AN INTERVIEW WITH PETER AGRE

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The Presidential Candidates on Biomedical Research

October 2008



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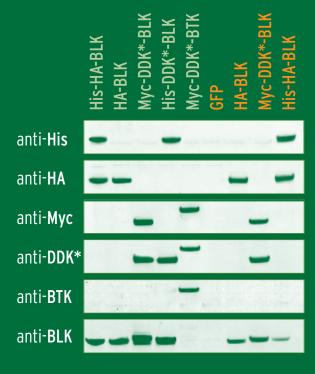
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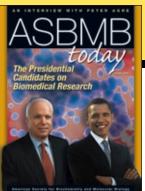
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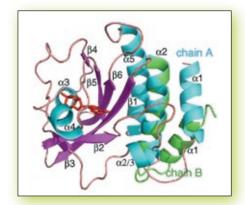


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### podcast summary

Download the September *JBC* podcast to hear an interview with David Graham, a professor of Chemistry and Biochemistry at the Institute for Cellular and Molecular Biology at the University of Texas, Austin, about his work with biosynthetic pathways in an extremophile. For this and other ASBMB AudioPhiles podcasts go to:

www.asbmb.org/audio.aspx



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# row the ecitor

### A Focus on Politics

BY NICOLE KRESGE

Ith the 2008 Presidential election just around the corner, we decided to focus this issue of *ASBMB Today* on politics. Our feature story on p. 14, entitled, "McCain, Obama, and Biomedical Research," provides a comprehensive look at the statements made by the McCain and Obama campaigns on several issues related to biomedical research. The article was written by ASBMB science policy fellow Angela Hvitved, who also writes about the insights she's gained from her position at ASBMB in the Career Insights column on p. 26 of this issue.

Following up on Hvitved's election article, ASBMB Public Affairs Officer Peter Farnham reports on a FASEB-sponsored forum entitled "Innovation & the Elections: Presidential Perspectives on Health" in which representatives from the McCain and Obama campaigns were supposed to debate about science and health policy but spent very little time focusing on science. Farnham's article can be found on p. 6.

The two candidates also recently responded to 14 questions about science and technology posed earlier this summer by a coalition of scientific organizations, including ASBMB. The questions and answers can be found at http://www.sciencedebate2008.com/www/index.php?id=42.

We also have an interview with Nobel laureate and political activist Peter Agre who considered running for U.S. Senate earlier this year. In the interview on p. 18, Agre, who is currently director of The Johns Hopkins Malaria Research Institute, discusses some of his views on the role of science in the public eye and the upcoming election.

And finally, in our new science and technology communication column, Sci.Comm, Sarah Crespi explores the science blogosphere and gives a rundown of what's out there, complete with tips on finding science blogs with political topics such as global warming, stem cell research, and, of course, the Presidential race.

ASBMB has also recently started its own blog called Chiral Comments, which can be found at http://chiralcomments.blogspot.com. The blog will contain posts from ASBMB Today writers, ASBMB committee members and journal editors, and guest bloggers. It will be used to communicate with our members and the public and to provide a forum in which people can discuss issues important to scientists. If you are interested in contributing to the blog, you can contact us at tekkie@asbmb.org. W

Niolo Kneye

# president's wessage

# Having an Impact (Factor)\*

BY GREGORY A PETSKO

The place: The entrance to The Pearly Gates. There are fluffy clouds everywhere. In the center is a podium with an enormous open book. A tall figure in white robes with white hair and beard stands at the podium. Approaching is a thin, middle-aged man with glasses and a bewildered expression. He is the soul of a recently deceased genome biologist.

GB: My gosh is this...? Are you...? Am I really...?

**ST. PETER:** Yes, I'm St. Peter. And yes, this is where souls such as yours enter heaven.

**GB:** Wow. I mean, I didn't expect to live forever, but still, this is something of a shock. (Pauses.) OK, I guess I can live with it. Uh, I mean ...

ST. PETER: I know.

**GB:** Well, at least I'm here. I'm not thrilled to be dead, but it's a relief to know I'm going to heaven.

**ST. PETER:** I'm afraid it's not that simple. We have to check.

**GB:** Check what?

**ST. PETER:** Your life history. (He leafs through the enormous book.) It's all here, you know.

**GB:** I'm sure it is. I can imagine you guys keep records that make PubMed seem like a stack of index cards. I'm a little surprised you don't use something more up-to-date, though.

**ST. PETER:** If you mean a personal computer, no—we don't. After all, they were invented elsewhere.

GB: You mean on earth?

**ST. PETER:** No, somewhere a lot warmer. (He stops at a page.) Here you are.

**GB:** Hey, I'm not worried. I was a good scientist, a good citizen, a good family man, I think, too. I never...

**ST. PETER:** Yes, yes, I'm sure, but you see, none of that matters. The only thing that matters is your IF.

GB: IF?

**ST. PETER:** Your impact factor. That's all we use now. If your IF is above 10, then you enter here. If it's lower, well...

**GB:** My impact factor? What the hell—oops, sorry—is that?

**ST. PETER:** It's something we borrowed from you science chaps on

earth. Oh, we used to do it the hard way: send a fledgling angel down to check on your deeds; look at how your life affected your friends and family, consider your intentions versus your actions. All that sort of thing. It was tedious and required huge numbers of new angels, who have become somewhat scarce since free-market capitalism became all the rage down there. Then we noticed that you scientists never bothered to do anything like that. If you had to evaluate someone, all you did was look at this number called the impact factor. So we did the same thing. Now when anyone comes here, all we do is look up their number.

**GB**: A single number? Are you nuts? You can't sum up someone's whole life in a single number!

**ST. PETER:** You do. At least, you sum up their career that way, when you decide if they've published in the best journals or done the best work. It's how you work out who gets promoted and who's a star and who gets funded and...

**GB:** Yes, but it's a terrible idea! We should never have done it. It ruined European science in a matter of a few years, and then it spread to Australia, China, and Japan, and finally to Canada and the United States; and before too long, science was totally controlled by unimaginative bureaucrats who just used that number for everything. It was a disaster!

ST. PETER: That's not what St. Garfield thinks.

**GB:** Saint who?

**ST. PETER:** St. Eugene Garfield, Ph.D. He invented citation analysis, remember? He thought using the IF was a great idea—really, a logical extension of his own work creating the Citation Index. So we set it up: for example, I see here that you contributed regularly to several local charities.

**GB:** Of course. They do good work. I never did it because I thought it would get me into heaven, but...

ST. PETER: Just as well, because it won't. Local charities,

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you know. Small impact factor. Doesn't really add much to your total. Besides, how bad could the idea be? Why, the journal *Genome Biology* advertises its impact factor right at the top of their website. Didn't you use to write a column for them? (He looks at the ledger again.) Oh my, I see that won't add much to your total either.

**GB:** But that's all ridiculous! It's the whole problem I was trying to explain to you. That's like saying that a paper only has significant impact if it's published in *Nature*, *Science*, or *Cell*. Once you do that, then the impact factor of where you publish becomes a surrogate for the use of your own judgment. No one bothers to read anyone's papers when they're up for a fellowship or being considered for a job or for a promotion or having their grant proposal evaluated; all you do is look to see how many papers they've published in high-impact journals. No one considers whether the work was better suited to a more specialized journal or a journal where other work that puts it in context was published previously; no one considers whether those handful of high impact-factor journals have the best referees or whether they in fact

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may have a disproportionate number of incorrect papers because of the pressure to publish there. And look, over-reliance on one stupid number gave a small bunch of editors enormous power over the careers of people who, for the most part, they never met or heard speak and whose body of work they never read. It was probably the worst idea since General Custer thought he could surround the whole Sioux Nation with a couple of hundred troops.

**ST. PETER:** Ah, yes. St. Sitting Bull still talks about that.

**GB**: Huh? (Shakes himself.) Look, once the impact factor dominated scientific judgments, creative people were doomed. Bureaucrats didn't need to know anything or have any wisdom; all they had to do was rely on arbitrary numbers. And now you're telling me you're doing that to determine who gets into heaven?

**ST. PETER:** Yes; it's a lot simpler. It doesn't matter if you were kind or tried hard or did good work or were pious or modest or generous. The only thing that matters is how big an impact we calculate you had.

**GB:** But that's just wrong! Look, maybe I could talk to the people who thought up that idea and pushed for its use. If I can just get in for a minute...

**ST. PETER:** Oh, they're not here. (He waves his hand and an image appears on a cloud. It shows a huge pit of boiling sulfur and brimstone. In it, up almost to their necks, are a bunch of men in business suits.) As you can see, they're in a warmer climate.

**GB:** Well, at least, that seems fair somehow. Wait a minute—is that George W. Bush?

ST. PETER: Yes.

**GB:** But his impact factor should have been huge.

**ST. PETER:** Oh, the absolute value was off the charts. But we do take the sign into consideration...

**GB**: Then why is he only in brimstone up to his knees?

**ST. PETER:** Oh. He's standing on Dick Cheney's shoulders. (The image vanishes.) Now let's get back to you...

**GB**: But don't you see, the idea that you can determine someone's impact in the future from where they publish today is totally absurd. On that basis, God would have an impact factor of zero. I mean, He did his best work a long time ago; it has never been repeated by anyone; and all His ideas were published in a book, not in a peer-reviewed journal!

**ST. PETER:** Very funny. Go to hell. W

<sup>\*</sup>Reprinted with permission from Genome Biol. (2008) 9, 107.

# washington update

# Firebombs at UC Santa Cruz the Latest in Animal Rights Extremist Activity

BY CARRIE D. WOLINETZ

long-running animal rights campaign against researchers in the University of California system escalated recently with the firebombing of two faculty members' houses in Santa Cruz. "Unfortunately, this is only the latest in a rising wave of violence aimed at scientists who conduct life-saving biomedical research using animal models," said FASEB President Richard Marchase. "The public outrage being displayed in Santa Cruz should be echoed nationwide."

Firebombs have been used by animal rights extremists in the past, including the attempted bombing of a UCLA scientist's home in June 2006 and two undetonated devices placed under researchers' cars in June 2007. "It is one thing to exercise one's First Amendment rights for a cause one believes in," Marchase stated. "But threatening the lives of researchers and their families, including the young children who were forced to flee their burning home in Santa Cruz, is not a form of protest. These are reprehensible, criminal acts." Other incidents have included numerous "home visits" (loud, harassing protests staged on the researcher's front lawn), the flooding of a scientist's home, bomb threats leading to evacuation of research facilities, and a physical assault against a researcher's spouse. UC Berkeley alone has reported more than two dozen faculty, scientists, and staff who have been harassed at home or in their office in the past year. Similar campaigns are ongoing in Utah and Oregon.

Unfortunately, it seems as if no scientist is safe from becoming a target. Although many of the past campaigns have focused primarily on researchers working with mammals like primates or cats, one of the UC Santa Cruz firebomb victims worked with fruit flies and the other with mice. Jerry Vlasak, a spokesperson for the underground animal rights extremist organizations responded to the UC Santa Cruz bombings, stating, "The inconvenience and the suffering of any children or any family members pales in comparison with the suffering and oppression that goes on in these animal laboratories." This is a typical quote from Vlasak, who has also advocated the killing of scientists to save the lives of lab animals. According to the National Association for Biomedical Research, animal

rights extremism activity has increased in recent years, not only in number of incidents but also in the violence of the activities.

FASEB has been outspoken in opposing animal rights extremism for many years and was part of a successful lobbying effort to pass the Animal Enterprise Terrorism Act (AETA) to grant law enforcement additional tools to prosecute crimes against animal research facilities and scientists. A major victory was achieved in 2006 with the conviction of a number of activists associated with the extremist group, Stop Huntington Animal Cruelty USA (SHAC-USA) in New Jersey. With the leaders of that organization serving prison sentences, there seems to have been a decrease in terrorist activity associated with animal rights on the east coast. State legislatures are also becoming engaged in protecting scientists. The California legislature has passed a bill to grant law enforcement new tools to find and prosecute animal rights extremists, and local councils in Utah have passed laws to protect private information about researchers from being released.

The UC Santa Cruz firebombings have certainly garnered more national attention to this issue than previous incidents. Marchase praised the mainstream animal rights protection organization, the Humane Society for the United States, for contributing to a reward to find the activists involved in the firebombs. "It is our sincere hope that all stakeholders with an interest in human and animal health can speak with one voice in censuring those who would advocate arson, personal violence, and vandalism as a means to an end," he said.

There are a number of resources available to help researchers who become the targets of animal rights activists. For more information, please contact Carrie Wolinetz at the FASEB Office of Public Affairs at (301) 634-7650 or cwolinetz@faseb.org. You may also wish to take a look at the *Guideline for Crisis Management* assembled by the Society for Neuroscience at: www.sfn. org/skins/main/pdf/gpa/Crisis\_Management.pdf. N

Carrie D. Wolinetz is Director of Scientific Affairs and Public Relations for the Office of Public Affairs at FASEB. She can be reached at cwolinetz@faseb.org.

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# news from the hill

### The "Science" Debate that Wasn't

BY PETER FARNHAM<sup>1</sup>

Staffers for presidential candidates Barack Obama and John McCain squared off at the George Washington University on September 18 in what had been billed as a debate about science and health policy. What the audience got was a lot of debate about health policy, but precious little about science.

The 90-minute debate was arranged by Scientists and Engineers for America (ASBMB was one of nine organizations cosponsoring the event) and one would have thought that the very name of the organization arranging the event would have clued in the two campaigns as to what the subject of the debate was to be.

But the debaters—Jay Khosla (McCain) and Dora Hughes (Obama)—both hold the title of "health policy adviser" (not science policy adviser) in the respective campaigns. In fact, Khosla could not (or would not) name McCain's science advisers, referring a questioner to the campaign's communications office. Hughes also declined to name any of Obama's science advisers except for former NIH Director Harold Varmus, who has already been mentioned in the press as spearheading an Obama support group among scientists (several other members of Obama's science advisory group are mentioned on the campaign website).

### **Opening Statements**

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Hughes' opening statement started off at least somewhat promisingly. After spending several minutes discussing Obama's health care plan, she described several basic tenets of his science policy: a doubling of basic research funding over the next decade; making the R&D tax credit permanent; and supporting embryonic stem cell research. She also alluded to well-publicized incidents in recent years involving manipulation of policy to conform to political considerations, and said that an Obama administration would not continue the practice.

Hughes also spent a significant portion of her time attacking McCain throughout the debate, noting, for example, that McCain had voted "at least ten times" against increases for research and development funding over the past decade. In a rare response to these attacks, Khosla noted that McCain had voted consistently to double the NIH budget.

For his part, Khosla did not mention science in his opening statement, instead focusing almost entirely on McCain's health care policy.

### Doubling...What?

It was not entirely clear which agencies would be involved in the Obama pledge to double the R&D budget in ten years. This may have been an allusion to the America Competes Act agencies (primarily the National Science Foundation, National Institute of Standards and Technology, and the Department of Energy's Office of Science). Obama mentions physical sciences and engineering in a policy paper on his website. But, the paper has a separate section for biomedical science, and unfortunately does not give a specific budget number for that. McCain's online answer on this point spends a fair chunk of its space discussing better stewardship of existing funding, and specifically mentions tight budgets. So, it might be fair to say that he is looking to lower expectations.

Science came up peripherally a couple of times in the question period, which occupied the last hour of the debate. In response to a question about minority health disparities, for example, Khosla noted (among other ways to address the problem) that clinical trials should include a diverse population that represents the diversity of those expected to use the therapy in question.

By far the most relevant scientific topic considered at the debate (except for the brief allusion to funding increases mentioned above) was the discussion focusing on human embryonic stem cell research.

#### Stem Cells

Khosla was asked if McCain would lift the ban on most federal funding for human embryonic stem cell research that the Bush administration imposed in August 2001. Khosla said that McCain had consistently supported human embryonic stem cell research during multiple votes in the Senate, but was eager for new approaches to be developed based on current research, rendering the current debate moot. He did not indicate, however, that McCain would lift the ban. Hughes said the Obama campaign strongly supported human embryonic stem cell research.



The answers given during the debate were pretty cursory, but if one reviews the campaigns' online discussions of the stem cell issue one finds that Obama states that he has co-sponsored legislation to provide "greater federal government funding on a wider array of stem cell lines," and to permit research on unused, so-called "surplus" embryos in storage at in vitro fertilization clinics that would otherwise be discarded (with ethical safeguards). He also pledges to lift the August 2001 executive order: "I believe that the restrictions that President Bush has placed on funding of human embryonic stem cell research have handcuffed our scientists and hindered our ability to compete with other nations. As president, I will lift the current administration's ban on federal funding of research on embryonic stem cell lines created after August 9, 2001 through executive order, and I will ensure

that all research on stem cells is conducted ethically and with rigorous oversight."

McCain's online response notes his continued support for embryonic stem cell research, but then moves into support for "funding for other research programs, including amniotic fluid and adult stem cell research which hold much scientific promise and do not involve the use of embryos. I oppose the intentional creation of human embryos for research purposes and I voted to ban the practice of 'fetal farming,' making it a federal crime for researchers to use cells or fetal tissue from an embryo created for research purposes." It is unclear what else, if anything, he would advocate changing from the current policy.

One questioner asked if the McCain campaign was planning to ban in vitro fertilization, and if not, why not?

Khosla appeared not to understand the question, confounding IVF with the stem cell debate. He said he would contact the McCain campaign for additional information on the topic. Hughes said Obama would not ban IVF.

Both candidates pledged to make the R&D Tax Credit permanent. This tax credit rewards companies that spend more money in a given year on R&D than the year before. It has been a fixture of the tax code since the early 1980s, but is typically reenacted on an annual basis. It is unclear how effective it has been as a spur to additional R&D, but the small business and high tech communities strongly support it.

For additional information on the two campaigns' positions on issues involving science and technology, please visit the ASBMB homepage, where there are links to both McCain's and Obama's answers to the 14 questions posed to them by Scientists and Engineers for America. Also, one can see the entire debate by going to the group's website: www.SHARP. SEforA.org

A second debate on science issues—this time focusing on energy and the environment—will occur in October.  $\ensuremath{\text{NV}}$ 

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

#### FOOTNOTE:

 ASBMB Science Policy Fellow Allen Dodson contributed to this article.

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# asbub member spot ight

### **Bryant's JBC Paper Honored**



Donald A. Bryant has received a prize for the best basic research paper of 2007 from the Rebeiz Foundation. The paper for which the award was given was published in the Journal of Biological Chemistry. A goal of the Rebeiz Foundation for Basic Research is to promote chloroplast and bioengineering research.

Bryant is the Ernest C. Pollard Professor of Biotechnology at Pennsylvania State University. He shares the award with Aline Gomez Maqueo Chew, a former Ph.D. student in

Bryant's research focuses on photosynthesis in bacteria. His long-term objectives are to understand the structure, function, assembly, and regulation of expression of the photosynthetic apparatuses of cyanobacteria and green-sulfur bacteria.

his laboratory, with whom he co-authored the paper.

Bryant has helped to sequence the genomes of 3 species of cyanobacteria, 13 species of green-sulfur bacteria, 7 species of filamentous anoxygenic phototrophs, and 1 acidobacterium. These data have helped him to discover and characterize important genes that are involved in photosynthesis. The paper for which he won the Rebeiz Foundation award is titled "Characterization of a plant-like protochlorophyllide a divinyl reductase in green sulfur bacteria" (JBC 282, 2967-2975).

### **Chen Receives New Investigator Award**



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Xi Chen, an assistant professor of chemistry at the University of California, Davis, has received the American Chemical Society's Division of Carbohydrate Chemistry New Investigator Award. The award, which acknowledges outstanding contributions to research in carbohydrate chemistry by scientists in their first independent faculty position, was presented to Chen during the

fall ACS national meeting in Philadelphia.

The main focus of Chen's research is employing molecular biology and enzymatic methods to synthesize complex carbohydrates and glycoconjugates related to human health, as well as biochemical characterization of involved enzymes and products. Four major research areas of the lab are as follows: 1) combinatorial biosynthesis of pathogenic bacterial capsular polysaccharide vaccines; 2) development of carbohydrate-based cancer vaccines; 3) synthesis of homogeneous glycoproteins based on chemoenzymatic methods; and 4) investigation on the interaction of carbohydrates and proteins using synthetic carbohydrate probes. N

### **Lefkowitz and O'Malley** to Be Awarded National Medal of Science



LEFKOWITZ



O'MALLEY

President George W. Bush named Robert J. Lefkowitz, a Howard Hughes Medical Institute investigator at Duke University Medical Center, and Bert W. O'Malley, Chair, Molecular and Cellular Biology, Baylor College of Medicine, recipients of the National Medal of Science for contributions to the biological sciences.

President Bush presented Lefkowitz and O'Malley with the medal, which is the nation's highest honor for science, at a ceremony at the White House in September.

The National Medal of Science was established by Congress in 1959 as a Presidential Award to be given to individuals "deserving of special recognition by reason of their outstanding contributions to knowledge in the physical, biological,

mathematical, or engineering sciences." This recognition now also includes the social and behavioral sciences. A committee of 12 scientists and engineers is appointed by the president to evaluate nominees for the award.

Lefkowitz's work with G protein-coupled receptors, the largest and most pervasive family of cell receptors, began in 1982 with the identification of the gene for the B-adrenergic receptor, which helps regulate the body's fight-or-flight response by reacting to epinephrine. Shortly thereafter, he discovered seven additional adrenergic receptors. These receptors—and all G-protein receptors—share a basic structure, in which the molecule weaves its way back and forth seven times across a cell's membrane. When the portion of the molecule that lies outside the cell connects with the receptor's favored signaling molecule, the internal portions of the molecule can trigger the appropriate cellular response.

O'Malley is being recognized for his pioneering work on the molecular mechanisms of steroid hormone action and hormone receptors. His work has greatly contributed to the understanding of the role of steroid hormones in normal development and in diseases, including cancer. N



# **Sharp and Baltimore Named Honorary Academicians**

Nobel laureates Phillip A. Sharp, professor at the Massachusetts Institute of Technology, and David Baltimore, Professor and President of California Institute of Technology, have been named honorary academicians of the Academia Sinica, Taiwan's most prestigious research institution.

Sharp and Baltimore were two of eight honorary academicians elected by Academia Sinica's convocation, which is comprised of the institution's academicians in three divisions. The newly elected are tasked with promoting domestic and international academic cooperation and directing the research profile of the institution. In addition to the eight honorary academicians, the Academia Sinica currently has a total of 249 domestic and foreign academicians.

Sharp shared the 1993 Nobel Prize in Physiology or Medicine with Richard J. Roberts for "the discovery that genes in eukaryotes are not contiguous strings but contain introns, and that the splicing of messenger RNA to delete those introns can occur in different ways, yielding different proteins from the same DNA sequence."

Baltimore's 1975 Nobel Prize in Physiology or Medicine was for "discoveries concerning the interaction between tumor viruses and the genetic material of the cell." He shared the prize with Howard Temin and Renato Dulbecco. **W** 

### Weibel Wins Young Investigator Award



Douglas Weibel, Assistant Professor,
Department of Biochemistry, University of
Wisconsin, Madison, has won the 2008
American Society for Microbiology (ASM)
ICAAC Young Investigator Award.
Sponsored by the ASM, this award
recognizes early career scientists for
excellence in research in microbiology and
infectious diseases.

Weibel's work as a graduate student at Cornell University focused on revealing the structures of natural products that are used by insects for defense. Using his chemistry background, Weibel was able to make great advances in this area. Presently, Weibel investigates how bacteria respond to the environment. He has found a way to control the peptidoglycan synthesis of *E. coli*, which was shown by his ability to transform these cells into different shapes. Through this research he hopes to explore the role specific bacterial proteins play in determining cell shape. Weibel also investigates how the chemical and mechanical properties of surfaces play a role in the differentiation and growth of bacterial cells, which has implications for understanding microbial life cycles. N

## Strahl, Varshavsky, and Davidson Receive EUREKA Grants

Brian D. Strahl, Alexander J. Varshavsky, and Beverly Davidson are recipients of National Institutes of Health EUREKA (Exceptional, Unconventional Research Enabling Knowledge Acceleration) grants. The new EUREKA program is intended to help investigators test novel, often unconventional hypotheses or tackle major methodological or technical challenges.

The NIH has awarded a total of \$42.2 million to fund 38 of these exceptionally innovative research projects that could have an extraordinarily significant impact on many areas of science.

"EUREKA projects promise remarkable outcomes that could revolutionize science," said NIH Director Elias A. Zerhouni. "The program reflects NIH's commitment to supporting potentially transformative research, even if it carries a greater than usual degree of scientific risk."

Strahl, who is an assistant professor in the Department of Biochemistry & Biophysics at the University of North Carolina School of Medicine, will use the grant for experiments on a highthroughput approach for deciphering the histone code.

Varshavsky, the Howard and Gwen Laurie Smits Professor of Cell Biology at the California Institute of Technology, submitted a grant entitled "Split Proteins as Boolean Circuits and Drugs of a New Kind."

Davidson's grant is entitled "RNA Aptamers for Brain Delivery." She is currently Professor of Medicine, Neurology and Physiology & Biophysics at the University of Iowa, as well as Carver Trust-Roy J. Carver Biomedical Chair in Internal Medicine, and Associate Director of the Gene Therapy Center for Cystic Fibrosis and Other Genetic Diseases. (W

### **Taniguchi Awarded IUBMB Medal**



Naoyuki Taniguchi recently received the IUBMB medal at the 33rd FEBS/11th IUBMB Congress held in Athens, Greece.

The award honors Taniguchi's pioneering work in the field of glycoscience and particularly on the importance of *N*-glycans in diseases. The medal also symbolizes Taniguchi's achievement as an exceptionally successful scientist in the field of

biochemistry and molecular biology.

Taniguchi graduated from the Hokkaido University School of Medicine in 1967, and completed his doctorate at the Hokkaido University School of Medicine in 1972. He was then appointed assistant professor at the Hokkaido University School of Medicine in 1975. In 1986 he joined the faculty of Osaka University Medical School as Professor and Chairman of the Department of Biochemistry. Taniguchi is an honorary member of the American Society for Biochemistry and Molecular Biology and has served on the editorial board of the *Journal of Biological Chemistry*.

# asbmbnews

## Glycerolipids Thematic Reviews in JLR

BY MARY L. CHANG

The glycerolipids' thematic review series, which debuted in the June issue of the *Journal of Lipid Research* continues this fall. The series is being coordinated by Stephen G. Young of the University of California, Los Angeles, who is an associate editor of the journal. The following is an overview of some of the upcoming articles.

In the October issue of *JLR*, Ruth E. Gimeno and Jingsong Cao of Wyeth Research discuss the roles glycerol-3-phosphate acyltransferases (GPATs) play in fatty acid metabolism and disease pathology. GPATs serve as the initial catalyst in the *de novo* synthesis of triglycerides and glycerophospholipids. Gimeno and Cao will comprehensively review what has been discovered about GPATs' properties from enzymatic studies. They will also suggest a major area of interest for future research—the characterization of human GPATs, including focus on the structure of and nutritional and hormonal regulation of GPATs.

Robert V. Farese, Jr. and colleagues from the University of California, San Francisco; University of Wisconsin; and University of Saskatchewan will provide a closer examination of triglyceride synthesis and the catalytic function of acyl-CoA:diacylglycerol acyltransferases (DGATs) in

November. DGATs, unlike GPATs, are active at the final and committed step of triglyceride biosynthesis. Additionally, this review will explore the genetics, biochemistry, tissue expression, regulation, and functions of DGATs, and touch on the possible agronomic applications of DGAT research.

The lipin family of proteins will be profiled in a review in December by Karen Reue of the University of California, Los Angeles, and David N. Brindley of the University of Alberta, Edmonton. The activity of lipin proteins (in the form of phosphatidate phosphatase-1 (PAP1) enzymes) is essential in triglyceride synthesis in most mammalian tissues, including adipose tissue, muscle, and the liver. This review will look at the previous research in both mice and humans suggesting that lipin proteins are significantly involved with lipid homeostasis in these key metabolic tissues. Reue and Brindley will also discuss possible PAP1 involvement in signal transduction, the regulation of lipin-1 expression and activity, and genetic variation in lipin genes and the correlation to human diseases.

Mary Chang is the Managing Editor of the *Journal of Lipid Research*. She can be reached at mchang@asbmb.org.

### October Issue of MCP Focuses on Clinical Proteomics

The application of proteomics to clinical issues, also known as clinical proteomics, is an emerging interdisciplinary research field that brings together scientists from many different areas of biomedical research to translate basic scientific knowledge into clinical applications. Some clinical areas expected to benefit from the application of proteomics include early detection and diagnosis of disease, prediction of how a disease will behave over time, how a patient will respond to treatment, and identification of novel targets for therapeutic intervention.

In 2002, *Molecular and Cellular Proteomics* made a decision to catalyze and nurture the development of clinical proteomics by providing a forum to promote, guide, and stimulate the discipline. As part of this effort, the October 2008 issue of *Molecular and Cellular Proteomics* focuses specifically on clinical proteomics. The issue, which was compiled by *MCP* Associate Editor Julio E. Celis of the Institute of Cancer Biology and the Danish Centre for Translational Breast Cancer

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Research, and Jose M. A. Moreira of the Danish Centre for Translational Breast Cancer Research, contains contributions by invited authors as well as a small selected number of regular articles submitted to the journal.

"We very much hope the reviews and articles in this special issue will provide new and stimulating insights into the opportunities that clinical proteomics continues to hold for the future of molecular medicine in particular and medical sciences in general," explain Celis and Moreira in their editorial.

The October journal is divided into four major sections: Biomarkers of Disease and Conditions; Pathway Proteomics and Post-translational Modifications; Methodologies; and Essential Resources. Some of the titles that appear in the special issue include: Sperm Chromatin: Fertile Grounds for Proteomic Discovery of Clinical Tools; Proteomic Contributions to Personalized Cancer Care; The Role of Proteomics in Clinical Cardiovascular Biomarker Discovery; and Banking of Biological Fluids for Studies of Protein Biomarkers.

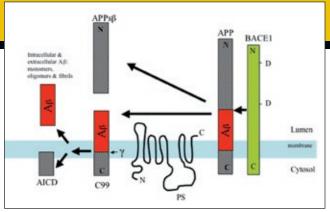
# JBC Series Looks at Alzheimer Disease

Alzheimer disease (AD) is a debilitating neurodegenerative disorder that directly affects millions of people and indirectly affects the lives of tens of millions of others who must deal with many years of cognitive decline of their loved ones. This devastating disorder, for which no cure is available at present, now strikes someone in America every 71 seconds.

AD is pathologically characterized by the presence of senile plaques containing amyloid  $\beta$  (A $\beta$ ) and neurofibrillary tangles containing tau protein in the brain. Although these pathological hallmarks were recognized more than a 100 years ago, only within the past decade have real advances been made in determining the molecular, biochemical basis of AD.

The latest *Journal of Biological Chemistry (JBC)* thematic minireview series looks at the current understanding of the biochemistry of the molecules involved in AD with a view toward solving the pathobiology of and finding potential treatments for AD. The series was coordinated by Kenneth E. Neet of the Rosalind Franklin University of Medicine and Science, and Gopal Thinakaran of the University of Chicago. Neet is a *JBC* Associate Editor, and Thinakaran is an Editorial Board member. The series will begin in the October 31 issue of the journal.

The first part of the series deals with the metabolism and function of amyloid precursor protein (APP) and how this may affect AD. The first minireview, "APP Trafficking, Processing, and Function" by Gopal Thinakaran and Edward H. Koo, discusses the biology of APP, and its relatives APLP1 and APLP2, with a particular focus on trafficking through the secretory, endocytic, and recycling pathways. The next minireview by Sarah L. Cole and Bob Vassar, "The Role of APP Processing by BACE1, the β-Secretase, in AD Pathophysiology," initiates a detailed discussion of APP processing by BACE1, the enzyme that generates the N terminus of AB. "Intramembrane Proteolysis by γ-Secretase" by Harald Steiner, Regina Fluhrer, and Christian Haass then develops the story of the elusive nature of  $\gamma$ -secretase, the enzyme that releases  $A\beta$  by cleavage of APP C-terminal fragments. Phosphorylation is a main regulatory theme in any biological system, and it certainly holds form for consideration of regulation of APP as detailed in the minireview "Regu-



BACE1 and the  $\gamma\text{-secretase}$  complex sequentially cleave APP to generate A $\beta.$ 

lation of APP by Phosphorylation and Protein Interactions" by Toshiharu Suzuki and Tadashi Nakaya.

Part two of this series looks at β-amyloid, believed to be the pathogenic product of APP cleavage, in terms of its fibrillization, toxicity, and degradation. In "Structural Classification of Toxic Amyloid Oligomers," Charles Glabe considers various "prefibrillar" forms of AB and proposes that conformationally sensitive antibodies might be the best means now for classifying structural types of AB oligomers, rather than size. "Amyloid β-Protein Assembly and Alzheimer Disease" by Robin Roychaudhuri, Mingfeng Yang, Minako Hoshi, and David Teplow ranges from a description of the pathway of assembly of A $\beta$  into soluble oligomers and protofibrils to the toxic effects of these assemblies via membrane effects, metals, and reactive oxygen species, mitochondrial interactions, and ultimately apoptosis of neurons. Bruce Yankner and Tao Lu consider the pathobiological role of  $A\beta$  in the minireview "Amyloid  $\beta\text{-Protein}$  Toxicity and the Pathogenesis of Alzheimer Disease." And finally, the importance of  $A\beta$ degradation as a natural or medicinal means of regulating A $\beta$  levels is discussed in "The A $\beta$ Cs of A $\beta$ -Cleaving Proteases" by Malcolm Leissring.

The series will conclude with a discussion of tau etiology, a look at the important role of ApoE in mediating effects of AD, and a review of the contribution of mouse models toward understanding AD pathology. The role and putative mechanism(s) of aberrant tau are discussed in "Tau Mutations in Neurodegenerative Diseases" by Michael Wolfe. The genetic association between ApoE4 and AD is explored at the molecular level by Ning Zhong and Karl Weisgraber in "Understanding the Association of APOE4 with AD: Clues from its Structure." And finally, "Relevance of Transgenic Mouse Models to Human AD" by Debbi Morrissette, Anna Parachikova, Kim Green, and Frank LaFerla looks at the advantages and disadvantages of current mouse models and where this approach will fit in the future.

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# publishing series

# Scheming to Present

This article is eighth 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.

isplaying a chemical formula in a print environment can be a challenge. Many of the symbols and special characters needed for scientific pre-

sentations are difficult to represent in the fonts available with a standard word processing package. Cadmus recommends using the "normal" or "symbol" fonts in Microsoft Word when preparing your manuscript. This reduces the chance that your characters will drop out or convert to an unexpected symbol during production. In fact, that's one reason Cadmus requests that a PDF of your manuscript be included. We can refer to the PDF just in case an unusual symbol appears when the author text has been converted and the copy editor is reviewing the document.

Often, however, the scientific symbols needed to represent the equation accurately are not included in the normal or symbol font packages. How, then, should you prepare your formulae?

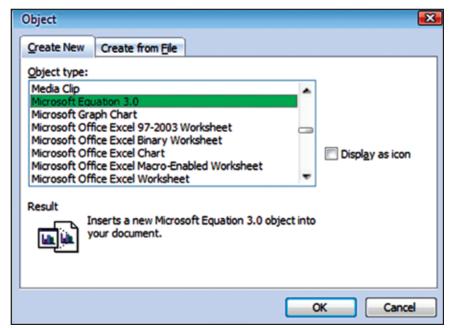
Microsoft has an equation editor package that may be useful for creating scientific symbols. In Word 2003 the equation editor can be accessed by going to the Insert menu and clicking on Object. In the Create

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New Object tab, scroll down to Microsoft Equation Editor (Fig. 1). A toolbar appears that will allow you to choose many mathematical and scientific symbols useful for developing equations or formulae. Overbars and arrows, sigmas and Greek characters, infinity symbols and chemical points—all of these are included in the equation editor toolbar (Fig. 2).

For even greater options, you may want to investigate the MathType application package. Created by Design Science, MathType is a much more powerful equation editor. Hundreds of additional math symbols are available, and translators allow output to scientific languages such as TeX or LaTeX.

### FIGURE ONE



Accessing Equation Editor in Word.

### **FIGURE TWO**



Equation Editor symbols available in Word.

jbc

# Chemical Formulae

#### FIGURE THREE

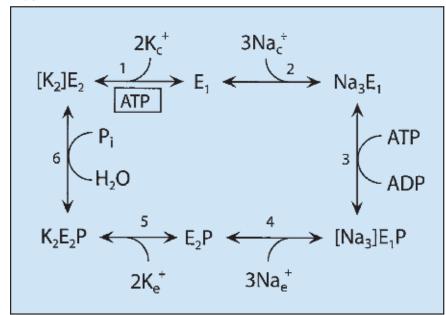
$$f_{mp} = f_{eta} imes \ln(r_{\it f}) - f_{eta} imes \ln(k_{
m off} imes f_{eta})$$
 (Eq. 2)

Fig. 3. An equation as set in the proof.

#### FIGURE FOUR

A sample scheme.

#### **FIGURE FIVE**



A formula saved as a graphic

Chemical equations should be labeled as Eq. 1, Eq. 2, Eq. 3, etc. throughout the article. Each equation should be set as centered in the line in the column of text, with the abbreviation labeling the equation set in parentheses on the same line with the equation but flush right (Fig. 3). Text following the equation is set flush left and starts with

a lowercase letter, unless of course the word is at the start of a sentence or a proper noun.

Reactions, schemes, and other displayed material are set fairly similarly to equations, except the label goes below the material and is centered in the column. The word REACTION or SCHEME is set in all capital letters, numbered in sequence, and centered beneath the graphic (Fig. 4).

The copy editor will review simple equations and formulae—those that can be presented in a single horizontal line of text in print—and edit them for consistency and clarity. More complex equations, formulae, and schemes such as those in Fig. 5 should be prepared as graphic images and will not be copyedited; they will be reproduced as presented.

If you, as an author, prefer to present your work in TeX or LaTeX, please be aware that the text and mathematical expressions are converted to Word for editing and then imported into XyVision for proof generation. Therefore, the appearance of the symbols in the formula or equation in the proof will be very similar but may not be exactly the same as it is in LaTeX. To ensure that the equation is exactly the same in appearance as you intended, cre-

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ate your equation as a graphic, as you would a scheme or figure, in a TIF or PDF format.

The inclusion of chemical formulae and equations in any *JBC* paper may be crucial to the understanding of the author's message. This information may be of assistance in presenting vital facts clearly and accurately. N

# special interest

# McCain, Obama, and Biomedical Research

BY ANGELA HVITVED

uring an election in which there are so many factors to consider, such as energy independence, tax policy, climate change, two ongoing wars, and health care, no one would dare argue that such an important decision should be made on the basis of a single issue. However, biomedical research is an important topic, especially to scientists. To that end, this article contains various statements the campaigns have made on issues we believe are of interest to our members. The information provided in the table was obtained from public

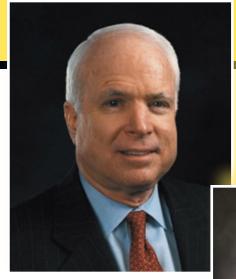
web sites that are noted under each section. Keep in mind that political positions change (for better or worse), and it is a good idea to visit the web sites yourself for more current information. That said, hopefully this profile will serve as a useful starting point for readers who want to know more about science and biomedical research issues in the upcoming presidential election.

Angela Hvitved was the 2007/2008 ASBMB Science Policy Fellow. She can be reached at angela.hvitved@gmail.com.

### **Web Sites and Resources**

The information listed here is just a snapshot of the candidates' positions on a limited set of issues. Below are the web sites used for this article along with brief descriptions of additional information the sites can provide.

- Scientists and Engineers for America
   (www.sefora.org) have two voter education
   initiatives underway. Their SHARP (Science,
   Health, and Related Policies) Network
   (www.SHARP.SEforA.org) is a wiki-based web
   site that tracks the science and health policy
   positions of candidates, presidential as well as
   congressional. Registered users can contribute
   information to candidates' profiles, including
   current policy statements, basic biographical
   information, and voting records on relevant
   legislation. Additionally, they, along with several
   other organizations, have asked the presidential
   candidates to respond to a questionnaire on
   science and innovation issues. At the time of
- writing, only the Obama campaign had posted a response, but the McCain campaign had replied that a response would be posted soon.
- Research!America's "Your Candidates, Your Health" (www.yourcandidatesyourhealth.org) web site posts candidate responses to a questionnaire focused specifically on health and biomedical research issues. Both the Obama and McCain campaigns have posted responses.
- The campaign web sites are the most direct sources for information released by the campaigns and are updated frequently. Visit www.johnmccain.com and www.barackobama.com to read their policy statements.
- Text, summaries, and voting records for legislation can be found at www.thomas.gov, a searchable database maintained by the Library of Congress.



John McCain

Sarah Palin



Barack Obama Joseph Biden



# Candidates Information & Responses



#### **Current Office**

cCAIN

Republican Senator from Arizona

BAMA

Democratic Senator from Illinois

#### **Senate Committees**

Accain

 $\label{lem:commerce} \textbf{Armed Services; Indian Affairs; and Commerce, Science and Transportation}$ 

BAMA

Foreign Relations; Veterans' Affairs; Health, Education, Labor and Pensions; and Homeland Security and Governmental Affairs

#### **Education and Background**



Born in Panama Canal Zone, August 29, 1936

United States Naval Academy, Annapolis, MD, 1958; National War College, Washington, DC, 1973; pilot, United States Navy 1958-1981; prisoner of war in Vietnam 1967-1973; elected to Congress as a Republican in 1982 and served until 1987; elected to the Senate in 1986; reelected in 1992, 1998, and 2004

AMA

Born in Honolulu, Hawaii, August 4, 1961

Occidental College, Los Angeles, CA; Columbia University, New York City; Harvard, J.D. 1992; first African American president of the Harvard Law Review; lecturer, University of Chicago; Illinois State Senate 1997-2004; elected as a Democrat to the U.S. Senate in 2004

### **Embryonic Stem Cell Research**



Voted to overturn President Bush's embryonic stem cell funding ban.

-www.thomas.gov

"While I do support federal funding for embryonic stem cell research, I also believe that clear lines should be drawn to reflect a refusal to sacrifice moral values and ethical principles for the sake of scientific progress. Moreover, I believe that recent scientific breakthroughs raise the hope that one day this debate will be rendered academic. I also support funding for other research programs, including amniotic fluid and adult stem cell research, which hold much scientific promise and do not involve the use of embryos. I strongly oppose the intentional creation of human embryos for research purposes. I voted to ban the practice of "fetal farming," making it a federal crime for researchers to use cells or fetal tissue from an embryo created for research purposes."

---www.yourcandidatesyourhealth.org

DBAMA

 Co-sponsored Stem Cell Research Enhancement Act of 2007 to allow research of human embryonic stem cells, voted to overturn President Bush's embryonic stem cell funding ban.

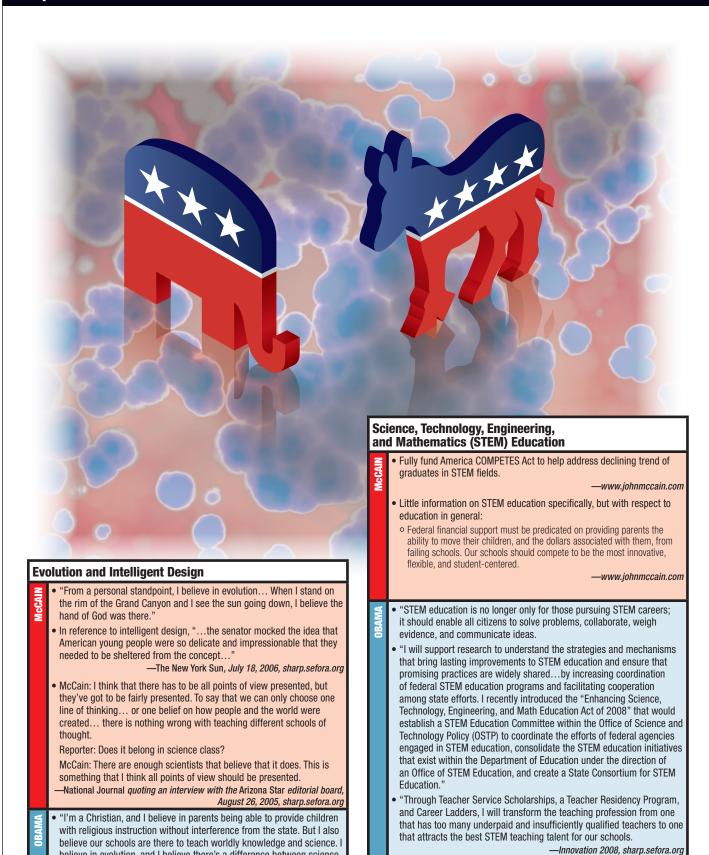
-www.thomas.gov

- "We owe it to the American public to explore the potential of stem cells to treat the millions of people suffering from debilitating and life-threatening diseases... I would:
- Promote Embryonic Stem Cell Research: ...introduced legislation while a member of the Illinois Senate that specifically permitted embryonic stem cell research...
- Expand the Number of Stem Cell Lines Available for Research: ...reverse [Bush's] policy that has allowed hundreds of thousands of frozen embryos, left over from in vitro fertilization, to simply be discarded instead of being used to potentially save lives.
- Ensure Ethical Standards: ...stem cell research needs to be conducted with the highest ethical standards. ...the Stem Cell Research Enhancement Act maintains high ethical standards by ensuring that only those embryos that would otherwise be discarded could be used and that the donors would have to provide written consent for the use of the embryos. I also support greater research to explore the viability of adult stem cells and cord blood."

#### -www.yourcandidatesyourhealth.org

- "...embryonic stem cells remain the "gold standard," and studies of all types of stem cells should continue in parallel for the foreseeable future."
- "I favor responsible oversight...in accord with recent reports from the National Research Council.... An expanded, federally supported stem cell research program will encourage talented U.S. scientists to engage in this important new field, will allow more effective oversight, and will signal to other countries our commitment to compete in this exciting area of medical research."

-Innovation 2008, sharp.sefora.org



ASBMB Today October 2008

• "I will launch a Service Scholarship program that pays undergraduate

in a high-need school, and I will prioritize math and science teachers. ...increase National Science Foundation (NSF) graduate fellowships."

or graduate teaching education costs for those who commit to teaching

-Innovation 2008, sharp.sefora.org

believe in evolution, and I believe there's a difference between science and faith. That doesn't make faith any less important than science. It

just means they're two different things. And I think it's a mistake to try

to cloud the teaching of science with theories that frankly don't hold up

-York Daily Record, March 30, 2008, sharp.sefora.org

to scientific inquiry."

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### **Federal Funding for Basic Research**

### McCAII

 "I strongly support funding for the NIH. NIH plays an integral part in ensuring that America is on the leading edge of medical innovation against devastating diseases like cancer, Parkinson's and Alzheimer's."

--www.yourcandidatesyourhealth.org

 "I strongly support FDA funding. We need to ensure that FDA has the proper resources to maintain its duty as the guardians of our nation's drug and food supply in an era of growing global economy. FDA can also play an important role in promoting greater market competition, especially in drug sector, by having more streamlined processes for drug approval."

---www.yourcandidatesyourhealth.org

 "I strongly support funding for CDC. CDC plays an important role in not only promoting better health for Americans through better management of chronic care diseases and encouraging healthier lifestyle habits but also strengthens our homeland security by combating bioterrorism threats, pandemics, and promoting emergency preparedness."

-www.yourcandidatesyourhealth.org

 John McCain will direct the USDA to carry out a comprehensive research approach to help develop more drought-resistant higher yield crops and increase production per acre.

-www.johnmccain.com

### BAMA

 "My administration will increase funding for basic research in physical and life sciences, mathematics, and engineering at a rate that would double basic research budgets over the next decade. We will increase research grants for early-career researchers to keep young scientists entering these fields. We will increase support for high-risk, high-payoff research portfolios at our science agencies."

-Innovation 2008, sharp.sefora.org

- "While the outcomes of specific projects are never predictable, basic research has been a reliable source of new knowledge...! believe that continued investment in fundamental research is essential for ensuring healthier lives, better sources of energy, superior military capacity, and high-wage jobs for our nation's future. ... the NIH budget has been steadily losing buying power for the past 6 years... arresting the careers of our young scientists and blocking our ability to pursue many remarkable recent advances. Furthermore, in this environment, scientists are less likely to pursue the risky research that may lead to the most important breakthroughs."
- "Sustained and predictable increases in research funding will allow...
  greater support for high-risk, high-return research and for young
  scientists at the beginning of their careers."

Innovation 2008, sharp.sefora.org

 "I strongly support increasing funding for the NIH. Even though biomedical research costs are increasing each year, annual funding for the National Institutes of Health (NIH) has not kept up."

-www.yourcandidatesyourhealth.org

 "I believe that the CDC plays a critical role in our nation's health care and national security infrastructure, and I will ensure the CDC has the resources it needs to fulfill its public health mission."

---www.yourcandidatesyourhealth.org

- "The Food and Drug Administration is a critical protector of our food supply, and assures our medicines are safe and effective. It regulates a full quarter of the American economy. Yet the FDA is badly underfunded for its responsibilities. As our economy brings a rising tide of imported products, the FDA urgently needs expert staff and technology to more rigorously inspect imported food, drugs, and other products like pet food.
- The FDA must also be freed from the Bush Administration's ideological straightjacket to protect the public health on the basis of sound science."
   —www.yourcandidatesyourhealth.org
- "This year...the Department of Defense (DoD) requested a sharp
  increase in the basic research budget for breakthrough technologies.
  More is needed. My administration will put basic defense research on a
  path to double and will assure strong funding for investments in DoD's
  applied research programs...My administration will build a strong and
  more productive research program in the Department of Homeland
  Security (DHS) that will include critical work on cyber and bio security."

-Innovation 2008, sharp.sefora.org

### Innovation and Competitiveness

Accain

John McCain will establish a permanent tax credit equal to 10 percent
of wages spent on R&D. This reform will simplify the tax code, reward
activity in the U.S., and make us more competitive with other countries.
A permanent credit will provide an incentive to innovate and remove
uncertainty. . . . will lower the corporate tax rate to 25% to retain
investment in U.S. technologies.

-www.johnmccain.com

• "I believe we are standing on the threshold of a new era: the innovation age. New information and communications technologies are the leading edge of technology innovations that will permeate every aspect of our society, and I am committed to federal policies that ensure America's competitive edge in technology and innovation. Maintaining our tech edge requires robust basic research and sustained development efforts. I will support innovation by funding basic research and reforming and making permanent the R&D tax credit. We also need to keep the Internet tax-free. I recently sponsored legislation that extended that tax ban for seven years, and seeks to permanently ban taxing access to this source of innovation and growth. I also continue to be a strong supporter of H1-B expansion, but mere expansion is not enough. Reforms should eliminate the artificial limits, and allow the Department of Labor to set a level of visas appropriate for market conditions."

-www.yourcandidatesyourhealth.org

BAMA

 "I believe that the U.S. has the potential to lose its global competitive edge in science, technology, and innovation unless we take steps to change the current trend."

--www.yourcandidatesyourhealth.org

• "America has long led the world in innovation. But [the Bush] Administration's hostility to science has taken a toll. At a time when technology helps shape our future, we devote a smaller and smaller share of our national resources to research and development. . . . We will make science, technology, engineering, and math education a national priority. We will double federal funding for basic research, invest in a strong and inspirational vision for space exploration, and make the Research and Development Tax Credit permanent. . . . We will ensure that our patent laws protect legitimate rights while not stifling innovation and creativity. We will end the Bush Administration's war on science, restore scientific integrity, and return to evidence-based decision-making."

-www.barackobama.com

 "I support the principles behind Sarbanes-Oxley reforms and believe compliance should not be overly burdensome for smaller firms and start-ups."

---www.yourcandidatesyourhealth.org

 "...the Bush administration has failed to take full advantage of the Bioshield initiative. ...I will stress the need for broad-gauged vaccines and drugs and for more agile and responsive drug development and production systems. This effort will strengthen the U.S. biotech and pharmaceutical industry and create high-wage jobs."

-Innovation 2008, sharp.sefora.org

- "I will:
- Establish the nation's first Chief Technology Officer (CTO) to ensure that our government and all its agencies have the right infrastructure, policies, and services for the 21st century. The CTO will lead an interagency effort on best-in-class technologies, sharing of best practices, and safeguarding of our networks;
- Strengthen the role of the President's Council of Advisors on Science and Technology (PCAST) by appointing experts who are charged to provide independent advice on critical issues of science and technology. The PCAST will once again be advisory to the president;
- Restore the science integrity of government and restore transparency of decision-making by issuing an Executive Order establishing clear guidelines for the review and release of government publications, guaranteeing that results are released in a timely manner and not distorted by the ideological biases of political appointees. I will strengthen protection for "whistle blowers" who report abuses of these processes."

-- Innovation 2008, sharp.sefora.org

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# special interest

# ASBMB Round Table: Peter Agre

BY NICK ZAGORSKI

In the world, spoken with government leaders, and even squared off with Stephen Colbert. Yet through it all Peter Agre has retained the humble demeanor of the Minnesota schoolboy (and classmate of future governor Jesse Ventura) who grew up admiring two scientific heroes: his father (a chemistry professor at St. Olaf and Augsburg Colleges) and Linus Pauling. In his actions, though, he has been far from modest, tirelessly advocating on the behalf of science to all who would listen. However, this noted ASBMB member, currently serving as the Director of The Johns Hopkins Malaria Research Institute, has graciously taken some time out of his schedule to discuss some of his views on the role of science in both the public eye and the upcoming election.

**ASBMB:** Over the past several years you've emerged as a strong advocate for communicating the importance of science to both policymakers and the public. Has this been a lifelong passion of yours?

Agre: I never had a life plan to become politically active, though I've always been fascinated with decision making and policy. I remember taking a trip to Washington D.C. in the 9th grade and being completely drawn in by the experience, standing in the capitol of the most powerful country in the world.

As I matured as a scientist I faced limitations and frustrations and I thought, what could I do about it? I could whine to my lab, but that wouldn't help; I could complain to my departmental chairman, but that wouldn't accomplish much; or, I could get active as a scientist and, together with other scientists, try and educate people about why the science we do is important.

**ASBMB:** And do you think that the public, in general, is receptive to learning about science?

Agre: Absolutely; whenever I'm on a train or plane and start chatting with my seating neighbor, they almost always are interested and engaging to talk to. Naturally, health-related issues tend to generate more interest, because everyone can relate to that on a personal level; but I think the

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taxpayers and politicians realize that the men and women working in all manner of science are doing some wonderful things, and we scientists just need to do more to communicate better with them.

**ASBMB:** So you don't believe the notion that scientists may be hesitant to discuss their work because the general public simply won't understand?

Agre: I think the general public is more savvy than many people give them credit for, and if we take the time to tell them about science, they will get it. When I was a medical student at Johns Hopkins, we had a wonderful scientist there named Daniel Nathans; and I remember when reporters came to his lab after he won the National Medal of Science and said that they wouldn't understand his work. Then he replied, "Just a moment; yes, the details of science are hopelessly complex, but the principles are elegant and simple," and then proceeded to explain DNA restriction enzymes.

The key, of course, is to be able to explain it well, which is where a problem lies. Two great communicators who come to mind are Harold Varmus and Tom Pollard, and it's no surprise to learn that Varmus was an English major and Pollard was captain of the debate team. Unfortunately, most scientists don't communicate well because they haven't been trained.

**ASBMB:** In that regard, though, scientific journalists, not to mention the media staff at universities, can be a big help.

Agre: They are definitely an important resource that scientists should tap. I know there can be reasons for reluctance, but I've always felt comfortable talking to journalists, and it can be a great experience. Now, it won't always be *New York Times* articles or appearances on *The Colbert Report*; but even small, local papers are a valuable tool to educate people about science. On the journalist side, I think it's also important not to rush and simply try to get a story out; take some time and talk to the scientist about his or her work and really try and appreciate it.

**ASBMB:** Among the many advocacy groups you've joined is ScienceDebate08, which hopes to encourage more scientific



discourse by the candidates. How has that movement been progressing?

Agre: I think the political parties are beginning to show more interest in science. I saw former Virginia Governor Mark Warner talk at the Democratic Convention, and he could have talked about anything, but he spent a lot of time emphasizing the importance of science and technology in our society. And he made an excellent point about why this is important: our economy is based on innovation.

Think back to the differences between modern society and our ancestors; they had hard lives and typically died young of malnutrition, hypothermia, or infectious diseases. And all the innovations that have improved our quality of life are based in the sciences, be it medicine, engineering, or agriculture. That being said, I do understand that science will not be the major issue of this election, nor will it decide the outcome.

**ASBMB:** And how do you think the election outcome, however it turns out, will shape scientists' futures?

Agre: Well, I'm optimistic that whoever wins, the scientific enterprise will be in better shape than now, although personally, I am a Democrat, so I do think the Obama team will be more favorable; in either case, we scientists will have to work hard with the new leadership to improve the current situation.

Now, it should be stressed that "pro-science" is not a Republican or Democrat platform. The most recent Republican leadership has been science-averse, but I grew up in the Eisenhower era, and that was a period when American science really took off. There are science advocates on both sides of the party line, like Congressman Bill Foster

(D-Illinois), who used to be a physicist at Fermi labs, and former Congressman John Porter (R-Illinois). These are the people we need to reach out to.

ASBMB: The current "hot topic" science issues could be called the four "E"s (environment, energy, evolution, and embryos). Is there some other critical scientific issue that should be receiving more attention?

Agre: I would say public health. Now, being a recent convert to this area I might be a little biased, but we definitely need to develop a better flow of health information. Take HIV, for example; it's a totally preventable disease—you're not going to catch it from the drinking

water—but why is it still a problem given all that we know about it? Well, in part, at least, it's because of some touchy political decisions on what can and can't be talked about.

I believe great strides can be made if we put more effort into this area. Just look back at recent U.S. history; one of our greatest health achievements has been reducing tobacco use in this country. Far fewer people smoke today than 40 years ago, and that's basically because of a national public health campaign.

**ASBMB:** So what can scientists do to help spread the word about public health and other important science issues?

Agre: I don't even know if it's an issue of what we can do. We as scientists owe it to the citizens that pay the taxes and the politicians who supply our funding to report our business to the public. When it comes to volunteering our time, it's not a charity, it's a reality. Now students, postdocs, and new professors have a hard enough time just staying above water, but I think every tenured faculty should appoint some time for community service.

Now, it would be great if we could get more scientists into Congress—we have only two senators with M.D.s (though neither is science-friendly) and a handful of representatives with Ph.D.s—but that may not be realistic. But Tip O'Neill once said "all politics is local," and that couldn't be truer. So go out and run for a local position on a school board or city council, or give back in another way like teaching biology merit badges for scouts. Whining by itself will not solve any problems.

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# 2009 annual meeting



### **Drug Discovery in the 21st Century**

BY DARIA HAZUDA AND BRIAN SHOICHET

he genomics era is changing how we treat complex human diseases and approach drug discovery. In some senses, the field is changing back to an earlier view of disease and drug action. The first drugs were discovered by testing agents in complex biological systems, typically in tissues, organs, or whole animals. Whereas such testing gave a view of efficacy at the organismal level, it had distinct drawbacks. Structure-activity relationships (SAR) were convoluted with many non-target effects, and the very identity of the specific targets of the drugs was unknown. With the advent of molecular biology in the 1980s, the screening of what we might now call biological systems was largely abandoned in favor of pure targets; typically proteins were heterologously expressed and assayed in reductionist biochemical systems. Whereas this approach has made SAR easier, the translation back to biological activity in cells and organisms was often lost. The failure to ensure biological penetrance and to account for the polygenic nature of many diseases increased the failure rates from "hit" to "lead" to clinical candidate to drug. The high failure rate of the single target biochemical approach has revived interest in the "unbiased" systemsbased screening approaches and fueled a renewed enthusiasm for the concept of polypharmacy to attack multiple targets or complex biological pathways.

The next decade offers unprecedented challenges and opportunities for drug discovery. Advances such as sequencing of the human genome, new genomics and proteomics technologies, and the associations and pathways emerging from systems biology are being combined with the mechanisms and often the target structures that have been the cornerstones of the molecular approach. These combinations provide the field with an unprecedented opportunity to marry

the heretofore largely disparate target- and pathway-based approaches. The elucidation of complex pathways associated with disease phenotypes via chemical genomics or phenotypic screening, i.e. testing libraries of compounds to determine whether they elicit phenotypic changes in cellular systems or model organisms, has been revitalized by new technologies that can quantify complex phenotypes rapidly and in a high throughput manner on a multiple cell or single cell scale. The retrospective identification of the genetic basis for a phenotypic response offers the advantage of providing earlier proof of biology. It also can provide powerful support to target-based approaches as lead compounds are developed and structure-activity relationships elucidated, thus facilitating structural studies and structure-based design. Conversely, the development of target-based chemical tools derived from detailed structural information can elucidate and deconstruct complex biological processes in phenotypebased screens.

Four sessions at the 2008 ASBMB meeting in the Drug Discovery thematic session explore advances in molecular and more systems-oriented approaches to drug discovery, from initial target discovery and validation to small molecule inhibitor lead identification. These talks will also highlight examples of the marriage of these methodologies, including both forward and reverse chemical genetics, structurally based mechanistic approaches, and applications of polypharmacy. The speakers work at the forefront of these fields, in both the academic and pharmaceutical setting, and will cover a range of therapeutic areas from oncology and neuroscience to infectious disease, illustrating the widespread applicability and potential impact of these opportunities in treating human disease.

# **Drug Discovery** & Design

### Symposium: Membrane Proteins as Targets

- Probing Protein Structure and Function of Ion Channels,
   Pamela M. England
- HIV gp120/CD4 Interactions or GPCR Structures, Wayne Hendrickson
- Title TBA, Jeff Abramson

### Symposium: High Content Approaches

- A Combined Chemical Genetic/RNAi Approach: New Tools to Study Cell Division, Ulrike Eggert
- Title TBA, Alanna Schepartz
- Integrating High Content Screening and RNAi for Novel Drug Discovery, Bonnie Howell

### Symposium: Target Identification and Pathway Mining

- Tissue-to-Tissue Networks Elucidate the Circuits of Metabolic Diseases, Eric Schadt
- Small Molecule Approaches to Bacterial Pathogenesis,
   Deborah Hung
- A Protein Chip Approach to Analyzing Regulatory Networks, Heng Zhu

### Symposium: Polypharmacology and Drug Repurposing

- Predicting Drug Off-Target Effects, Brian Shoichet
- Massively Parallel Screening of the Receptorome for Discovery and Validation of Therapeutic Targets, Bryan Roth
- Real and Virtual Polypharmacology for Target Identification and Lead Finding, Jeremy Jenkins

# education and training



The following is one of a series of occasional articles we publish from the National Postdoctoral Association.

# Postdocs Getting Involved: Why the Impediment?

BY JOSEPH MARX AND JONATHAN GITLIN

s mentioned in a recent issue of *ASBMB Today*, the National Postdoctoral Association held its annual meeting this past May in Boston. The 1st day of the meeting focused on workshops for both postdoctoral associations (PDAs) and postdoctoral offices (PDOs), and how those groups can make the best use of their resources.

The opening PDA session served two purposes: first, to familiarize new PDA leaders with the issues that PDAs face; and second, to provide a way to identify and propose solutions for these problems.

Despite the large number of attendees present, we were able to accurately poll everyone on a list of questions regarding progress that the community has made in the years since the National Academies' Committee on Science, Engineering, and Public Policy (COSEPUP) issued their report in 2000¹.

The workshop employed an audience response system (ARS) donated by SmartRoom Learning Solutions (www.smartroom.com/), which provided real time feedback from the audience to stimulate discussions on issues that PDAs are facing.

The singular concern voiced by PDA leaders was not lack of institutional buy-in. Rather, the postdoctoral community itself appears to be the one needing motivation. Whereas many institutions still do not have a fully supported PDA, a significant number of institutions are supporting PDA activities, with over 70% of the polled PDAs utilizing an operating budget of \$2000 or more. PDAs are using the institutional support to host a variety of activities and promote adoption of postdoctoral policies, from workshops on grant writing and interview skills to social events, networking opportunities, and symposia.

The clear need for additional participation by stakeholders to promote beneficial postdoctoral experiences echoes throughout the PDA community. At the conference, many postdocs asked why they should donate their (often limited) time to PDA activities. The ensuing discussions, which carried on until the close of the day, highlighted several benefits.

At a time when funding for research is at a low and the research environment is very competitive, the need to be best at the bench weighs heavy on postdocs. However, with only 20% of postdocs finding a tenure track faculty position, one might think that more young scientists would look to PDAs and other organizations to provide opportunities to sharpen skills not found in the laboratory. This need to for independent career development should be driving postdocs to participate in PDAs.

Translational or "soft" skills are often neglected in the career development of young scientists. Regardless of the eventual career path of the young researcher, those seemingly intangible traits, from teamwork to leadership, and other interpersonal skills in between are applicable in the lab and outside the lab. The chance to work on and develop an effective combination of these traits presents itself in the opportunity to participate with other stakeholders through PDAs.

Overwhelmingly, participants reported that the most common misconception when attracting volunteers for PDAs is often that involvement will use up what little free time they seem to have. As with most professional societies run by volunteers, PDAs work on a simple premise: "do what you can."

Sometimes the payoff for involvement can be seen in the short term: helping develop institutional policies, holding an event, and so on. However, other results can be more long term. At some point, postdocs stop being postdocs, and when finding a position, the network from involvement with a PDA can be invaluable.

There was broad consensus that job hunting young scientists armed with connections across disciplines and institutions along with a basket of translational skills developed through involvement with the postdoctoral community were at an advantage over their peers. Your papers can separate you from the pack technically, but what else can you do?

Joseph Marx is Chair of the NPA's Outreach Committee, and Jonathan Gitlin is Vice-Chair of the NPA.

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### **Entering the World of Biomolecules**

# Physical Models Give Way to Holistic Approaches for Teaching Structure/Function Relationships

BY DUANE SEARS

The 2008 Proteins in Active Learning Models (PALM) Workshop was hosted this past spring in the newly situated Center for BioMolecular Modeling (CBM) at the Milwaukee School of Engineering (MSOE). About 25 science educators from a variety of professions—including secondary schoolteachers, university and community college professors and lecturers, a post-doctoral fellow, a textbook writer, and a professional biomolecular artist and writer—convened for an intense 3-day exposure to the educational resources and physical learning models that the CBM has developed over the years for the purpose of helping students learn about the nature and nuances of biomolecular structures and their functions.

Tim Herman, a biomolecular guru of sorts with unbounded raw energy and pure enthusiasm, is the brainchild behind the CBM. For about half of the workshop, he and his associates guided attendees through the myriad of tactile models and ancillary learning activities that the CBM has created for educators. The physical models can be obtained on loan from the MSOE Model Lending Library for just the cost of return shipping, or the models and other resources can be purchased with modest pricing. The models themselves range from simple water kits containing several geometrically accurate space-filled water molecules with embedded magnets for simulating the H-bonding properties of H<sub>2</sub>O; to semi-flexible foam-covered wire "Toobers" for modeling protein and polynucleotide backbone structures; to hand-sized, molecularly accurate threedimensional molecular models of literally hundreds of structures, only a scant few of which are actually displayed on the CBM model gallery website.

The latter models deserve special mention because Herman was among the first to realize that a widely used engineering method called rapid prototyping, which is used to produce physical mockups of computer-generated images, can be adapted to produce accurate three-dimensional (3-D) physical models of biomolecules based on their atomic coordinates<sup>1</sup>. In the simplest of explanations, the rapid prototyping machine effectively "photocopies" a 3-D image by depositing a plaster powder in a series of thin two-dimensional (2-D) layers (from bottom to top) with spot applications of glue at any point where a structure is contiguous between adjacent 2-D planes. The end product is a

rectangular 3-D block that, after being subjected to an air blower (to whisk away any unglued plaster powder), leaves behind a rigidly connected 3-D model accurately representing the computer image from which it was generated.

Herman and his colleagues, including the very talented Mark Hoelzer who is the lead designer at CBM, have introduced many useful modifications to this technique so the resulting models are light and resilient. They have also found ways to automatically introduce custom colors into specific portions of the model during the prototyping process, thereby eliminating any need to "paint" specific features on the models after they are produced. These models look every bit like the *Jmol* or *Chime* 3-D images we are accustomed to seeing on the computer screen, but they can be manipulated by hand, thereby lending a tactile dimension to a student's understanding of molecular structure. This effect is greatly enhanced by the modularity of some of the models where different segments are held precisely in place by magnets so that the segments can easily be separated for closer inspection of the underlying features. The CBM has created hundreds of models in this way.

What eventually became apparent during the workshop is that the CBM is actively evolving toward a more comprehensive and rigorous educational approach where structural models are only one part of a broader educational package. This holistic shift in approach is spearheaded in large part by Margaret Franzen, who recently became a permanent CBM staff member and who has won both local and national recognition for her teaching innovations. One particularly novel innovation is her NSF-funded guide for instructors that was developed to help students learn about the relationship between the evolutionary resistance of mosquitoes to insecticides and the evolutionary alterations in mosquito acetylcholinesterase, the target of some insecticides. Various exercises employ a modular 3-D model of the enzyme active site, which is available from the MSOE Model Lending Library, where wild-type and mutant enzyme structures are easily interconverted so as to illustrate the resulting effects on the binding of removable substrate and inhibitor molecules that are included with the model.

This is but one of several CBM projects aimed at placing biomolecular structure/function teaching activities under

the larger umbrella of bioinformatics. Such efforts have produced yet another highly innovative instructional aid and learning activity, the Bioinformatics Map of the β-Globin Gene®, which is also available from the CBM. In a nutshell, the entire  $\beta$ -globin gene sequence is laid out on an ~5-inch x 15-foot laminated sheet (that is easily rolled up for storage) with three potential translated reading frames running below the sequence. As described by those at the meeting who had already used this remarkably simple learning tool, it is an effective guide for deepening and integrating students' understanding of a host of related biological concepts that crossover between genetics, gene structure, transcription, RNA processing, translation, protein structure, etc.

To help the CBM enter this new phase of developing teaching activities that meld biological structures with the larger knowledge base of bioinformatics, meeting participants were asked to share their teaching experiences with existing CBM resources, or other types of visual and tactile learning aids. Participants worked together in small groups on various "assignments" that were set up to spur discussion. Ultimately, these activities

led to brainstorming sessions about future directions and new projects that the CBM might undertake. No project, however ambitious and seemingly complex, appears to be off limits as long as the educational payoff merits the effort. One such project that perfectly fits this bill is the structure and function of the nuclear pore complex as described at the workshop by Jody Franke from The Rockefeller University, who brought attendees up to date on what is currently known about this structure and the nature of the supporting experimental evidence. As a seemingly perfect gesture to what might eventually be a grand undertaking by the CBM, meeting participants, while waiting for their conference dinners to be served, spontaneously assembled into a nuclear pore complex-like structure under the high foyer ceiling of the Grohmann Museum of the MSOE.

Confessing that I had only been vaguely aware of the CBM and its educational mission prior to attending this workshop, I came away a convert to the power of the



Guided by Jody Franke (in the baseball hat at the *right*), participants at the 2008 PALM Workshop spontaneously assembled into a human 3-D model of the nuclear pore complex.

approaches being undertaken for rigorous science education. The extreme versatility of the types of models and resources that are already available was illustrated again and again by the diversity of approaches and applications described by the participants. The CBM is a fabulous teaching resource, and biochemists and biologists alike are bound to find unique teaching tools here that students will find interesting, relevant, and even exciting. The future looks bright for the CBM, and I look forward to what emerges from this unique educational center in the years to come. N

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# minority affairs



### Is It a Conscious Decision?

BY TAKITA SUMTER

recent article in the May 18th edition of the *Boston Globe* entitled "The Freedom to Say 'No" revisits the gender bias that impedes the entry of women into science and engineering careers. This article concludes that fewer women pursue careers in these fields because of a lack of interest. As a woman in science who trained under the direction of both male and female academicians, I feel that I have a reasonable level of appreciation for the problems that women in science face as they carve out their niches while climbing the ivory tower. And even though I

understand, I'm still unable to wholeheartedly agree or disagree with the *Boston Globe* report.

There are those who would disagree with the notion that gender biases in physical sciences exist as a result of self-selection. In fact, the contributions of women, like any other minority, are often marginalized in male-dominated fields. In some cases, issues are matters of obvious discrimination. In other cases, familiarity and personal relationships come into play. A recent

report suggested that 80% of professional positions are filled as a result of networking. Therefore, if males are more predominant in high paying technical positions, they are more likely to recommend a male friend than a female. Males are also more likely to promote themselves more aggressively than females, and this may have an impact on the gender gaps. It is also hard to believe that so many women would simply rather "do something else" when so many more women than men successfully matriculate through undergraduate science programs. In response, several studies attribute the departure of women with substantial math and science backgrounds to a preference for working with living things. This would suggest that the many barriers to tenure and promotion among women at research institutions should be less apparent in the life sciences. This is one of the main reasons that the notion of self-selection as a source of the gender gap is so controversial.

On the other hand, it is also possible that talented female scientists consciously choose to pursue non-scientific careers because of the nature of the work. Studies

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show that clashes between the tenure track and family planning years are a major consideration. Women who start a family while on the tenure track may be perceived by some as not being serious about their careers. Therefore, it is sometimes recommended that women postpone motherhood until the timing is right. Moreover, those who choose to start families while on the tenure track may be discouraged by the workload of academics, whereas others find the flexible schedule to be ideal for the child-rearing years. The rapid evolution of science has

also been credited as a major factor in a woman's preference for social sciences over physical sciences. A 1-year sabbatical in the humanities will have a less dramatic effect on one's skill set than in the physical sciences. The technical nature of the discipline when compared with social sciences can also influence the level of work-related pressures. For instance, would a professor in the social sciences require the same level of grant funding as one in the physical or life sciences? If not, is there a great level

of work involved in securing the extra funding? These various factors may dissuade women from entering into the sciences; it's also possible that women are just not interested in high paying positions in technical fields.

When given the freedom to choose, I believe that there are many women who would pursue and succeed in competitive careers in science and research. In fact, there are many testaments to that effect. I also believe that there is a certain level of gender discrimination that exists. Given their abilities, women are making intelligent decisions to pursue careers that are most suitable for their personal interests. There is clearly a great deal of work to be done in developing appropriate policies that ensure a fair and cooperative work environment in the sciences. We can all help by educating ourselves and holding frank discussions about discriminations in our own work settings.

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# sci comm



### Science in the Blogosphere

BY SARAH CRESPI

In honor of this month's political theme, I decided to survey the most political part of the world: the blogosphere.

Blogging has been around for a while, and was one of the the first sources of user-generated content. Anyone can start a blog, but in my opinion, the best sites come from writers with specialized knowledge writing about their favorite topics. And when it comes to scientists, these topics seem to be science, politics, and skepticism (leaving aside mundane matters of everyday life that almost no blogger can resist writing about). If you can get past the posts on housecleaning and oil changes, science blogs have much to offer. They provide a forum for scientists to explain their research and the research of others in their own terms, targeting the audience of their choice. Blogs let scientists speak before a reporter asks a question. In fact, speaking as a former journalism student, journalists use blogs to find opinionated experts or areas of contention to write about.

Blogging can also be a useful exercise for the reluctant author. Sitting down to write once or twice a day about science or an ongoing political debate helps keeps the feeling of writing fresh in the mind. Depending on the audience, blogging can also help a researcher practice finding words to describe their research in common terms, a priceless skill.

For some, blogging is an outlet for scientific awe. It's just a way to get to say: this finding is amazing! Can you believe how this works?

Finding a good blog can be tough because it is about more than just good writing. The comments of an engaged and informed community around the blog add so much more. The easiest science blog community to navigate is *ScienceBlogs* (part of Seed Media), a group of over 70 bloggers covering topics in the life sciences, physical science, medicine, and technology.

ScienceBlogs doesn't rank its writers, but the name does guarantee that the author has something of a science background. The front page of the site is a great place to catch up on what the science-minded segment of the blogosphere is currently discussing. Aggregation sites like this provide a place to scan headlines or delve deep into the latest debate.

On *ScienceBlogs*, Adventures in Ethics is writen by a philosophy professor and Ph.D. in chemistry. Her interesting posts on ethical dilemmas in biology stimulate wide-ranging

discussions among thoughtful commenters. See her post on the relationship between peer review and gaining truths via science for a taste.

ScienceBlogs members write on topics such as evolution versus creationism/intelligent design, global warming, and stem cell research, but many ScienceBlog authors also pontificate on the gamut of politics, from the presidential race to USDA rulings.

P. Z. Myers, a biology professor at the University of Minnesota, writes one of most popular science blogs on the internet, *Pharyngula*, and is not afraid of treading contentious territory such as atheists' rights and intelligent design. Visit for your daily dose of outrage or cephalopod. For more on the evolution "debate," check out the *Panda's Thumb*.

Mostly, if politics comes up in science blogs it's lab politics, office politics, small time politics. But navigating tenure, funding, publishing, and managing a lab can be tricky. One blogger, a Natural Scientist, does a good job doling out advice on choosing a lab, running a lab on the cheap, and what to expect from a realistic advisor.

It's hard to find consistent "science blogging," a spot where the authors spend all their time reading research reports and handing down a considered opinion. Most blogs are a mix of personal information and science chat. Recently, a new service called researchblogging.org has come on the scene. Researchblogging.org filters *Science-Blog* members' posts on journal offerings and presents them all in the same place.

Blogs hosted by journals, or related to their networks, are another safe bet when it comes to seeking out likeminded science fiends. *Discover* magazine and *Nature Network's* bloggers are interesting and wide ranging. Once you find something you like, check out the "blog roll" or list of blogs the blog author likes, and you are off into unchartered science blogging territory.

You can find links to these blogs at *Chiral Comments*, ASBMB's slowly building blog. This column will appear as a post there, and I invite you to respond in the comments or via email at tekkie@asbmb.org. Do you think blogging could help professors interact with their students or the community? Where do you spend your internet time? N

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# careerinsights

# Insight from an ASBMB Science Policy Fellow

BY ANGELA HVITVED

hen asked to write an article titled "Career Insights," I was hesitant because it sounds like someone looking back over a career and imparting the wisdom gained. Given that I defended my thesis less than a year ago, there's only so much looking back that can be done! Despite that, I have been surprised at how many graduate students I've met who are interested in moving from the lab to science policy, and how much I've learned in just 11 short months. With that in mind, consider this less of a "how I found the perfect job" article and more of a "how I'm looking for the perfect job" article.

It would be misleading to say that I have always known exactly what I wanted to do, but it also hasn't been the result of random chance—I guess you could call it "directed luck." In eighth grade I decided I would be a molecular biologist, the result of a great junior high science teacher and a wonderful, albeit nerdy, summer at molecular biology "camp." In hindsight I had a surprising lack of doubt about this decision and essentially went through college without considering anything else. Granted, I tried a lot of things and ended up with another bachelor's degree in philosophy but, at the time, it was mainly because the classes were fun. However, as graduation neared, my interests in social justice and public policy became significant factors in the decisions I needed to make. Realizing that my love of science had not lessened—I was just piling other interests onto it-I started to think about other options that would combine my interest in science with my desire for

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public service. I couldn't put a name on it at the time, but I thought that the perfect job would be helping policymakers learn about science and the utility of scientific evidence in crafting public policy.

I decided that, regardless of what I ended up doing, I wanted to have a serious scientific background, and graduate school was a must. Looking back, I am surprised by the number of people who questioned my decision to get a Ph.D. with the intention of going into policy. Their arguments, such as the degree wasn't necessary and I was losing time that could be spent gaining policy experience, made sense and weren't meant to discourage me, but there is not a single day that I regret getting my Ph.D. Graduate research is an experience unlike any other, and I doubt I will ever again have the luxury of being paid to learn as much as I can about whatever interests me, and be surrounded by others who are doing the same.

What I did not anticipate in my somewhat "grand plan" was that I would start to culturally identify as a scientist; it was not just a technical training but a way of thinking and being. Additionally, I began to feel as though contributing to humanity's pool of knowledge through research was the noblest pursuit I could have. In fact, I started to feel that leaving research would be more than just a career change, it would be an identity change—and I wasn't convinced I would be as proud of my new one. Unwitting friends and family that asked about my plans during the last year of graduate school were subjected to an angst-ridden explanation of my possible options along



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with the associated fears and anxieties, and possibly a few tears thrown in on a particularly rough day.

Still, I had to acknowledge that throughout college and graduate school I was always involved in student government and various organizations as much I could be while maintaining the semblance of progress in my studies, and I knew I would continue struggling to divide my time between these activities and actually being at the bench. I applied for a few different positions and when the time came to make a decision, I had to give the policy thing a shot. I took a fellowship here at ASBMB and started one week after my thesis defense. It was a big move in many ways, career-wise and geographically, and I had the added pressure of making the decision for



two—the D.C. area was on a very short list of places my significant other could find a suitable postdoctoral position. So I made the switch and went from purifying proteins to attending congressional hearings in the span of a month.

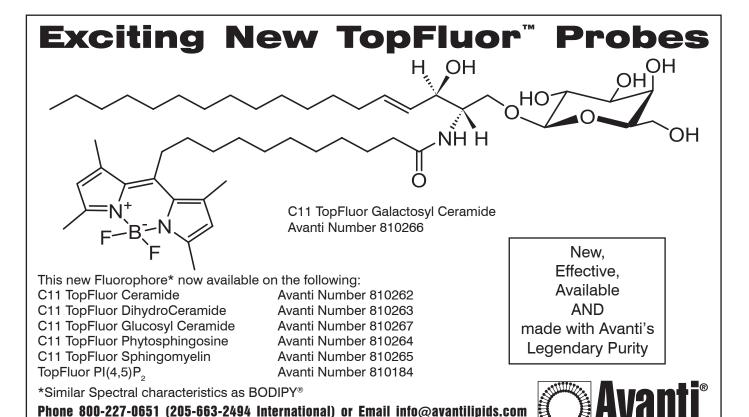
It was an abrupt transition, and some of the most mundane aspects were the most difficult. Sitting in front of a computer all day, alone in an office, felt like torture after years of working with my hands and enjoying the hustle and bustle of a lab. Dry cleaning and ironing (in addition to buying a closet full of "work" clothes) after years of doing just fine in jeans and sneakers seemed downright ridiculous. But the excitement of going to the Hill, learning the nuts and bolts of appropriations, the intricacies of various funding agencies, and so much more made me realize that

no matter what's next, I was gaining invaluable experience that would serve me well, in or out of the lab.

I eventually overcame my resistance to "networking" and learned that, ideally, it just means talking to interesting people about their work, and even got over feeling silly handing out my business card. Moving to D.C., I had imagined a cut-throat atmosphere of insiders who make newcomers prove themselves and fight their way into the circle; what I found was just the opposite. I am continually amazed by the friendliness and helpfulness of the colleagues I meet. Many of them have made decisions similar to mine and are more than happy to share their time and experience. Of course there are times that this close-up view of the political process makes me feel frustrated and cynical, but overall,

I am impressed by the enthusiasm and dedication that so many people have for making the government better serve its people.

It has been almost a year now, and after my ASBMB fellowship ends I will be moving to a fellowship at the National Science Foundation. I have enjoyed my crash course in advocacy and policy, but I am also looking forward to more scientifically oriented work. I am especially interested to see the funding process from inside a federal agency, having spent the past year learning about it from the applicant's perspective. There are still days that I miss the lab, and I know I have yet to find my niche, but I am learning more than I could have imagined 11 short months ago and meeting a lot of wonderful people along the way. W

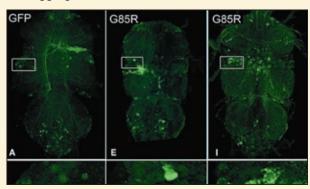


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# biobits asbmb journal science

### **A Fly Model for ALS**

Defects in superoxide dismutase 1 (SOD1) can contribute to amyotrophic lateral sclerosis (ALS), but how this occurs is a bit of a conundrum. Mutant SOD1 is found in all cells, yet the disease manifests only in motor neurons; on the other hand, mouse models have shown that expressing mutant SOD1 only in motor neurons does not trigger ALS. To help address this puzzle, the authors of this paper have developed a *Drosophila* model expressing human SOD1 selectively in motor neurons as a means of hopefully revealing some subtle neuronal defects caused by mutant SOD1. Indeed, they observed that disease-linked mutants induced progressive climbing deficits, which were accompanied by a progressive accumulation of SOD1 in neurons, defective neuronal electrophysiology, and a stress response in surrounding glial cells. The authors did not observe any significant neuron loss, though, suggesting other cells may contribute to this aspect of ALS or it occurs beyond the lifespan of the flies. Such fly models may help researchers address questions of relevance not only to ALS but to other diseases of protein folding and aggregation. W



Accumulation of mutant SOD1 in *Drosophila* neuronal foci at 1 (center) and 28 (right) days as compared with controls (left).

A *Drosophila* model for amyotrophic lateral sclerosis reveals motor neuron damage by human SOD1

Melanie R. Watson, Robert D. Lagow, Kexiang Xu, Bing Zhang, and Nancy M. Bonini

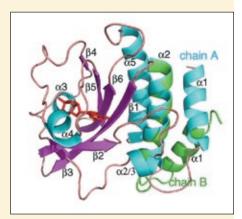
J. Biol. Chem. 2008, **283**, 24972–24981

# A Visually Stimulating Structure

The photoreceptor phosphodiesterase (PDE6) stimulates light detection by regulating the intracellular levels of cyclic GMP in rod and cone photoreceptors. Although the rod isoform of this protein has been well studied, less is known about the cone version, an oversight addressed in this study, in which the authors pres-

ent a 2.6 Å crystal structure of the cGMP-binding domain (GAF A) of chicken cone PDE6. Although the overall tertiary structure of PDE6C GAF A is similar to other cyclic

nucleotide-



Structure of PDE6C GAF A, with  $\alpha$ -helices shown in cyan,  $\beta$ -strands in purple, and loops in tan.

binding GAF domains, there are noticeable differences in the nucleotide contact sites. NMR studies on PDEC6 GAF A also revealed that this domain adopts a significantly altered structural state upon cGMP binding, indicating a conformational change that likely represents the basis of the reciprocal cooperativity between the binding of cGMP and the PDE6 P $\gamma$  inhibitory subunit. These results provide valuable information in understanding the allosteric regulation of both the visual signaling pathway and other GAF-containing proteins.  $\aleph$ 

The structure of the GAF A domain from the phosphodiesterase 6C reveals determinants of cGMP binding, a conserved binding surface, and a large cGMP-dependent conformational change

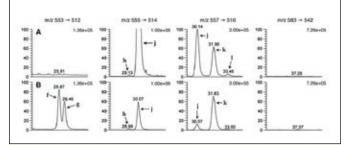
Sergio E. Martinez, Clemens C. Heikaus, Rachel E. Klevit, and Joseph A. Beavo

J. Biol. Chem. 2008, 283, 25913-25919



# **Giving Sterols** a Good Profile

Serum sterol analysis is a useful method to diagnose inherited disorders in cholesterol metabolism and to evaluate cholesterol biosynthesis and absorption in humans. As such, new methods of sterol analysis that combine simplicity, sensitivity, and specificity are continually being explored. In this study, the researchers present an innovative sterol analysis whereby neutral sterols in dried serum are derivatized into picolinyl esters (3β-picolinate), thus allowing reliable analysis using electrospray ionization (ESI) and liquid chromatography-tandem mass spectrometry (LC-ESI-MS/MS). With this approach, the researchers could simultaneously identify cholesterol, 19 cholesterol precursors, cholestanol, campesterol, sitosterol, and sitostanol in human serum samples-at detection limits lower than 1 pg. This LC-ESI method was shown to be both rapid and reproducible, which will greatly simplify the task of evaluating cholesterol biosynthesis and adsorption in a variety of experimental conditions, including cases where the sample blood volumes are small. N



Comparison of serum chromatograms obtained from a normal volunteer (A) and patient with Smith-Lemli-Opitz syndrome (SLOS) (B).

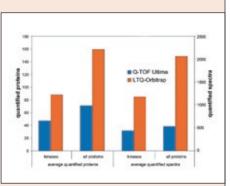
### Highly sensitive analysis of sterol profiles in human serum by LC-ESI-MS/MS

Akira Honda, Kouwa Yamashita, Hiroshi Miyazaki, Mutsumi Shirai, Tadashi Ikegami, Guorong Xu, Mitsuteru Numazawa, Takashi Hara, and Yasushi Matsuzaki

J. Lipid Res. 2008 49, 2063-2073

# Practical Isobaric Labeling

Isobaric
Iabeling techniques such
as iTRAQ
(isobaric tags
for relative
and absolute
quantification)
enable multiplex peptide
quantification
via reporter
ion signals;



Comparison of protein quantification using PQD on an LTQ-Orbitrap or CID on a QTOF Ultima.

as iTRAQ allows for as many as eight separate mass labels, it is an advancement over metabolic labeling (heavy isotopes) that only allows for 2 to 3 labels. Until recently, though, the poor recovery of low mass fragments observed in tandem mass spectra acquired on ion trap mass spectrometers precluded the use of iTRAQ on this widely available platform, and although a technique called Pulsed Q Dissociation (PQD) can overcome this limitation, it suffers from poor fragmentation efficiency. In this study, the authors show that careful optimization of certain instrument parameters (such as collision energy, delay time, and ion isolation width) can generate low m/z fragment ion intensities that enable accurate peptide quantification at low levels. They also demonstrate the significant analytical potential of iTRAQ quantification using PQD on an LTQ-Orbitrap spectrometer by measuring the kinase interaction profile of the small molecule drug Imatinib in K562 cells. N

# Robust and sensitive iTRAQ quantification on an LTQ-Orbitrap mass spectrometer

Marcus Bantscheff, Markus Boesche, Dirk Eberhard, Toby Matthieson, Gavain Sweetman, and Bernhard Kuster

Mol. Cell. Proteomics 2008 7, 1702-1713



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# science focus

# Michael Yaffe: Phospho-Signaling Modules and Networks

BY NICK ZAGORSKI

cientific epiphanies can arrive in many forms. For Michael Yaffe, the Howard S. and Linda B. Stern Associate Professor of Biology at the Massachusetts Institute of Technology (MIT), his inspiration to study biological signal transduction came from his days as a fellow in the surgical trauma unit at Harvard Medical School. "I started noticing that we would be performing the exact same procedures on critically ill patients but ended up getting vastly different outcomes. I began to realize that the details of the operation weren't the critical component, it was the substrate-in this case the state of the signaling networks within the patient's body prior to the procedure."

More specifically, Yaffe notes it's the patient's signaling pathways that

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define how their body responds to the stimuli produced during the operation, whether the anesthetic gas or the cut of a scalpel's blade. And thus a fascination with physiological signaling was born.

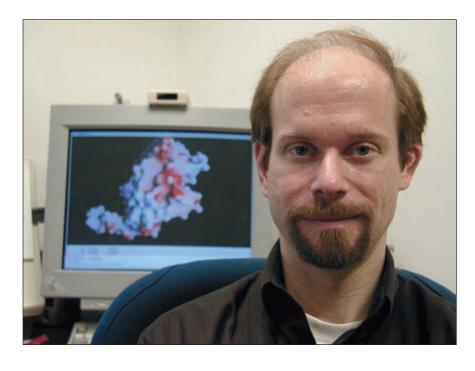
Many of Yaffe's contributions in this area have involved phosphodependent signaling modules. These small (typically 50-200 amino acids) peptides recognize and attach to specific phosphorylated sequences on target proteins, producing multi-subunit complexes that can produce different signaling outcomes depending on their composition. Over the past two decades, such work on modular signaling has reshaped the classical view of signaling cascades that neatly proceed from receptor to intermediates to substrate.

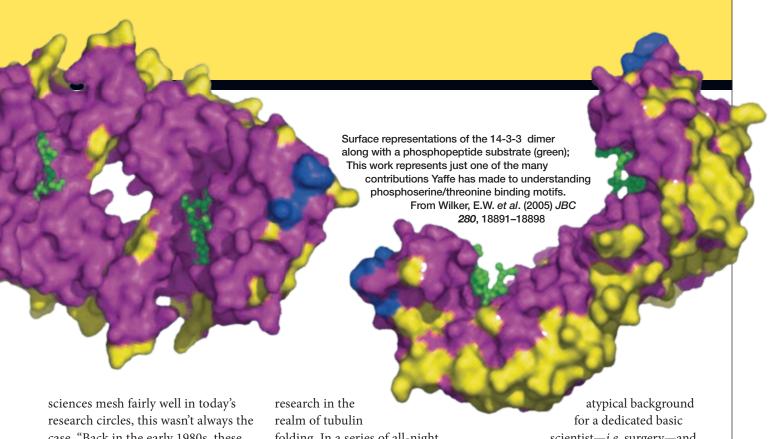
### A Material Boy

Science, in some form, has been a part of Yaffe's life since his childhood days in Baltimore, Maryland. Some of his earliest memories involve playing with his first chemistry set or sneaking down to the basement to watch his father, an engineer by trade, tinker with racks and racks of electrical equipment. He also received a good deal of positive influence from his family and educators (like a 9th grade science teacher who first encouraged Yaffe to carry out some simple physics experiments independently, and his biochemistry teacher who taught a watered-down version of Lehninger's textbook to high school seniors) to help keep those early interests in his mind.

In 1977, Yaffe went on to his undergraduate studies at Cornell University to get a degree in materials science and engineering. Initially, he thought he would specialize in organic chemistry, but over time he became more interested in physics, physical chemistry, and materials science. "It was probably a combination of being exposed to engineering at an early age and my love of mathematics that drew me into these quantitative fields," he says. Still, biochemistry was always creeping around in my head, and when I graduated I decided to follow a path where I could apply physics and math to biological questions."

As Yaffe moved on to Case Western Reserve University for an M.D/ Ph.D. program, he began to realize this wouldn't be an easy proposition. Although biological and physical





sciences mesh fairly well in today's research circles, this wasn't always the case. "Back in the early 1980s, these two disciplines were not as integrated as they are today." Therefore, he found it difficult to pursue his original research plan of studying growth factors as he couldn't find researchers who wanted to look at these biological molecules quantitatively.

Yaffe did find a more quantitative field in tubulin research, though. "These were some very hard-core scientists with strong backgrounds in chemistry and physics," he says. "Carefully measuring the rates of association and hydrolysis, calculating the kinetics of microtubule assembly; this was the kind of work that helped ease me into thinking about biology." So, he joined the lab of Himan Sternlicht and began examining the chemical and physical properties of individual tubulin subunits that promoted microtubule formation.

A few years later, during a break from his surgical residency, Yaffe returned to Case Western to conduct some postdoctoral research with Richard Eckert. On the weekends he also returned to the Sternlicht lab, where he still puzzled over some unresolved issues from his Ph.D. folding. In a series of all-night experiments he made the surprising observation that newly translated tubulin subunits seem to appear first in very high molecular weight complexes, from which they were released in an ATP-dependent manner. Ultimately, with the help of some of his old colleagues in Sternlicht's lab, he demonstrated that a protein called the TCP1 complex acted as a chaperone in folding tubulin. "TCP1 is the eukaryotic cytoplasmic homolog of mitochondrial Hsp60 (heat shock protein 60), and ultimately proved to be critical for folding tubulin, actin, and a variety of other cytoplasmic targets".

### From TCP to 14-3-3

After finishing his surgical residency and a fellowship in trauma and critical care at Harvard Medical School, Yaffe set out to do another postdoc with Harvard Professor Lewis Cantley, who worked on signaling pathways as they related to growth factors, molecules that Yaffe had been interested in working with previously. "I was very fortunate that Cantley took a chance on me, since I came from a rather

for a dedicated basic scientist—i.e. surgery—and had essentially no experience working on signaling. Maybe Lew agreed to take me on as a form of amusement," Yaffe says jokingly.

In a similar vein to his TCP1 research, Yaffe had heard about work from Joan Brugge's group that linked another chaperone, Hsp90, with the Src family of tyrosine kinases; and that led him to the idea, now well accepted but novel at the time, that Hsp90 might be a general kinase chaperone in signal transduction. He began looking at the interaction of Hsp90 (which was less understood than other Hsps at the time) and Raf, a kinase that was part of the Ras signaling pathway, as other studies had suggested that Hsp90 and Raf form a stable complex.

That work quickly took on a new purpose, however. "I would usually get some Hsp90 when I pulled out Raf from cells," Yaffe says, "but I also would get a whole lot of 14-3-3 protein (the nomenclature derives from the protein's position on separating gels)." What was particularly intriguing, though, was that the 14-3-3 protein only appeared to form a complex

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when Raf was phosphorylated on specific serine residues.

Using insights from Andrey Shaw's lab, and extending a peptide library screening approach that Cantley had pioneered, Yaffe went on to identify the specific amino acid sequences that mediated phosphoserine-dependent binding of proteins to 14-3-3, and working with scientists at the National Institute of Medical Research in London, Yaffe helped solve the crystal structure of the 14-3-3 zeta protein (one of the seven related 14-3-3 isoforms) complexed to a phospho-

evolved with multicellular development, while serine/threonine kinases and phosphoserine/threonine binding domains have been around since the dawn of eukaryotic life. They're far more ancient, yet their role in signaling is the more recent discovery."

### Kinase Networking

Upon completing his postdoc with Cantley, Yaffe remained at Harvard for a couple of years as an instructor of Surgery and Medicine before starting up his own lab in 2000 at nearby MIT. "MIT is a great school for techThese two domains highlight the general theme of serine/threonine binding modules, in that they regulate signaling involved in cell cycle control and DNA damage and repair. So, much like phosphotyrosine modules, which regulate cell growth and proliferation, these domains are deeply linked with cancer. "And one of our main goals is trying to develop small molecule inhibitors of these binding modules, and we have achieved some limited success in using these types of reagents to interfere with cell division."

# Yaffe's studies, together with those from Andrey Shaw's lab at Washington University in St. Louis, had turned the signaling world on its head.

serine-containing peptide, providing a molecular basis for 14-3-3 function.

Now, researchers had known that some proteins contained domains (like Src homology 2 domain and PTB domains) that recognized and bound to phosphorylated tyrosines to form multimolecular signaling complexes. But most everyone believed serine/threonine modifications (far more abundant than tyrosine) simply induced conformational changes or created some allosteric interference, rather than directly causing proteinprotein interactions through the phosphorylation site. Yaffe's studies, together with those from Andrey Shaw's lab at Washington University in St. Louis, had turned the signaling world on its head.

"It's kind of ironic," Yaffe notes. "Tyrosine kinases and phosphotyrosine binding domains generally

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nology, with exceptional students and colleagues, and it was a perfect place where I could draw upon my interests in math, engineering, and physical chemistry to study biology," he says. "For me, it was an ideal fit because, basically, I'm pretty geeky."

This science geek has been hard at work, however, characterizing phosphoserine/threonine binding domains and the peptide modules that dock with them. Using a variety of approaches—including peptide screening assays, structural biology, proteomics, and computational modeling—he has provided more details into the function of 14-3-3 proteins and uncovered additional modular signaling domains like Polobox domains that help control cell division and BRCT (BRCA1 carboxyterminal) repeats that are involved in DNA damage responses.

Although detailed studies on individual modules or pathways will produce some valuable data, Yaffe also understands they won't yield a complete picture. "I think to better appreciate how biological systems communicate information, we really need to know not just how

one or two particular kinases that control these pathways work, but how many kinases and phospho-binding domains work together," Yaffe says. Therefore, Yaffe has begun looking at signaling at the "network" level to try and find the connections between these many inter-related pathways. He and his MIT and Harvard colleagues Doug Lauffenburger, Peter Sorger, and Leona Samson have taken a moderate throughput approach to this networking problem, analyzing the kinase activity and cell response of between 5 and 10 different pathways (MAPK, NFκB, Akt, etc.) at once, in processes such as cytokinemediated apoptosis and the DNA damage response.

Such studies have produced quite a few insights into the adaptable nature of cell signaling, as well as some promising new therapeutic targets.

"During one of our studies looking at where information was flowing following DNA damage, our lab made an unusual observation regarding the responses of normal versus tumor cells," he says. "We found that a pathway usually involved in inflammation, working through the kinase MAP-KAP-K2 was critical for cancer cells, but not normal cells, to survive after DNA damage." The reason behind this difference was a change in p53 status. The p53 protein was mutated in the cancer cells, thus removing an important signaling node; however, the cells rewired their network and gave themselves new control points by essentially hijacking a pathway typically used for other things.

And naturally, Yaffe is always on the lookout for new types of signaling modules. Current research has uncovered seven distinct classes of phosphoserine/threonine binding domains (14-3-3, Polo-box, BRCT, WW, FHA, Rab, and WD-40), though Yaffe believes the total number might be double or even triple that. It will probably take a good deal of perseverance to find these other domains, but fortunately, that's just the kind of researcher Yaffe is. "I think most of my success is due to

### **Out of Focus:**

### **A Training Ground for Gold Medal Biochemistry**

Baltimore may currently be known as a breeding ground for world class Olympic swimmers, but it also boasts a bevy of scientific talent, in no small part due to the efforts of Yaffe's high school biochemistry teacher Ms. Mazur. "She seemed committed to turning a whole lot of us into budding biochemists. She taught college level biochemistry to high school seniors, and probably shaped a lot of careers in the process. It definitely made me want to incorporate biochemistry into my future research plans, even as I set off to study engineering" Yaffe says. And he's not alone; several noted scientists, it seems, have graced Mazur's classroom. "It isn't uncommon at all to meet other researchers at conferences and find out that we all went to the same high school and took Mazur's course," says Yaffe. "Inevitably as we start talking they'll mention her class as a major inspiration. It shows the profound influence a teacher can have on her students. In the grand scheme of things, she probably made a bigger impact on biological science than any single person could have made from working directly at the bench."

my tenaciousness, rather than to any particularly brilliant insights. I tend to not let go of scientific problems that bother me." N

Nick Zagorski is a science writer for ASBMB. He can be reached at nzagorski@asbmb.org.

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BETHESDA, MD www.mitochondrial2008.com E-mail: jennifer@strategicresults.com Tel.: 443-451-7254

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www.symporg.com/conferences/2008/
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Institute for Medical Research
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www.biophysics.org/discussions/2008%20 Meeting%20Program.htm

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NOVEMBER 6-7, 2008 SAN FRANCISCO, CA www.asms.org/Default.aspx?tabid=58

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www.grc.org/programs.aspx?year=2009 &program=plantlipid

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### PLA 3rd Annual Scientific Forum

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**APRIL 22-27, 2009** 

OLYMPIC VALLEY, CA

www.keystonesymposia.org/Meetings/ ViewMeetings.cfm?MeetingID=961

#### 2009 NLA Scientific Sessions

**APRIL 30-MAY 3, 2009** 

MIAMI, FL

www.lipid.org

### **MAY 2009**

### **57th ASMS Conference** on Mass Spectrometry

MAY 31-JUNE 4, 2009

PHILADELPHIA, PA

www.asms.org

E-mail: office@asms.org

Tel.: 505-989-4517

### **JUNE 2009**

### VIII European Symposium of the Protein Society

**JUNE 7-11, 2009** 

ZURICH, SWITZERLAND Organizer: Andreas Plückthun (University of Zurich)

www.proteinsociety.org

### 21st American Peptide Society Symposium

JUNE 7-12, 2009 BLOOMINGTON, IN www.21staps.org

### 3rd EuPA Meeting— Clinical Proteomics

JUNE 14-17, 2009

STOCKHOLM, SWEDEN

www.lakemedelsakademin.se/templates/ LMAstandard.aspx?id=2529

#### XV International Symposium on Atherosclerosis

JUNE 14–18, 2009 BOSTON, MA www.isa2009.org

### **JULY 2009**

### 23rd Annual Symposium of the Protein Society

JULY 25-29, 2009

BOSTON, MA

www.proteinsociety.org

### **APRIL 2010**

#### **ASBMB Annual Meeting**

**APRIL 24–28, 2010** 

NEW ORLEANS, LA www.asbmb.org/meetings.aspx

### **AUGUST 2010**

### 14th International Congress of Immunology

AUGUST 22-27, 2010 KOBE, JAPAN www.ici2010.org









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Early Registration Deadline: February 9, 2009

April 18–22, 2009

www.asbmb.org/annualmeeting.aspx

