, these presentations will explore the diversity of enzymatic activities required for regulated gene expression from chromatin.

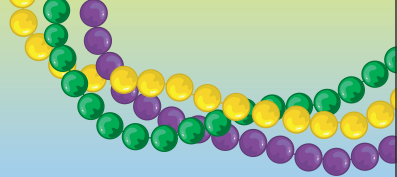
The “Genomic Chromatin” session will delve into the



Archer



Marmorstein



Chromatin Regulation

Symposium: Histone Modifications

- *Structural Basis of Protein Lysine Methylation*, Ray Trievel
- *The Complex Language of Histone and Factor Post-translational Modifications in Genomic Regulation*, Shelley Berger
- *New Surprises in Histone Acetylation*, Ronen Marmorstein

Symposium: Chromatin Recognition and Assembly

- *Molecular Modulation of Epigenetic Gene Transcription*, Ming-Ming Zhou
- *Recognition of Lysine-methylated Histone H3 Tail*, Sepideh Khorasanizadeh
- *Chromatin Assembly and Modification*, Paul Kaufman

Symposium: Chromatin Remodeling


- *Mechanisms of ATP-dependent Chromatin Remodeling Enzymes*, Geeta Narlikar
- *Protein Complexes That Modify Chromatin for Transcription*, Jerry Workman
- *To be Announced*, Trevor K. Archer

Symposium: Genomic Chromatin

- *Characterization of Mammalian Epigenomes*, Keji Zhao
- *Nuclear Dynamics and Genome Plasticity*, Geneviève Almouzni
- *Nucleosome Positioning*, Jonathan Widom

explosion of information revealed by the application of powerful genomic approaches to the structure and function of chromatin. Keji Zhao (NHLBI, National Institutes of Health) will describe the genome-wide changes of chromatin modifications that accompany differentiation of hematopoietic stem cells to erythroid precursor cells. Geneviève Almouzni (CNRS/Institut Curie) will report on the way DNA is packaged into chromatin within the cell nucleus and its relevance for chromatin function with a focus on histone dynamics during cell cycle and the involvement of histone variants and their chaperones. The final presentation from Jon Widom (Northwestern

University) will show that the genomic DNA sequence of yeast is predictive of the in vivo locations of most nucleosomes, discuss the molecular basis by which nucleosome positions are encoded, and examine how the encoded nucleosome positions facilitate specific chromosome functions.

These principal seminars will be complemented with short talks selected from submitted abstracts in the area of chromatin regulation. We anticipate exciting and informative sessions within the “Chromatin Regulation” theme and expect that many fruitful discussions will result from the presentations and associated poster sessions. 


News from the Hill *continued from page 6*

the congressional elections this fall, it is possible that nervous GOP lawmakers in tight races will vote against their very unpopular (and “lame duck”) President.

NSF Enjoys Broad Support

Both the House and Senate acted on NSF appropriations in mid-June. On June 17, the House Subcommittee on Commerce, Justice, and Science approved a \$6.85 billion budget for NSF for 2009, a \$790 million increase of 2008 (up 13%). The Senate subcommittee followed suit with an identical bill on June 19. This figure is in line with the President’s request for the agency. NSF thus is one of the bright spots in science funding this year.

VA Medical Research Gets a Boost—but Still Lags

Finally, the Department of Veterans Affairs medical research programs got a boost on June 24 when the House Appropriations Committee approved research funding at \$500 million. This restores the \$38 million the President wanted to cut, and it provides a net increase of \$20 million over 2008 funding. However, this falls well short of the level of funding recommended by the research community (including ASBMB) of \$555 million for FY 2009. 

Peter Farnham CAE is public affairs officer of the Society. He can be reached at pfarnham@asbmb.org.

Gene Regulation

BY SETH DARST AND JESPER SVEJSTRUP

The mechanism of gene regulation has been the focus of intense study over the past several decades in both bacterial and eukaryotic experimental systems. Our knowledge of the molecular processes governing transcriptional initiation is greatly improved, and much attention is now focused on the regulation of post-initiation events, such as promoter clearance, elongation, and termination. Moreover, a more general understanding of the dynamics of gene transcription in cells is emerging. The sessions on gene regulation at the ASBMB meeting in New Orleans will provide a unique overview of transcriptional regulation, from atomic resolution structures of RNA polymerases to the dynamics of transcription in living cells.

High resolution structures of cellular RNA polymerases from all three kingdoms of life are now available, providing many new clues into their operation. Seth Darst (The Rockefeller University), Katsuhiko Murakami (Pennsylvania State University), and Roger Kornberg (Stanford University) will compare and contrast RNA polymerase structure and function from bacteria, archaeobacteria, and eukaryotes (respectively) in the "Multisubunit RNA Polymerases: Lessons from the Structures" session.

The "Initiation: Mechanisms and Regulation" session will focus on transcriptional initiation. Richard Ebright (Howard Hughes Medical Institute, Rutgers University) has used single molecule methods to probe the behavior of bacterial RNA polymerase at promoters. Kevin Struhl (Harvard Medical School) has primarily used yeast, but also *Escherichia coli* and human cells, to understand basic mechanisms that underlie transcriptional regulation in living cells. Recently, this work has taken advantage of genome- and proteome-wide approaches

for uncovering general themes in gene regulation. Karen Wassarman (University of Wisconsin-Madison) has uncovered and investigated the role of 6 S RNA in the transcriptional reprogramming of bacterial cells in stationary phase.

In the "Initiation: Dynamics of Transcription" session, the focus will be on exciting new developments in our understanding of the dynamics of transcriptional regulation. Previously, it was thought that most, if not all, genes were regulated at the level of recruitment of factors to promoters. Recent results indicate that this cannot be true. Early work by John Lis showed that at the heat-shock inducible genes in the fruit fly, the polymerase is already engaged when the signal to transcribe is received, but this was thought to be the exception. However, Karen Adelman (National Institutes of Health) has shown that this is actually a common regulatory mechanism. John Lis (Cornell University) has continued his work on the dynamics of gene regulation at heat-shock loci in *Drosophila*, most recently by the use of two-photon microscopy in live polytene nuclei, which makes it possible to reconstruct images of transcriptional regulation in living cells. Robert Singer (Albert Einstein College of Medicine) also makes images of transcription in living cells by using a locus-specific reporter system, which allows precise single-cell kinetic measurements of promoter



Darst



Svejstrup

Gene Regulation

Symposium: Multisubunit RNA Polymerases: Lessons from the Structures

- *Bacterial RNA Polymerase*, Seth A. Darst
- *The X-ray Crystal Structure of RNA Polymerase from Archaea*, Katsuhiko Murakami
- *To be Announced*, Roger D. Kornberg

Symposium: Initiation: Mechanisms and Regulation

- *Single-Molecule Analysis of Transcription*, Richard Ebright
- *6 S RNA Regulation of Transcription*, Karen Wassarman
- *Transcriptional Regulatory Mechanisms in Yeast and Human Cells*, Kevin Struhl

Symposium: Initiation: Dynamics of Transcription

- *Promoter-proximal Stalling of Pol II Enhances Gene Expression*, Karen Adelman
- *The Dynamic Interplay of Transcription Factors and Chromatin during Gene Activation*, John T. Lis
- *Imaging Real-Time Gene Expression in Living Cells*, Robert Singer

Symposium: Elongation and Termination


- *Contending with Transcription Obstacles*, Jesper Q. Svejstrup
- *Regulation of Histone Modification and Transcription by the Yeast Paf1 Complex*, Karen Arndt
- *Role of the RNA Polymerase Trigger Loop in Transcript Elongation and Transcriptional Regulation*, Robert Landick

binding, initiation, and elongation.

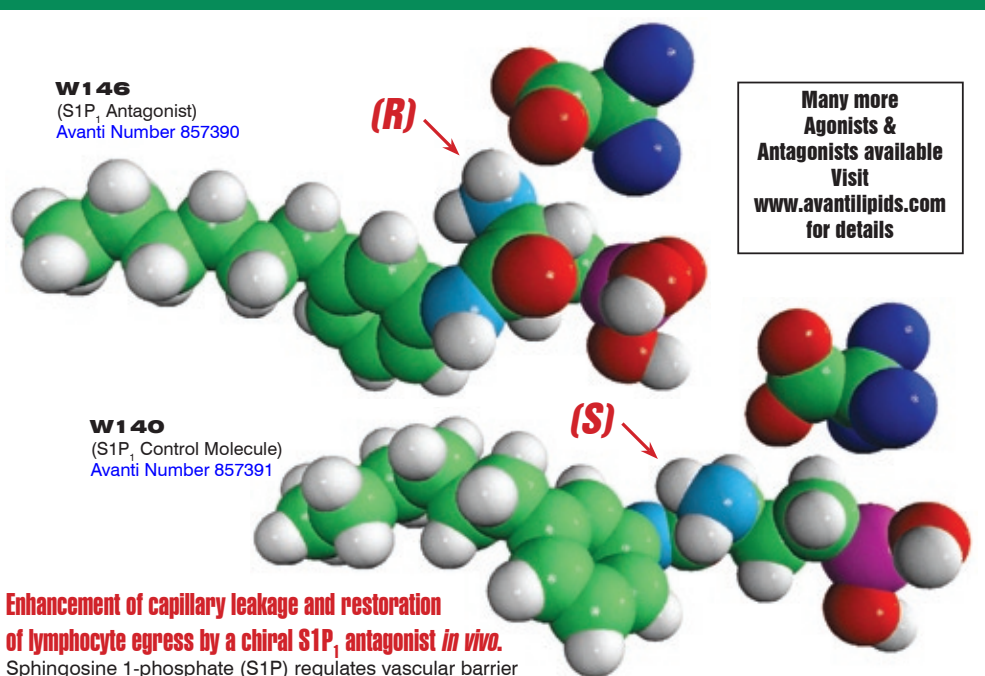
In the "Elongation and Termination" session, the focus will shift toward the later events of the transcription cycle. Bob Landick (University of Wisconsin-Madison) will discuss the regulation of transcription elongation and pausing, and Jesper Svejstrup (Cancer Research, UK) will continue on the theme of transcript elongation and

describe mechanisms used by cells to ensure that obstacles to transcription are not allowed to permanently block gene transcription. Karen Arndt (University of Pittsburgh) has shown that the so-called Paf complex has multiple functions in post-initiation events during gene transcription, including in co-transcriptional histone modification. Her lab has also found that the Paf complex

plays an important role in directing 3' end formation of nonpolyadenylated RNA polymerase II transcripts, such as small nucleolar RNAs.

Besides these principal talks, short talks will be selected for presentation from submitted abstracts in these areas. We look forward to many fruitful discussions in the ever dynamic field of gene regulation. 

NEW SELECTIVE ANTAGONIST - ONLY FROM AVANTI®



Enhancement of capillary leakage and restoration of lymphocyte egress by a chiral S1P₁ antagonist *in vivo*.

Sphingosine 1-phosphate (S1P) regulates vascular barrier and lymphoid development, as well as lymphocyte egress from lymphoid organs, by activating high-affinity S1P₁ receptors. We used reversible chemical probes (i) to gain mechanistic insights into S1P systems organization not accessible through genetic manipulations and (ii) to investigate their potential for therapeutic modulation. Vascular (but not airway) administration of the preferred R enantiomer of an *in vivo*-active chiral S1P₁ receptor antagonist induced loss of capillary integrity in mouse skin and lung. In contrast, the antagonist did not affect the number of constitutive blood lymphocytes. Instead, alteration of lymphocyte trafficking and phenotype required supraphysiological elevation of S1P₁ tone and was reversed by the antagonist. *In vivo* two-photon imaging of lymph nodes confirmed requirements for obligate agonism, and the data were consistent with the presence of a stromal barrier mechanism for gating lymphocyte egress. Thus, chemical modulation reveals differences in S1P-S1P₁ 'set points' among tissues and highlights both mechanistic advantages (lymphocyte sequestration) and risks (pulmonary edema) of therapeutic intervention.

M Germana Sanna, Sheng-Kai Wang, Pedro J Gonzalez-Cabrera, Anthony Don, David Marsolaïs, Melanie P Matheu, Sindy H Wei, Ian Parker, Euijung Jo, Wei-Chieh Cheng, Michael D Cahalan, Chi-Huey Wong & Hugh Rosen.
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FROM RESEARCH TO cGMP PRODUCTION - AVANTI'S HERE FOR YOU

RNA: Processing, Transport, and Regulatory Mechanisms

BY TRACI HALL AND BEN BLENCOWE

Following the sequencing of whole genomes of several eukaryotic species during the past decade, it became immediately apparent that differences in gene regulation, and not gene number or repertoire, likely account for much of the remarkable functional and phenotypic diversity among higher eukaryotes. Around the same time as the completion of these large scale projects, an explosion of discoveries revealed the enormous roles played in gene regulation by small RNAs and other RNA-mediated regulatory activities. RNA has since taken a center stage in our efforts to understand the complex and intertwined mechanisms that contribute to the myriad of fundamental biological processes.

The extremely rapid pace of discoveries in RNA biology makes it a challenge for any one researcher to keep pace with the many exciting and important discoveries being made. With this challenge in mind, we are delighted to be able to bring together a group of leading experts in diverse topics in the field of RNA in an ASBMB-sponsored theme entitled: "RNA: Processing, Transport, and Regulatory Mechanisms." This theme will feature sessions titled "Ribonucleoproteins (RNPs)," "RNA Regulation and Transport," "RNA Structure and Recognition," and "RNA Processing." The invited speakers' research runs the gamut of approaches, including biochemical, genetic, computational, structural, and cell biological strategies.

The session on RNPs will feature Joan Steitz (Yale University), whose discovery of, and continued work on, small nuclear and other RNPs forms the foundation of the topic of this session. Joining her will be Christine Guthrie (University of California, San Francisco) who has made pioneering discoveries on the spliceosome and will be presenting her latest work on splicing regulation in yeast. Maria Carmo-Fonseca (Institute of Molecular Medicine in Lisbon, Portugal) completes this remarkable group of speakers and will present her group's work on the *in vivo* dynamics of spliceosomal assembly.

The "RNA Regulation and Transport" session will highlight research on RNA-mediated gene regulation and transport and localization of RNA in the cell. Xuemei Chen (University of California, Riverside) will

present work on the generation and function of small RNAs in *Arabidopsis*. Phillip Zamore (University of Massachusetts Medical School) will describe the expanding world of small RNA species, their diverse activities and mechanisms of function. Adding a different perspective, Henry Krause (University of Toronto) will present new findings stemming from his group's recent genome-wide survey of RNA localization patterns in *Drosophila*.

The "RNA Structure and Recognition" session will cover a variety of aspects of RNA folding and molecular interactions. Kevin Weeks (University of North Carolina) will demonstrate how chemical probing can be used as a high throughput method to examine the structure of very large RNAs, such as viral genomes. Adrian Ferre-D'Amare (Fred Hutchinson Cancer Research Center) will describe how small molecules can modulate the functions of ribozymes and riboswitches. Traci Hall (National Institute of Environmental Health Sciences) will illustrate how both natural evolution and researchers have tailor-designed Pumilio family proteins for specific RNA recognition.

Rounding off the theme, the "RNA Processing" session will cover both genome-wide principles and focused mechanisms by which transcribed precursor RNAs are altered to produce mature, functional RNA molecules. V. Narry Kim (Seoul National University, Korea) will describe the intricate steps required for generating microRNAs (miRNAs) from primary miRNA precursors. Benjamin Blencowe (University of Toronto) will present new work on the regulatory factors that control alternative splicing in the mammalian nervous system. Christopher Burge (Massachusetts Institute of Technology) will present a genome-wide view of alternative splicing and the regulatory sequences that form




Blencowe



Hall

the underlying code controlling this process.

In addition to the invited speaker talks, we will include several short talks in the program based on submitted abstracts. These short talks will help promote young scientists with exciting new results and are expected to complement the main topics of the sessions. We encourage you and your colleagues to submit abstracts for consideration.

We hope that you will enjoy the sessions we have planned for ASBMB 2009, and we look forward to seeing you in New Orleans. 

RNA: Processing, Transport, and Regulatory Mechanisms

Symposium: Ribonucleoproteins

- *RNPs: Versatile Regulators of Gene Expression in Mammalian Cells*, Joan Steitz
- *New Insights into the Regulation of mRNA Splicing*, Christine Guthrie
- *In vivo Dynamics of Spliceosome Assembly*, Maria Carmo-Fonseca

Symposium: RNA Regulation and Transport

- *Small RNA Diversity and Function*, Phillip D. Zamore
- *Small RNA Metabolism in Arabidopsis*, Xuemei Chen
- *Genome-wide Analysis of Subcellular RNA Trafficking*, Henry Krause

Symposium: RNA Structure and Recognition

- *RNA Recognition by PUF Proteins*, Traci M. T. Hall
- *High-throughput Analysis of RNA Structure by SHAPE Chemistry*, Kevin Weeks
- *Ribozymes and Riboswitches: Modulation of RNA Function by Small Molecules*, Adrian Ferre-D'Amare

Symposium: RNA Processing

- *Alternative Splicing in the Mammalian Nervous System*, Benjamin Blencowe
- *Global Patterns in Alternative Pre-mRNA Processing*, Chris Burge
- *MicroRNA Biogenesis*, V. Narry Kim

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Genome Dynamics

BY WEI YANG AND ANINDYA DUTTA

DNA encodes the genetic blueprint of most organisms, so DNA replication and repair are essential to ensure the continuity of life. Changes in genomic DNA can give rise to evolution, but changes without checks and balances may lead to multiple disorders including cancer. The “Genome Dynamics” theme at the 2009 ASBMB annual meeting will contain four sessions: “Genetic Approaches to Studying Replication Initiation,” “Biochemical Advances in DNA Replication Initiation,” “Mechanisms of DNA Replication, Recombination, and Repair,” and “Genomic Integrity and Cancer Biology.” The sessions are organized to showcase the complexity of genome dynamics, timely advances, and the tools and approaches at the leading edge of research.

The regulated initiation of DNA replication at replication origins is a key process for maintaining genomic stability. The pre-replicative complex (preRC) binds to origins of replication in the early G1 phase of the cell cycle and triggers the firing of replication forks early in S phase. Stephen P. Bell (Massachusetts Institute of Technology) and Haruhiko Takisawa (Osaka University) study replication initiation in cell-free systems from yeast and *Xenopus*, respectively. In the “Biochemical Advances in DNA Replication Initiation” session, they will describe advances in how preRCs assemble, how replication forks begin at origins of replication, and how the

checkpoint system regulates replication in the presence of damaged DNA. Fragile sites are specific loci that display enhanced frequency of genomic instability, often due to replication fork collapse, and lead to many genetic diseases. Ellen Fanning (Vanderbilt University) will report on results connecting chromosomal fragile sites in mammalian cells to DNA replication origins and preRCs.

The session “Genetic Approaches to Studying Replication Initiation” will focus primarily on genetic techniques used to study the regulation of DNA replication. Anindya Dutta (University of Virginia) will describe how the genetic manipulation of selected replication initiation factors in mammalian cells leads to re-replication of chromosomal segments in the same cell cycle and how this causes genomic instability observed in cancers. David M. MacAlpine (Duke University Medical



Dutta



Yang

Genome Dynamics

Symposium: Biochemical Advances in DNA Replication Initiation

- *Initiation of Replication at a Eukaryotic Origin*, Stephen P. Bell
- *Initiation at the Fragile X (FMR1) Origin of Chromosomal Replication*, Ellen Fanning
- *Chromosomal DNA Replication in Xenopus Egg Extracts*, Haruhiko Takisawa

Symposium: Genetic Approaches to Studying Replication Initiation

- *Re-replication and Its Consequences*, Anindya Dutta
- *The Role of Local Transcription and Chromatin Structure in Establishing DNA Replication Origins*, David MacAlpine
- *The Initiation of Chromosomal DNA Replication in Budding Yeast*, Hiroyuki Araki

Symposium: Mechanism of DNA Repair, Replication, and Recombination

- *Repair of DNA Double-strand Breaks and Tumor Suppression*, Maria Jasin
- *Lesion Bypass in DNA Replication*, Wei Yang
- *Tales from Transposons*, Nancy L. Craig

Symposium: Genomic Integrity and Cancer Biology


- *A Multi-protein Complex Involved in the DNA Damage Response Network of Fanconi Anemia and Breast Cancer*, Weidong Wang
- *BRCA1 and DNA Damage Response*, Junjie Chen
- *Cancer or Premature Aging in Genome Instability Disorders*, Laura Niedernhofer

Center) will describe studies from the modENCODE project, which identifies and characterizes the functional DNA elements that regulate the replication program in a variety of *Drosophila* cell lines, tissue types, and developmental stages. Finally, Hiroyuki Araki (National Institute of Genetics, Japan) will return to the theme of the preRC in yeast, focusing on how preRCs are activated to initiate replication at the onset of S phase through the activity of cyclin-dependent kinases.

For the session titled "Mechanism of DNA Replication, Repair, and Recombination," three scientists specializing in genetics, biochemistry, and structural biology have been invited to share their research. Both Maria Jasin (Sloan-Kettering Institute) and Nancy L. Craig (Johns

Hopkins School of Medicine) study DNA breaks, both programmed and accidental. Their talks will highlight alternative pathways of processing double-strand breaks and the good, bad, or ugly consequences of DNA transposition and recombination. For every DNA transaction, a collection of macromolecules will have to come together to form a macromolecular assembly and disassemble after the process is complete. Wei Yang (National Institutes of Health) will discuss how she uses structural biology to provide a series of snapshots of these macromolecules at work.

Cancer and aging affect length and quality of life. The session titled "Genomic Integrity and Cancer Biology" will focus on how defects in genome maintenance accelerate aging and malignant growth. Many

cancers result from failure to properly repair DNA damage and a subsequent failure to eliminate defective cells. Junjie Chen (Yale University School of Medicine) studies the breast cancer susceptibility gene 1 (BRCA1) and its role in DNA damage checkpoint control. Laura Niedernhofer (University of Pittsburgh School of Medicine and Cancer Institute) uses a mouse model to study the DNA repair nuclease ERCC1-XPF and identifies strategies to prevent or delay age-related disease without promoting cancer. Weidong Wang (National Institutes of Health) studies the Fanconi anemia (FA) syndrome. He will discuss recent work on how a macromolecular machine containing multiple FA and Bloom Syndrome proteins functions in genome maintenance and prevents cancers. 

Register for the AAMC Minority Faculty Career Development Seminar!

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Health Disparities in Cancer

BY JEROME C. NWACHUKWU

A health disparity is observed when the health status of members of certain populations is unequal to the health status of members of other populations. In 1985, Margaret Heckler, the Secretary of the Department of Health and Human Services, issued the Report of the Secretary's Task Force on Black and Minority Health, which elucidated severe disparities in health status among Americans of different racial and ethnic groups¹. In this report, disparities against black men and women were observed in life expectancy and overall death rates, as well as in deaths attributed to several diseases, including cancer. As a result of this report, the Department of Health and Human Services created the Office of Minority Health. Two years later, the Center for Disease Control and Prevention followed suit and created its own office, which was later renamed the Office of Minority Health and Health Disparities.

The goals of both offices include eliminating health disparities for "vulnerable" populations, and both offices have clearly made substantial and progressive efforts toward addressing these disparities. However, this goal has proved to be particularly difficult to attain.

Today, cancer is the second leading cause of death in the United States. It is a complex disease characterized by malignant cell proliferation in a wide variety of organs or primary sites, and often leads to metastasis and tumor growth at secondary sites. Currently, the American Cancer Society keeps track of about 50 different types of cancers. The three most common types of cancers among whites, blacks, Asian/Pacific Islanders, Native Americans, and Hispanics are prostate (men) or breast (women), lung, and colorectal cancers.

Disparities in Cancer

Health disparities are tracked by three main statistics: the rate of incidence (*i.e.* the number of new cancer cases), the rate of mortality (*i.e.* the number of deaths due to cancer), and the rate of survival (*i.e.* the length of survival after diagnosis). Although cancer death rates have somewhat declined for most populations, there are significant differences in both cancer incidence and death rates among the different populations.

For example, in 1999 and in 2004, black men had

the highest death rates for prostate cancer and black women had the highest death rates for breast cancer. Another example of the disproportionate rates of cancer is observed in Native Americans/Alaska Natives who have the lowest incidence but not the lowest death rates of colorectal cancer in both 1999 and 2004. Interestingly, liver cancer, which is not one of the most common types of cancer, has the highest rates in Asian/Pacific Islanders. This type of cancer also had higher rates in blacks, Native Americans/Alaska Natives and Hispanics, compared with Whites. Liver cancer incidence and death rates generally increased between 1999 and 2004. The presence and persistence of such differences indicates a health disparity.

One common rationalization often used to explain or perhaps diminish the relevance of these disparities is the *de facto* correlation between socioeconomic status and access to good health care in the U.S. However, there are also cancers, for instance leukemia, lymphoma, and skin cancers, that have lower rates for all four groups compared with whites. Therefore, although low socioeconomic status may contribute to these differences, it does not appear to account for the existence and persistence of such disparities in cancer incidence and death rates.

Risk Factors, Prevention & Treatment

The common saying "Prevention is better than cure" is applicable only if "Prevention" is in fact possible. For the various types of cancers, the risk factors, growth rates, and most-effective treatment options are different. Arguably, the chances of preventing complex diseases such as cancer can be greatly increased through efforts directed at reducing or eliminating the effect of specific risk factors, provided that these risk factors are known. Risk factors for most cancers often include environmental, developmental, and genetic components.

In cancers where environmental risk factors are known, efforts can be made to reduce exposure to these factors. For example, smoking tobacco products can increase the risk of lung cancer; hence it is advisable to abstain from smoking. In addition, the National Institute for Occupational Safety and Health maintains a list of carcinogenic substances which can increase the risk of cancer incidence. Therefore, efforts to avoid exposure



to such substances are expected to help prevent or reduce cancer incidence.

However, the risk factors for the most common cancers also include developmental and genetic factors that are practically unavoidable. For instance, the risk of prostate cancer incidence is known to increase with age. The disease is prevalent in men over 65 and rare in men under 45 years of age. Furthermore, the National Cancer Institute now lists mutations in three genes (*BRCA1*, *BRCA2*, and *CHEK2*) as potential risk factors for breast cancer.

For some types of cancers, vaccination may provide a viable shot toward prevention. For example, human papillomavirus (HPV) infection is a major risk factor for cervical cancer, and in 2006, Gardasil, a new vaccine made by Merck & Co., Inc. to prevent infection from four types of HPV (two of which are accountable for approximately 70 percent of cervical cancer cases) was approved by the U.S. Food and Drug Administration. Therefore, cervical cancer prevention may have crossed an important milestone, unlike most common cancers, which are not yet understood well enough for scientists to develop drugs to prevent their occurrence.

The use of vaccines such as Gardasil could also provide insight to the efficacy and reliability of vaccinations in eliminating health disparities in cancer. However, once such cancers have been diagnosed, do additional risk factors that may differentially increase death rates among populations come into play? In other words, could it be that the risk factors for cancer incidence are perhaps slightly but significantly different from the risk factors for cancer deaths? If so, perhaps more efforts should be made toward identifying reliable risk factors for cancer deaths and reducing the effects of these risk factors among various populations.

Currently, the treatment regimen for common cancers includes a combination of surgery, radiation therapy, and chemotherapy/hormone therapy. Indeed several cancer cases are initially responsive to therapy, thanks to extensive research and drug development conducted in

A health disparity is observed when the health status of members of certain populations is unequal to the health status of members of other populations.

this area within the latter part of this century.

However, some cancers are resistant to current therapy, and many others acquire resistance during the course of the disease. In most cases, resistance to therapy and/or recurrence eventually leads to death. Disparities in cancer death rates (e.g. those observed in breast cancer) suggest that there are ethnicity-related risk factors for death from the disease. Therefore, determining why some cases are more likely than others to recur after therapy is very important and has become a rapidly growing aspect of molecular biology

and biochemistry research over the years. Potentially, the results of these studies could also help identify specific and reliable risk factors that differentially increase cancer death rates among the various populations.

Hence, whereas ethnicity-related differences in socioeconomic status and known risk factors may contribute to disparities in cancer incidence, they do not completely explain the existence and persistence of health disparities in cancer. So far, current therapies, which have been somewhat effective in reducing cancer death rates, do not seem to be effective in reducing the associated health disparities. Perhaps additional efforts should be directed toward cancer prevention and identifying reliable risk factors for cancer deaths to help reduce and eventually eliminate these disparities in cancer.

Jerome C. Nwachukwu is a Ph.D. candidate in the Molecular Pharmacology Training Program at the New York University School of Medicine Sackler Institute of Graduate Biomedical Sciences in New York City. He has served on the ASBMB MAC since 2006 and can be reached at jn462@med.nyu.edu.

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The Changing Face of Education in the Molecular Life Sciences

BY ELLIS BELL

In the last few years there has been a quiet revolution in the way we teach undergraduates biochemistry and molecular biology. Fueled by a variety of initiatives by both the Howard Hughes Medical Institute and the National Science Foundation, a focus on undergraduate research has become commonplace in the top undergraduate programs around the country. This focus takes a variety of forms. Some programs focus on summer research experiences, some on year-round research, and others on incorporating research into formal course work, all with success. Students learn more both in terms of skills and techniques as well as core knowledge. Project Kaleidoscope for many years has been promoting innovative classroom activities and training of college teachers to more fully engage students in the learning process, again with significant achievement. Recently a new bill was introduced in the U.S. House of Representative, H.R. 6104: Enhancing Science, Technology, Engineering, and Mathematics Education Act of 2008, “To provide for the coordination of the Nation’s science, technology, engineering, and mathematics education initiatives” by creating an office to design education programs. Likewise, the Department of Education is creating an office to work on solving these problems.


The Government already supports science education through the National Science Foundation by focusing on “broader impact” issues in the review of competitive research grants in its various directorates as well as a variety of science education programs aimed at all levels of education, administered through the “Education and Human Resources” directorate. The NSF supports education through investigator-initiated programs, and they are clearly starting to have an impact in both the research laboratory and the classroom. NIH also has significant educational activities, again at all levels. We should be increasing support for such ongoing, successful initiatives that harness the creative power of individual investigators rather than creating more infrastructure.

HHMI, in its current round of awards to liberal arts colleges, is again pushing the envelope in science education. Forty eight liberal arts institutions were recently awarded a total of \$60 million to “identify creative new ways to engage your students in the biological sciences.” The list of awardees

reads like a who’s who of liberal arts science education, rewarding schools that have been innovative and successful in the past while at the same time bringing new institutions into the mix, such as Gustavus Adolphus College in rural Minnesota, long known for producing outstanding undergraduates in biochemistry and molecular biology.

The schools that received the grants will use a number of innovative ways to include research in the undergraduate experience. For example, Barnard College will incorporate “real” research involving studies on pest attacks on tomatoes and potatoes into its formal laboratory courses, rather than the still prevalent “cookbook” approach to labs. Similarly, Smith College will move away from “cookbook” teaching by increasing its focus on experimental and problem-based learning, including an innovative new center focusing on K-12 outreach. Bowdoin College will initiate a program to give its undergraduates an enhanced research experience by providing for 1 to 2 years of full-time research before a student goes on to graduate school. Lewis and Clark College will combine a variety of student-faculty mentoring opportunities. And finally, Swarthmore College will utilize peer mentoring to enhance the involvement of new students with upper class students.

Perhaps the most significant aspect of the awards is the number of schools that will focus on the creation of interdisciplinary introductory courses to ensure that a new generation of students approach problems from an interdisciplinary perspective rather than being bound by old traditional departmental boundaries. For example, in perhaps the most ambitious project, the University of Richmond will invest significant faculty time from a number of departments to create a two semester interdisciplinary course that will replace the standard introductory course in computer science, biology, math, chemistry, and physics.

A read through of the various descriptions of the programs that these 48 schools will create gives the sense that the future of science education for all students is in good hands! 

Ellis Bell is Chair of the ASBMB Education and Professional Development Committee. He can be reached at jbell2@richmond.edu.



Postdoctoral Fellows and the Research Enterprise

BY LISA M. CURTIS, RASHADA ALEXANDER, JASON RAWLINGS, LU-ANN POZZI, AND JONATHAN GITLIN


Recently, three reports addressing aspects of the research enterprise with relevance to postdocs and their career advancement were released. The effects of decreased federal funding of biomedical research in the U.S. in recent years and the particular effects on junior investigators were addressed in “A Broken Pipeline? Flat funding of the NIH puts a generation at risk”, a commentary published by a consortium of institutions, as well as in the American Academy of Arts and Sciences’ white paper, “Advancing Research in Science and Engineering: Investing in early-career scientists and high-risk, high-reward research”. The effects on the proposal and undertaking of more speculative research projects in this climate of highly competitive governmental funding were also discussed in the American Academy paper. The 2007-2008 Peer Review Self-Study released by the National Institutes of Health (NIH) addressed the need for grants at different career stages and types. It also called for a realistic evaluation of the NIH’s “contribution to the optimal biomedical workforce needs,” and highlighted the need for data-driven analysis of NIH peer-review outcomes to propose more appropriate changes.

These issues, although primarily focused on junior investigators, have significant implications for postdoctoral fellows. The “pipeline” is fed by postdocs, and effects on grant funding opportunities and career advancement in academia directly impact their career choices and outcomes.

The development of research scholars with strong scientific and managerial skills is an arduous, time-consuming, and expensive effort. More than 70 percent of postdocs in the U.S. are supported by federal dollars, and the benefits of this investment are not reaped when these highly trained individuals leave the pipeline. As implied in the NIH’s Self-Study, the numbers of postdoctoral trainees should reflect the future needs of biomedical research. Furthermore, the ability of junior scientists to achieve independent funding is important not only for professional advancement but also for innovation in science. Stagnation of scientific thought occurs more readily in a climate of fierce competition; study sections are hesitant to invest in riskier explorations. This risk aversion most directly affects junior scientists.

Historically, the U.S. has occupied a preeminent position

in biomedical research, largely because of the financial support of taxpayers’ dollars through the NIH, NSF, and other governmental entities, as well as contributions by research institutions to support the higher education and training of postdocs. The doubling of NIH funding in the late 1990’s led to growth in the numbers of positions for postdocs at research institutions to pursue advanced training. Forward thinking regarding the inevitable fluctuations in governmental funding of research, however, has been lacking at both the governmental and institutional levels. In academia, increases in the numbers of postdocs advancing to non-tenure track positions or to research associate positions have increased in the last several years. These types of positions do not hold the same career advancement potential as their tenure-track counterparts. Furthermore, the number of independent funding opportunities for postdocs has not kept pace with the increased numbers of them in training positions.

As the national advocacy organization for postdocs, the National Postdoctoral Association (NPA) believes that this current imbalance needs to be addressed by all stakeholders. Continued progress in science requires a stable financial commitment from the NIH, as well as individual research institutions. Effective solutions for the funding of scientific research should address issues beginning with the pipeline of investigators at the postdoctoral level and continuing through to senior investigators who serve not only as experienced researchers but also as valuable advisors to those more junior. Finally, data collection on professional outcomes of postdocs, as well as on their success in acquiring independent grants, is essential to realizing the necessary changes to the scientific enterprise. Implementing responsible revisions to the training and advancement of postdocs will have a direct impact on the long term prospect of scientific research and ensure the U.S. continues to set the bar for the advancement of science. 

Lisa M. Curtis, Rashada Alexander, Jason Rawlings, and Lu-Ann Pozzi are members of the Advocacy Committee of the NPA. Jonathan Gitlin is Vice-Chair of the NPA. All authors contributed equally to this article.

Let the Wind be Your Guide: Unexpected Changes in a Science Career

BY CHRISTINE LOVE

Several years ago, I read an article reporting that up to 60 percent of people make a career switch in their lifetime. This number seemed low to me, considering my own switches and those of so many of my friends and colleagues. I've always thought it is unrealistic to expect that young adults entering college will truly know what they want to do with their lives. At 18, I couldn't even do my own laundry!

Unwilling to join the ranks of those misguided, unfortunate students who couldn't choose a major, I declared myself a biology major during my freshman year. Depending on one's point of view, I was either plagued or blessed with the desire to go in several different paths with my degree. Medicine crossed my mind, but after volunteering as a certified emergency medical technician and embarrassingly passing out on numerous occasions at the sight of blood, I decided research was a better fit.

After graduating, I embarked on a career as a research assistant at a biotechnology firm in Rockville, Maryland. The firm specialized in proteomics, a discipline analogous to genomics but with a focus on the structure and function of proteins. My position entailed preparing two-dimensional electrophoresis gels for analysis of proteins as well as developing ideas and protocols to streamline various laboratory processes. I felt virtuous to be part of a company that was developing therapeutic proteins to eventually

control and prevent diseases. Unfortunately, I found lab work to be isolating and monotonous, and I realized that I enjoyed *discussing* research more than actually *conducting* it.

Remembering that several people had told me that I had a knack for explaining complex concepts, I decided to augment my biology degree with a master's in communication. Once again, I found myself struggling to decide which path to take. There are so many career options in the communications field, but I resisted straying too far from my original loves of health and science. Finally, I decided on a dual concentration of health communication and organizational communication. The health communication knowledge became especially helpful when, several months after enrolling in the master's program, I took a position as a health writer/information specialist for a government contracting firm. It was an exciting change from the lab environment, and the position gave me the opportunity to wear many "hats."

My department had a contract with the National Institutes of Health and its subsidiaries. Under this contract, my primary responsibility was editing and abstracting protocols for HIV/AIDS-related clinical trials. However, my role continued to expand, and I began performing similar duties for the National Institute of Mental Health and the National Center for Complementary and Alternative Medicine. Additionally,



Love

Christine Love is a marketing communications writer for SWCA Environmental Consultants in Phoenix, Arizona. She has a B.S. in Biology from James Madison University and an M.A. in Communications from George Mason University. In 2007, Christine started her own editing company, Love Editing, which provides proofreading and editing services for academia, business, and healthcare. Christine can be reached at info@loveediting.com or clove@swca.com.

I helped to develop a series of consumer-targeted HIV fact sheets, and I worked as a "behind the scenes" HIV specialist, providing interactive web-based information to the public.

When my husband's job required a cross-country move to Phoenix, Arizona, I initially lamented my resignation and distance from all the health and science resources available in the Washington, D.C. metro area. Fortunately, my immediate love affair with the sunny western city eased my sorrow



and helped me look forward to a new chapter in my career.

It was a pleasant surprise to discover that Phoenix has a great deal to offer in terms of jobs, but the city is not without its issues. As anyone who has spent time in the Valley of the Sun will tell you, the impending water restrictions and possible water shortage in the future is in the back of many Phoenixians' minds, if not on the tips of their tongues. I thought it might be an interesting challenge to take a step back from health related roles and go to work for an organization whose objectives were more directly science oriented.


I accepted a marketing communications writer position at an environ-

mental consulting firm. The company, SWCA Environmental Consultants, specializes in the management of natural resources, such as water, and cultural resources. They also assist private and public sector clients in obtaining the necessary environmental permits to complete their projects. My responsibilities include writing for and editing internal and external corporate newsletters; developing, editing, and disseminating messages from our executive management team; leading all public relations efforts; and acting as a corporate representative at industry conferences. I've been with SWCA for 2.5 years and I really enjoy my role, particularly the aspects of it that allow

me to correspond with different scientists. From hydrologists and geologists to archaeologists and anthropologists, professionals of every discipline work together and offer a unique perspective on what one can do with a passion for science.

Am I where I once thought I would be, doing what I once thought I would be doing? No.

Am I content and fulfilled in my current career? Yes.

I sort of like not knowing what the future holds, and I figure that as long as I'm doing something I enjoy—something that, in my mind, makes a difference—I'll be happy. After all, isn't that what life's all about? 

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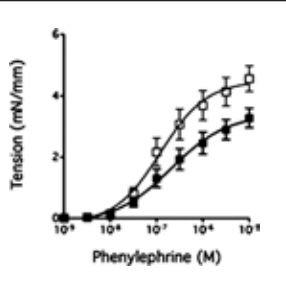
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Another Role for AMP-activated Protein Kinase

AMP-activated protein kinase (AMPK) was first identified as a cellular energy sensor, but recently its role has been expanding into other biological processes.

As discussed in this study, smooth muscle contraction might now be added to this growing list. The researchers have demonstrated that AMPK phosphorylates myosin light chain kinase (MLCK) in the calmodulin-binding domain (Ser⁸¹⁵). Phosphorylation desensitizes MLCK to calcium-triggered calmodulin activation and reduces its ability to trigger myosin cross-bridge formation and subsequent muscle contraction.



The aortic rings of $\alpha 1$ -AMPK knock-out mice (*open box*) display stronger contractions than wild-type animals (*black box*) when stimulated by phenylephrine.

In primary smooth cell cultures, the addition of vasoconstrictors could activate AMPK in a calcium-dependent manner, and likewise mice lacking the smooth muscle isoform of AMPK experienced stronger contractions in the aortic ring. This study defines a potentially new signaling pathway controlling smooth muscle activity, in which AMPK attenuates contractions by phosphorylating MLCK. This attenuation might contribute to reduced ATP turnover in the tonic phase of smooth muscle contraction. 

AMP-activated Protein Kinase Phosphorylates and Desensitizes Smooth Muscle Myosin Light Chain Kinase

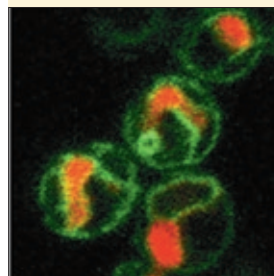
Sandrine Horman, Nicole Morel, Didier Vertommen, Nusrat Hussain, Dietbert Neumann, Christophe Beauloye, Nicole El Najjar, Christelle Forcet, Benoit Viollet, Michael P. Walsh, Louis Hue, and Mark H. Rider

J. Biol. Chem. 2008, **283**, 18505–18512


jbc

Expand Your Nuclear Horizons

A cell's nuclear membrane undergoes extensive remodeling during the progression of the cell cycle. How this remodeling is coordinated remains a mystery, although it is likely coupled to phospholipid biosynthesis somehow. In a pair of related studies, joint researchers have identified and characterized an unusual type of diacylglycerol kinase (*DGK1*) that helps regulate nuclear membrane growth in yeast. In contrast to all other known diacylglycerol kinases that rely on ATP, this enzyme uses CTP as the phosphate donor to generate phosphatidic acid from diacylglycerol (this substitution may explain why a *DGK* gene has not been identified in yeast until now). The researchers found that overexpressing *DGK1* resulted in phosphatidic acid-enriched membranes and nuclear envelope expansion, whereas mutations that abolished diacylglycerol kinase activity reduced phosphatidic acid levels and nuclear membrane growth. This nuclear expansion phenotype was similar to that of mutants



Overexpressing the diacylglycerol kinase in yeast leads to an expansion of the nuclear membrane.

defective in *PAH1* (phosphatidic acid phosphatase), and mutations in both *DGK1* and *PAH1* restored normal phosphatidic acid content and nuclear membrane structure. This suggests a coordinated regulation of diacylglycerol kinase and phosphatidic acid phosphatase activities in remodeling the nuclear membrane. 

Characterization of the Yeast *DGK1*-encoded CTP-dependent Diacylglycerol Kinase

Gil-Soo Han, Laura O'Hara, Symeon Siniosoglou, and George M. Carman

J. Biol. Chem. 2008, **283**, 20433–20442

An Unconventional Diacylglycerol Kinase that Regulates Phospholipid Synthesis and Nuclear Membrane Growth

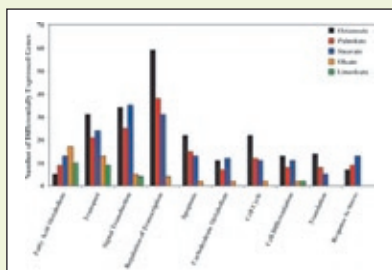
Gil-Soo Han, Laura O'Hara, George M. Carman, and Symeon Siniosoglou

J. Biol. Chem. 2008, **283**, 20443–20453


jbc

Good Fats, Bad Fats

Depending on their chain length and saturation level, fatty acids (FAs) can exert varied biological effects on the heart ranging from toxic to protective, although the mechanisms mediating these observations are unclear. In this study, the authors investigated these differential effects by subjecting adult rat cardiomyocytes to 0.4 mM octanoate (8:0), palmitate (16:0), stearate (18:0), oleate (18:1), or linoleate (18:2) for 24 h. They then used microarray analysis to compare gene expression patterns in response to the distinct FAs, finding that saturated FAs influenced significantly more genes (590-1,188) than unsaturated



Analysis of gene expression in adult rat cardiomyocytes 24 h after challenge with octanoate, palmitate, stearate, oleate, or linoleate.

ones (65-83). In general, cardioprotective FAs like oleate increased expression of genes promoting FA oxidation to a greater extent, whereas cardiotoxic FAs like palmitate induced markers of endoplasmic reticulum and oxidative stress. In addition, saturated and unsaturated FAs had distinct time- and concentration-dependent effects on similar target genes; for example, stearate- and palmitate-mediated *ucp3* induction tended to be transient, whereas oleate-mediated induction was sustained. These findings may provide new insights into why diets high in unsaturated FAs are beneficial, whereas diets rich in saturated FAs are not. 

Bioinformatic Profiling of the Transcriptional Response of Adult Rat Cardiomyocytes to Distinct Fatty Acids

Joseph B. Lockridge, Mary L. Sailors, David J. Durgan, Oluwaseun Egbejimi, William J. Jeong, Molly S. Bray, William C. Stanley, and Martin E. Young

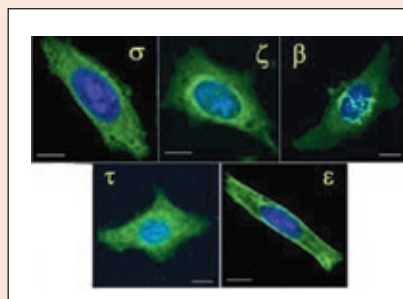
J. Lipid Res. 2008 **49**, 1395-1408




A 14-3-3 Framework

The 14-3-3 proteins constitute a family of highly conserved and broadly expressed multifunctional proteins that are involved in numerous important cellular processes.

So far more than 300 cellular proteins have been reported to interact with the 14-3-3 family, which contains seven isoforms.



Cellular distribution of 14-3-3 isoforms in transformed human amnion (AMA) interphase cells.

In this study, the authors examined how these isoforms differ in expression, post-translational modifications, and subcellular localization in transformed human amnion (AMA) cells. Five of the seven isoforms (β , ϵ , σ , τ , and ζ) were present in AMA cells, and they were all expressed at analogous levels throughout the cell cycle, suggesting that cell cycle-mediated events are not a major regulatory mechanism of 14-3-3 proteins, at least in the AMA cell system. There were noticeable differences in phosphorylation status and localization, however. The authors subsequently analyzed the isoforms in over 20 established cell lines and tissue specimens, revealing that cellular context produces dramatic changes in expression and localization. The data presented in this study could prove to be a valuable resource for other researchers working with 14-3-3 proteins. 

A Combined Proteome and Ultrastructural Localization Analysis of 14-3-3 Proteins in Transformed Human Amnion (AMA) Cells: Definition of a Framework to Study Isoform-specific Differences

José M. A. Moreira, Tao Shen, Gita Ohlsson, Pavel Gromov, Irina Gromova, and Julio E. Celis

Mol. Cell. Proteomics 2008 **7**, 1225-1240



Karen Vasquez: *Understanding Genome Structure and Stability*

BY NICK ZAGORSKI

The discovery of the DNA double helix was truly a monumental event that ushered in a new age of molecular biology. However, we should note that Watson and Crick—and Wilkins and Franklin—discovered the A and B conformations of DNA, but not the “only” conformations of DNA. Since that 1953 breakthrough, researchers like Robert Wells and Alexander Rich have discovered that DNA can come together in a variety of helical forms, including a left-handed Z-DNA helix and even triple-helical H-DNA.

The exact reasons DNA adopts these nontraditional conformations are still being worked out, and among those looking into DNA structure is Karen Vasquez, Associate Professor in the Department of Carcinogenesis at the University of Texas M.D. Anderson Cancer Center. Since starting her lab in 2000, Vasquez has been studying the mechanisms of DNA damage and repair from the perspective of how DNA secondary structures, particularly triple helix DNA, can influence these events. She hopes that she can exploit her findings to create new strategies for targeted therapies, such as inducing recombination events in specific regions of DNA.

Good Things Come in Threes

Vasquez grew up in Michigan, surrounded by 40 acres and six siblings, including her identical twin sister Kim (who currently works as a police

officer in, coincidentally, the Houston area). “And when I wasn’t working, I was exploring,” she says, noting that such adventures around her home nurtured a love of nature and biology. She eventually became interested in marine biology, and as the Midwest didn’t really provide a suitable environment for such a pursuit, Vasquez went south to the University of Miami where she majored in marine science and biology, with a minor in chemistry for good measure.

Near the end of her undergraduate studies, however, Vasquez took a moment to reassess her goals. “I definitely enjoyed marine science, but I was also interested in working in areas that could be directly applied to human health, and marine biology didn’t seem like the optimal field for that.” (Vasquez notes, however, that the marine world has contributed greatly to medicine through the numerous natural products uncovered from marine organisms.)

Although Vasquez intended to go to graduate school, “my first order of business was saving some money and paying off my loans.” So, after graduating from the University of Miami in 1987, she worked as a research technician at the Nucleic Acid Research Institute in Costa Mesa, California, where she assisted in projects developing nucleoside analogs as anticancer agents. In 1990 she moved to Houston and worked for Michael Hogan at Baylor College of Medicine, where, she says, “I fell in

love with triplex technology.”

Triplex technology arose from the observations that some single-stranded DNA pieces could bind to bases in the major groove of double-stranded DNA through a pattern called Hoogsteen hydrogen bonding, thus creating a triple helix. In a practical sense (much like RNA interference, which operates to inhibit gene activity by causing the destruction of gene-specific mRNA), forming a triple helix at targeted sites in the DNA can alter the expression of genes of interest at the DNA level. “For simply inhibiting gene expression, RNA-based techniques are somewhat better,” she says, “but if you want to directly modify the DNA, then triplex technology is the way to go.”

It was such possible applications that convinced Vasquez to stay at Baylor College of Medicine for her graduate work. “I saw the potential in applying triplex techniques for gene therapy,” she says. In 1991, she joined Baylor’s Biochemistry Department in the laboratory of John Wilson, who was studying DNA recombination and its applications in disease, particularly eye diseases. She began designing triplex-forming oligonucleotides (TFOs) and using them to induce DNA changes; for example, by adding a cross-linking agent to a TFO she could create site-specific damage and force the repair of that region of the DNA.

Through her and Wilson’s work, Vasquez found that TFOs could

increase both the rates of spontaneous mutations and homologous recombination in cells, making this approach suitable to both insert and remove specific gene mutations. “This was pretty exciting because limitations of homologous recombination for gene therapeutic applications include its low frequency and its tendency for random insertions,” she says. “And TFOs might be able to overcome both of those.”

After conducting a post-doc at Yale School of Medicine with Peter Glazer, applying triplex technology to mutagenesis studies with mice, Vasquez returned to Texas to start her own lab at the University of Texas M.D. Anderson Cancer Center, Science-Park Research Division, located away from the main campus in Houston, near the small town of Smithville.

The Science Park-Research Division is completely surrounded by Buescher State Park in the edge of the Texas Hill Country—“How many research facilities can provide a location like that?” she says.

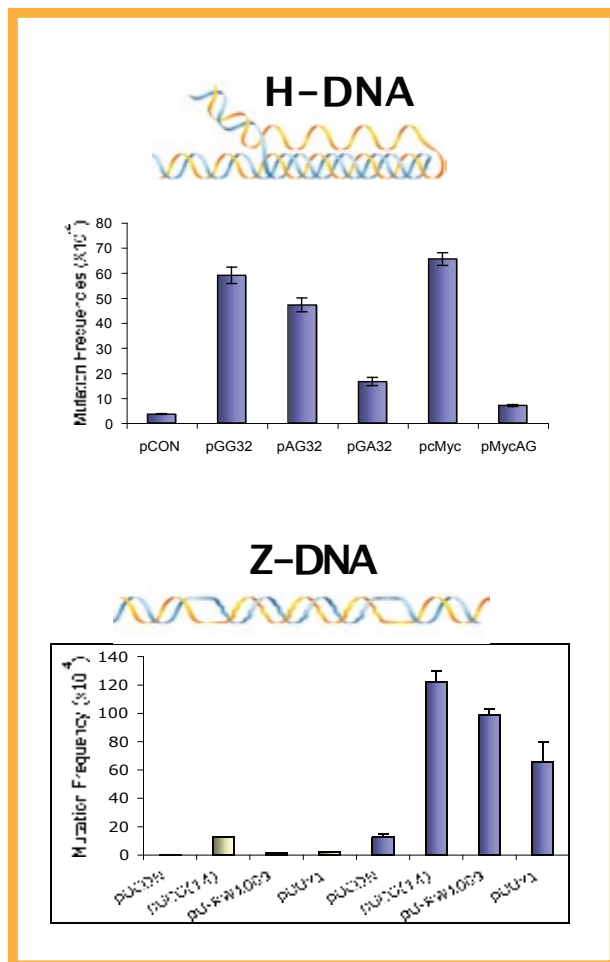
A New Twist on DNA

Whereas TFOs can induce chromosomal DNA changes by creating an unnatural DNA structure, such unusual helix formations also occur naturally, typically in regions rich in repetitive sequences. Estimates have suggested that about 1 in every 5,000

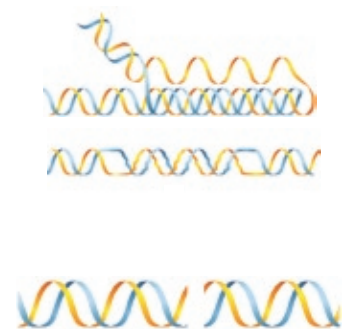
bases can form backwards-winding and strain-inducing Z-DNA, whereas 1 in every 50,000 bases might form triple-helical H-DNA (also known as “hinge DNA” because a piece of duplex dislodges and wraps backwards to form the triplex, while creating a small section of single-stranded DNA as well). Such odds may look long, but when you consider that human DNA has billions of base pairs in each cell, it adds up.

Through her studies with H- and Z-DNA in mammalian cells, Vasquez has found that like TFOs these conformations can create fragility, instability, and mutations in the DNA. “But

what’s interesting about this is that there are no external factors producing DNA damage,” notes Vasquez. “The DNA itself is the mutagen.” Vasquez believes that the H- and Z-DNA forms are often incorrectly recognized as “damaged DNA” by repair enzymes; the enzymes might then perform an abortive repair, which can lead to DNA strand breaks and translocation events. Vasquez found that such may be the case with the well known oncogene *c-MYC*, which has an H-DNA “hot spot” in its promoter region. She adds that H-DNA creates other problems as well, as it exposes single-stranded regions of DNA that



Both H- and Z-DNA structures can increase the mutation rate of plasmid DNA in *E. coli* (*gold*) or COS-7 cells (*blue*).



Double Strand Breaks

Deletion
Recombination
Translocation

are highly susceptible to radiation or chemical insult.

Considering the great risks they pose, a natural question that arises is why have these unusual structural variants persisted from bacteria to man? “That’s one of the active questions in this field,” says Vasquez, “but one possibility might be that these structures help spur evolution by inducing double-stranded breaks and recombination, providing genetic diversity. In addition, we’ve recently found that H- and Z-DNA structures can both interfere with gene transcription, so they may also serve as yet another mechanism to regulate gene expression.”

Beneficial as they might be for a species, however, unstable DNA structures are still potentially disastrous for individuals; as in c-MYC, promoters

and other upstream elements of genes frequently contain H- and Z-DNA susceptible sequences. In fact, Vasquez points out that some work suggests that up to 90 percent of cancers can arise from defects in DNA repair or recombination. Thus, another impor-

tant aspect of Vasquez’s work has been examining the molecular basis of DNA damage recognition by the various repair protein complexes, as well refining how DNA repair enzymes process unusual DNA structures and site-specific DNA lesions.

Out of Focus: It Swims in the Family

Karen Vasquez had ambitions of becoming a marine biologist while growing up, and still likes to visit the beach when she can, so it may be no surprise that her 5-year-old daughter Samantha currently also has career aspirations related to the marine field. However, Samantha is certainly taking Karen’s goals one step further. “She wants to be a mermaid when she grows up,” Vasquez says. It’s not the most feasible career goal, but the important thing, Vasquez notes, is that her daughter has the right motives. “She wants to be a mermaid so she can help people, because in all the stories she hears that’s what mermaids do.




Vasquez and her lab instructor (and former post-doc) Guliang Wang look at some yeast.

Family Ties

Instability may have some positive effects on DNA, but the same can't be said for a research laboratory, an idea Vasquez has taken to heart. "One of my biggest goals as a teacher and mentor is to encourage students interested in science, especially women, to stick with a career in science," she says, adding that she doesn't restrict a "science career" to research. "It could be through teaching, writing, advocacy, or many other things, but I try to help young people interested in science find some way to use that interest to benefit science as a whole, because all these different careers paths do intersect and work together."

Vasquez acknowledges that a major element that drives youngsters away from science is not necessar-

ily frustrations in work, but rather a negative experience with the PI or colleagues, and she strives to make her own lab as positive as possible. "The lab consists of research assistants, postdocs, students, and an instructor (a non-tenure track faculty position), Dr. Guliang Wang, who has performed much of the work on non-B DNA structures in the laboratory. Although they all have their own independent projects, we all work together as well. I genuinely feel like my lab members are part of my family, and that this sentiment helps ensure success for my team because it really fosters the sort of a cooperative setting that breeds happiness in life and innovation in science. It works out well for me too because I never feel like I'm going to work; I'm just switching between families." 

Nick Zagorski, Ph.D., a graduate of Johns Hopkins and Cornell Universities, is a science writer for ASBMB. He can be reached at nzagorski@asbmb.org.

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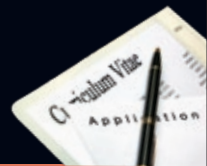
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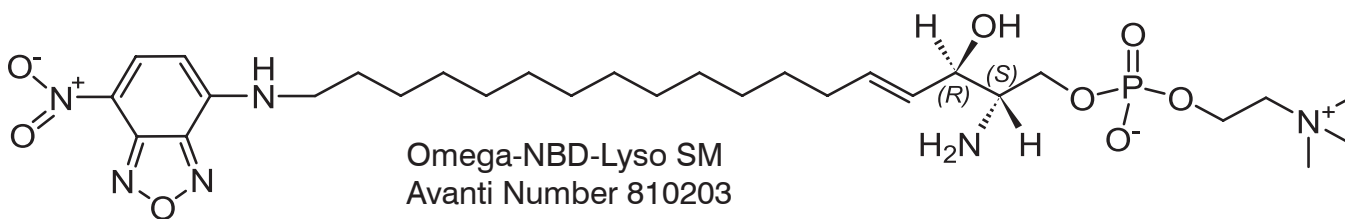
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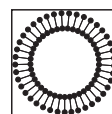
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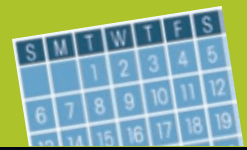
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PLENARY LECTURER: Robert Molday, *University of British Columbia*

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OCTOBER 23-26, 2008

Granlibakken, Lake Tahoe

ORGANIZERS: Katalin F. Medzihradzky, and
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