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January 2009

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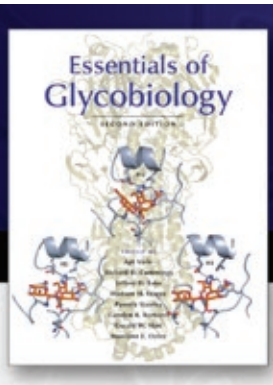
American Society for Biochemistry and Molecular Biology



ESSENTIALS OF GLYCOBIOLOGY

SECOND EDITION

Edited by Ajit Varki, *University of California, San Diego,* Richard D. Cummings, *Emory University School of Medicine, Atlanta,* Jeffrey D. Esko, *University of California, San Diego,* Hudson H. Freeze, *Burnham Institute for Medical Research, La Jolla,* Pamela Stanley, *Albert Einstein College of Medicine of Yeshiva University, New York,* Carolyn R. Bertozzi, *University of California, Berkeley,* Gerald W. Hart, *Johns Hopkins University of School of Medicine, Baltimore,* and Marilynn E. Etzler, *University of California, Davis*

The sugar chains of cells—known collectively as glycans—play a variety of impressive, critical, and often surprising roles in biological systems. Glycobiology is the study of the roles of glycans in the growth and development, function, and survival of an organism. Glyco-related processes, described in vivid detail in the text, have become increasingly significant in many areas of basic research as well as biomedicine and biotechnology.

This new edition of *Essentials of Glycobiology* covers the general principles and describes the structure and biosynthesis, diversity, and function of glycans and their relevance to both normal physiologic processes and human disease. Several new chapters present significant advances that have occurred since the publication of the first edition. Three sections of note describe organismal diversity, advances in our understanding of disease states and related therapeutic applications, and the genomic view of glycobiology. "Glycomics," analogous to genomics and proteomics, is the systematic study of all glycan structures of a given cell type or organism and paves the way for a more thorough understanding of the functions of these ubiquitous molecules.

The first edition of *Essentials of Glycobiology* represented also a notable experiment in publishing, as it became one of the first electronic textbooks. And, now, in recognition of its wide audience and the changing ways in which researchers and students learn and access information, the new edition of *Essentials* will be made available online simultaneously with the print edition. This novel experiment is the result of the collaborative efforts of the Cold Spring Harbor Laboratory Press, the National Center for Biotechnology Information, and the editors of the book. Written and edited by glycobiologists with experience in teaching and in research, this volume will be an invaluable resource, both for students and for established investigators in fields such as developmental biology, cell biology, neuroscience, immunology, and biochemistry who require a complete yet concise introduction to this burgeoning field.

Published in October 2008, 784 pp., illus., glossary, study guide, index
Hardcover $158 **ISBN 978-087969770-9**

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Advance praise for the Second Edition:

"The basic principles of glycobiology are clearly articulated in this volume, and the roles of complex carbohydrates in disease are an important read for all biomedical scientists." —*Peter Agre, M.D., Nobel Laureate in Chemistry, 2003*

"*Essentials of Glycobiology* is a major resource for understanding these post-translational biochemical reactions that affect the function and fate of proteins produced by the genes that are profoundly changed by their added sugars." —*Baruch S. Blumberg, Nobel Laureate in Medicine, 1976*

"The second edition of *Essentials of Glycobiology*, superbly printed and illustrated, develops in simple and absolutely precise terms the complicated intricacies of glycobiology. I would have killed to get this encyclopedic treatise 40 years ago when I was working my way through this field." —*Edmond H. Fischer, Nobel Laureate in Medicine, 1992*

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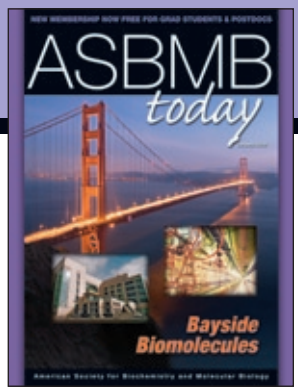

JANUARY 2009

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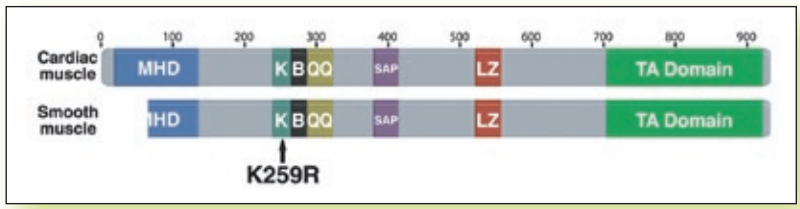

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Download the January *Journal of Biological Chemistry* News podcast to hear *JBC* Deputy Editor Robert Simoni interview a Paper of the Week author.

This and other podcasts are available at: www.asbmb.org/Interactive.aspx.

ASBMB today

A monthly publication of
The American Society for
Biochemistry and Molecular Biology

from the **editor**

2009 Rings Golden for the *Journal of Lipid Research*

BY MARY L. CHANG

The inaugural issue of the *Journal of Lipid Research* (*JLR*) debuted in October 1959. In that edition, the Journal's first editor-in-chief, Donald B. Zilversmit, announced, "[*JLR*] will offer to its readers a representative selection of original work in the chemistry, biochemistry, enzymology, histochemistry, and physiology of the lipids." Initially intended as a quarterly publication, it quickly expanded to six issues a year in 1966, eight issues in 1978, nine issues in 1982, and finally became a monthly journal in 1983. Fifty years later, *JLR* is still going strong and is the most cited journal in lipid research. In 2009, the Journal will be celebrating its 50th anniversary with several exciting events throughout the year.

A special issue of about 70 short, forward-looking reviews covering the entire breadth of lipid research will be published as a supplement to the April 2009 issue. The special issue will be divided into nine sections, including Enzymology, Metabolism, Lipoprotein Metabolism, Oxidized Lipids, Signaling, Receptors, Membranes and Lipid Domains, Atherogenesis, and Lipids in Health and Disease. The best lipid researchers were invited to participate in this special anniversary project, so this issue will be a useful and informative reference for all in the field, and the reviews are expected to be highly cited for years to come.

The golden celebration continues in April at the 2009 ASBMB Annual Meeting in New Orleans. On Saturday, Apr. 18, from 8 AM to 1 PM, the LIPID MAPS Consortium (www.lipidmaps.org) will conduct an open Lipidomics Workshop, where experts in the field will discuss methods that have been developed under NIH (National Institute of General Medical Sciences (NIGMS)) Glue Grant U54 GM069338 for analysis of neutral glycerolipids, phospholipids, eicosanoids, sterols, sphingolipids, prenols, and novel lipids by mass spectrometry as well as related issues such as sample extraction, internal standards, data handling and display, and nomenclature. Attendance is free (registration for FASEB Experimental Biology is not required), but those interested in attending are encouraged to contact Workshop Chair Al Merrill, Jr. by email at al.merrill@biology.gatech.edu (please use the subject heading "Lipidomics workshop" in your email). The workshop is being presented under the auspices of ASBMB with funding from the LIPID MAPS Glue grant and Avanti Polar Lipids.

Lipid Signaling and Metabolism Meeting

Organizers: Suzanne Scarlata, Stony Brook University and Russell A. DeBose-Boyd, Univ. of Texas Southwestern Medical Center

Role of Membrane Domains in Cell Signaling

SUNDAY, APR. 19
9:55 AM - 12:15 PM

Suzanne Scarlata, *Stony Brook University*
Regulation of G protein Signals by Membrane Domains

Michael Sheetz, *Columbia University*
Membrane-Cytoskeleton Adhesion; Mechanical Controls and PIP2 Dynamics

Sergio Grinstein, *the Hospital for Sick Children*
Lipids Dictate Surface Charge and Direct Signaling During Phagocytosis

Advances in Lipid Metabolism: A Golden (50th) Anniversary Celebration for the *Journal of Lipid Research*

SUNDAY, APR. 19
3:30 PM - 5:50 PM

Edward A. Dennis
Introduction

Michael S. Brown and Joseph L. Goldstein, *Univ. of Texas Southwestern Medical Center*
Cholesterol Feedback: A Tale of Two Membrane Proteins and Two Sterol Sensors

Jeffrey Gordon, *Washington University*
The Human Microbiome Project: Exploring the Microbial Side of Ourselves

Nobuyo Maeda, *University of North Carolina*
Genetic Variations in Atherosclerosis: "Humans to Mice" and "Mice to Humans"

Avanti Award in Lipids

SUNDAY, APR. 19
2:10 – 3:10 PM

Sarah Spiegel, *Virginia Commonwealth University School of Medicine*
The Outs and the Ins of the Pleiotropic Lipid Mediator Sphingosine-1-Phosphate

Novel Lipid-Mediated Signaling Events

MONDAY, APR. 20
3:30 PM - 5:50 PM

Russell A. DeBose-Boyd, *University of Texas Southwestern Medical Center*
Sterol-Accelerated Ubiquitination and Degradation of HMG CoA Reductase

Jerold Chun, *The Scripps Research Institute*
New Insights from Lysophospholipid Receptor-Null Mice

Susan A. Henry, *Cornell University*
The Role of Phospholipid Synthesis in Lipid-Mediated Signaling and Regulation in Yeast

Thematic Meeting Reception for Lipid Signaling and Metabolism

MONDAY, APR. 20
5:50 PM - 6:30 PM

Phosphatidylinositol Signaling and Metabolism

TUESDAY, APR. 21
9:55 AM - 12:15 PM

Shamshad Cockcroft, *University College London*
Coordination of Vesicle Delivery and Signaling by Phosphatidylinositol Transfer Proteins

Bertil Hille, *University of Washington School of Medicine*
Dynamics of PIP2 Regulation of Kv7 (KCNQ)K Channels

Peter N. Devreotes, *Johns Hopkins University School of Medicine*
Signaling Networks in Chemotaxis and Cytokinesis

Mechanisms for Lipid Storage and Transport

WEDNESDAY, APR. 22
12:50 PM - 3:10 PM

Karen Reue, *David Geffen School of Medicine at UCLA*
The Role of Lipin Proteins in Lipid Storage and Metabolism

Dawn Brasaemle, *Rutgers University*
Control of Triacylglycerol Metabolism by Lipid Droplet Proteins

John M. Dietschy, *University of Texas Southwestern Medical Center*
Mutations in NPC1 and Cholesterol Metabolism in the Brain

In addition to the Lipid Signaling and Metabolism Meeting at the Annual Meeting (see sidebar), there will be a special *JLR* symposium entitled, "Advances in Lipid Metabolism: A Golden (50th) Anniversary Celebration for the *Journal of Lipid Research*" from 3:30 to 5:50 PM on Sunday, Apr. 19th. The invited speakers for this session will be Michael S. Brown and Joseph L. Goldstein of the University of Texas Southwestern Medical Center, Jeffrey Gordon of Washington University, and Nobuyo Maeda of the University of North Carolina-Chapel Hill. The session will be chaired by *JLR* Associate Editor Stephen G. Young of University of California, Los Angeles, and will be introduced by *JLR* Editor-in-Chief Edward A. Dennis of the University of California, San Diego. All are welcome to attend. The meeting will also feature a lecture by Avanti Award in Lipids winner Sarah Spiegel, on Sunday, Apr. 19 at 2:10 PM. More details on Spiegel and the award lecture can be found on p. 17 of this issue of *ASBMB Today.*

And finally, the Journal will also be sponsoring eight special lectureships at lipid-related meetings in 2009. Details can be found in the accompanying table (see box).

Mary L. Chang is managing editor of *JLR.* She can be reached at mchang@asbmb.org.

JLR-sponsored Lectureships

Benjamin F. Cravatt, *The Scripps Research Institute*
Deuel Lipid Conference
BORREGO SPRINGS, CA
MAR. 3–6, 2009

Takao Shimizu, *University of Tokyo*
Keystone Symposium: Complex Lipids in Biology
OLYMPIC VALLEY, CA
APR. 22–27, 2009

Jay D. Horton, *UT-Southwestern Medical Center, Dallas*
Arteriosclerosis, Thrombosis, and Vascular Biology Annual Conference
WASHINGTON, D.C.
APR. 29–MAY 1, 2009

Stanley L. Hazen, *Cleveland Clinic*
Atherosclerosis Gordon Conference
TILTON, NH
JUN. 21–26, 2009

Karen Reue, *University of California, Los Angeles*
Gordon Conference: Molecular & Cellular Biology of Lipids
WATERVILLE VALLEY, NH
JUL. 19–24, 2009

Gerrit van Meer, *University of Utrecht*
FASEB Conference of Protein Lipidation, Signaling, and Membrane Domains
SAXTONS RIVER, VT
JUL. 26–31, 2009

Christopher K. Glass, *University of California, San Diego*
Kern Aspen Lipid Conference
ASPEN, CO
AUG. 22–25, 2009

Joseph L. Witztum, *University of California, San Diego*
Bioactive Lipids in Cancer, Inflammation, and Related Diseases
CANCUN, MEXICO
OCT. 25–28, 2009

The Gift That Keeps On Giving

BY GREG PETSKO

Kris Kringle
C/O Toy Shop
The North Pole

Dear Santa,

Sorry this is a bit late this year; there's been quite a lot going on, as I'm sure you know. If you've read the letters we've been getting at ASBMB Today, you've seen that there are some people who would claim that I haven't been a very good boy this year, but since you have a great sense of humor (that whole "right jolly old elf" thing), I'm hoping you won't be as hard on me as they are. Besides, being elected president of the ASBMB was enough of a lump of coal for anybody's stocking.

So let's get right to it: my gift list. As usual, I'll start by telling you what I'd like you to bring to some other people, and then I'll let you know what I'm hoping to find under my tree on December 25th.

For President-elect Barack Obama: a better economy, quickly, so that he can implement some of his important objectives, including doubling funding for scientific research, across the board, over a ten-year period.

For new Health and Human Services Secretary Tom Daschle: a terrific director of the NIH, so he can concentrate on health care reform and leave the science to scientists.

For the scientific community: a presidential science advisor with stature and vision, and, ideally, cabinet-rank.

For the ASBMB staff: stockings filled with all the things they wish for, and one thing they probably didn't, but will have anyway, namely, my deep gratitude for putting up with me and for jobs well done.

For Sarah Palin: a long and happy life—in Alaska. If you can't manage that, Santa, then please, for all our sakes, give her the ability to put subject, verb, and object together in a sentence in the appropriate order, and, if you're feeling generous, the ability to string two sentences together that actually make sense.

For all my local friends and neighbors: another shot at the Super Bowl for the New England Patriots (and for those of you out there who feel differently, well, when you write your own letters to Santa, you can ask for something for your own team).

And now for my list. You'll be surprised, I know, Santa, to learn that I have only one wish this year. Before I tell you what it is, let me explain where it came from. We did a survey recently of our membership here at the ASBMB, and for the most part, it was very gratifying. We learned that members in general are pretty satisfied with the benefits of belonging to the Society: they love the *Journal of Biological Chemistry*, despite the fact that each issue is starting to resemble the Manhattan phone directory in size, and they enjoy the chance to go to our meetings. Some of them even professed to really like *ASBMB Today*.

We also found out that people who join the Society usually remain members for their whole career and even beyond. That suggests we're doing a number of things right, because once someone becomes a member, they find it worthwhile to continue being one. We don't lose too many people.

In addition, we were surprised, and delighted, to find out that our international membership is growing rapidly—faster, in fact, than our American rolls. That means, of course, that we need to

examine what we do in that light and make sure that we deliver benefits to foreign members too, and we will. It may even mean that some day we might want to consider changing our name to reflect our global reach, but that's another topic for another day.

But there was one thing that we learned from our survey that wasn't so good, and it's the reason for my wish this year. We learned that our membership is top-heavy: we have a lot more senior scientists than junior ones, a lot more people around my age than the age of the people who work in my lab. If we really want to represent biochemistry and molecular biology properly, we need input from all age groups, which means we need more young members. That's what I want in my stocking this year.

Of course, I realize that's a pretty tall order for you to fill, what with delivering all those toys and all, and I'm not sure that a couple thousand young scientists would fit on your sled, either. So I reckon you're going to need some help, and I've got an idea where it could come from: our existing members.

If each current member of the ASBMB who has an active research group would, during this coming year, nominate at least one young person in their group for membership, I bet we would get all the new young members that I'm wishing for. To make it easier for them to do that, we here at the Society have included an application form in this issue of *ASBMB Today* so that in just a few minutes, a member can sponsor a graduate student or postdoctoral fellow for membership, and we will do the rest.

Now, Santa, I also realize that you may be worried that, with the economy in such bad shape, it's not exactly trivial to expect a young person to spend his or her own money on membership dues, even with the deep discount we give to people who don't have an independent position yet. We're worried about that too, and we have an idea that may help: we're going to make membership in the ASBMB dues-free for the first year for any graduate student or postdoctoral fellow who joins as the result of being nominated by a member through our new young-membership drive.

Frankly, Santa, this isn't our only membership wish; we'd also love to see more industrial members—the Society is weighted rather heavily towards academic biochemists, and that probably doesn't reflect the occupational distribution in our science any more. But since, as you've seen, people who join the ASBMB usually remain in it, I think if we get a big influx of young members, we'll also solve that problem, because a large number of young biochemists now go into industry (typically biotech and pharma), so if they are already members when they do, our industrial membership ranks will grow.

I hope you'll use your powers to persuade our members to help you fulfill my wish this holiday season. Starting in January 2009, we'd like for each of them to nominate at least one person from their lab for membership—and teachers could do the same, of course, for one or more of their best students. Then, it will be up to us to make sure that the services and benefits we deliver will meet the needs of this bolus of young biochemists. But since we will have lots of them to tell us what they want and to help us establish a community of scholars in which they feel comfortable and have their needs looked after, I'm confident we will learn how to serve them well.

That's pretty much it for this year, Santa. The milk and cookies will be in their usual place by the tree, and I'll make sure the dogs expect you, so there won't be a repetition of that unfortunate incident of a few years ago. Oh, and one more thing: if you could park the reindeer on the lawn this time, instead of landing on the roof, I'd sure appreciate it. Those prancing and pawing little hooves really tore up the shingles. Thanks for listening.

Your friend,

Gregory A. Petsko

The Elections: and the Winner Is… Science?

BY JENNIFER ZEITZER

The Society for Neuroscience recently hosted a special forum to discuss the impact of the 2008 election on science issues. A condensed summary of the event appears below.

John Morrison, chair of the SfN Government and Public Affairs Committee began the briefing by mentioning that science brings us not only new knowledge and new treatments, but also additional jobs. He also referenced former House Speaker Newt Gingrich's advocacy on behalf of increased funding for science and noted that all scientists have a responsibility to become advocates due to their unique ability to explain how science improves lives. He announced that SfN will build a grassroots advocates network over the next several years, sponsor Capitol Hill lobby days, and provide resources for scientists to host lab tours for members of Congress.

Katrina Kelner, deputy editor, Life Sciences, at *Science* magazine summarized the outcome of the Congressional elections, noting that the Democrats will control the House of Representatives 255-174 after gaining 22 seats. Democrats also picked up six Senate seats and will control the chamber 57-40[1]. Kelner mentioned that there is a sense of optimism about the new administration's commitment to science, despite the uncertain funding situation created by the current financial crisis.

Former NIH director Harold Varmus was the first panel speaker and provided various perspectives on where science funding issues will land on the 111th Congress' agenda, and what the research advocacy community can do to ensure that science funding is a top priority for the Obama administration. He noted that the current situation is very similar to the environment in 1993, when he was confirmed as NIH director. Then, as now, the scientific community was demoralized due to low grant success rates, a rising budget deficit, a lack of enthusiasm for NIH in Congress and animosity toward the intramural program, and the fact that several NIH-funded scientists were facing charges of misconduct.

However, a combination of advocacy by the scientific community and the efforts of former Congressman John Porter made the case for a long range investment in science which eventually led to the doubling of NIH's budget over five years. He mentioned the lack of significant funding increases for NIH over the last six years, warning that a failure to make sustained investments in science is a threat to America's competitiveness. He also said that insufficient funding for NIH is beginning to dismantle the multi-disciplinary teams of scientists that were one of the hallmarks of the doubling. Varmus encouraged all scientists to make an effort to educate their elected officials and the general public about the value of science and the need for steady, predictable increases in federal funding for science agencies. He advocated for a doubling of NIH's budget over ten years, which represents the typical growth pattern for NIH over history. He urged advocates to emphasize that investing in science stimulates the economy through the creation of jobs and purchases of lab equipment and supplies.

Kelner mentioned that there is a sense of optimism about the new administration's commitment to science,

Wendell Primus, senior policy advisor to Speaker Nancy Pelosi, mentioned that Pelosi is an enthusiastic supporter of science funding. He predicted that Congress would not pass a second economic stimulus bill until early 2009. Furthermore, Primus noted that the Congressional Budget Office will release a new budget estimate in mid-January that will project a $7 to $9 trillion budget

deficit. He urged advocates to make the case that investments in science have a long term payoff and pointed out that more emphasis should be placed on translating research findings into clinical practice. Other national priorities, Primus commented, such as the economic crisis, energy independence, and homeland security will impact funding for science.

Primus also gave an overview of the anticipated legislative agenda for next year. The first bill introduced by the House Democratic leadership will focus on economic recovery. The House will then resume debate on the Fiscal Year 2009 appropriations bills. He predicted that funding for NIH, CDC, and other public health agencies will be increased but would not speculate about specific funding levels. Instead, Primus indicated that the House will probably "multi-task" on other issues, including improving the nation's infrastructure, promoting energy independence, and initiating health care reform. Next year, Primus noted, controversial issues such as comparative effectiveness and health care payment reform would likely be under debate.

despite the uncertain funding situation created by the current financial crisis.

Former Congressman John Porter described the last six years as a "disaster" for science funding and noted that change will not happen unless the entire scientific community gets involved in advocacy. He offered several suggestions for steps the community can take to ensure that science issues are a high priority for the Obama administration:

- **Watch for how quickly Obama names a science advisor and if it is a cabinet-level position with an office in the Old Executive Office Building.**
- **Listen to President Obama's first State of the Union address which should note that a sustained investment in basic and translational research drives the U.S. economic engine.**
- **Look for a strong commitment to sustained science funding in the first Obama budget. Porter recommended a three percent plus biomedical research inflation increase for NIH annually over the next five years.**

Additionally, Porter encouraged the biomedical and physical science communities to coordinate advocacy efforts to ensure the consistency of their message. He urged scientists to explain how scientific advances benefit members of Congress' constituents and what role local research facilities play in advancing research breakthroughs, reminding the audience that the science community has a good opportunity to affect change because Obama "believes in science." He also noted that scientist advocates must impact not only policymakers but also the general public in order to inspire individuals to take action.

Several additional points were made during a question and answer session following the panel presentation:

- **Funding to train young scientists is critically important. Some believe that doubling NIH's budget was a mistake because it advanced the careers of older scientists without helping younger investigators. The doubling was not the problem, however; the problem was the lack of a "post-doubling" plan. Policymakers need to develop and adopt a five-to-ten year science funding plan.**
- **Scientists should contact their members of Congress and offer to create a "Science Advisory Committee" of local experts who are available to brief members of Congress and their staff about key science issues.**
- **The NIH reauthorization, adopted in 2006, expires in 2009, but Congress is not expected to deal with it next year. The 2006 reauthorization accomplished several good things, some of which haven't been fully implemented yet. Structural changes to NIH that have been adopted in prior reauthorizations have led to several positive developments, such as the creation of the Foundation for NIH in the 1993 reauthorization legislation.**

Jennifer Zeitzer is Director of Federal Relations at FASEB. She can be reached at jzeitzer@faseb.org.

FOOTNOTE:
1. On November 19th, Ted Stevens conceded the contested Alaska Senate seat to Mark Begich, giving the Democrats a 58-seat majority.

PAAC Reorganization

BY RALPH A. BRADSHAW, WILLIAM MERRICK, MARY HENDRIX, AND PETER FARNHAM

There are many complex and vexing issues that confront science today, ranging from diminishing research support to regulatory burdens and societal issues, such as the teaching of intelligent design as science and limits on stem cell research. These issues impact the membership of ASBMB and its ability to pursue the scientific enterprise. Within the society, the responsibility of the Public Affairs Advisory Committee (PAAC) is to address these problems, prepare responses for the ASBMB president and Council, keep the membership informed, and conduct advocacy activities with the view of increasing public awareness of the importance of biomedical research and its support. Over the past year, the committee has undergone significant changes to improve its efficiency and generate greater involvement of both the society as a whole and committee members. This article gives a brief description of the "new" PAAC and its plans.

The organizational changes that have been introduced required significant alterations in the by-laws and converted the PAAC to a standing committee of the council (as is the case for similar entities such as the Finance and Publications Committees). Importantly, in doing so, it defined the size of the committee, the terms of the members, and how they are to be appointed. In keeping with earlier by-law changes, the PAAC was reduced to 15 members, with each member serving a three-year term. This was accomplished by retiring a few long term members whose terms were actually over this year. The remaining members were reorganized into three 'classes,' staggered over the next three years so that the committee will have an orderly turnover (with no more than a third of the members going off in any one year). New members will be added each year by a combination of presidential appointments (3) and general membership election (2). The latter slate will be prepared by the PAAC Executive Committee (four individuals will be nominated for the two places) and placed on the general Society ballot. Members may be elected or appointed for a second term.

The chair of the committee will be appointed (as chair-elect) by the president from those who have already been members for one year and will serve one year in this capacity before becoming chair. The term for the chair is two years, requiring that the chair be automatically appointed for a second term. Retiring chairs will then serve a year as past-chair. One of the important innovations introduced into PAAC (before the by-law changes) was to subdivide the committee into three working groups: advocacy issues, funding agencies, and regulatory and societal matters. Although not specified in the by-laws, the chairs of these three groups along with the chair and chair-elect (or past-chair) form an executive committee, with the president of the Society and the president-elect (or past-president) serving ad hoc (both on the full PAAC and the executive committee). This group is assigned the task of reviewing issues as they arise and preparing them for presentation to the whole committee for discus-

sion and vote. The full roster of the PAAC, including the executive committee and their terms of office, can be found on the ASBMB web site.

Following the adoption of the by-law changes in July, a retreat was scheduled at the beginning of October in San Francisco to review the role of PAAC and to formulate a five-year strategic plan. The council felt, at the time they were deliberating on the proposed by-law changes, that public affairs had become quite complex, and that it was important to assess and plan what the Society's agenda should be and how this coincided with the agendas of other groups with which the Society has an affiliation. Since many of these associations involve fiscal commitments, the Council felt it was particularly important not to duplicate efforts needlessly. It also felt that PAAC should opine on invitations to join other groups that might arise in the future and provide assessments on the pros and cons of these possible arrangements to the Council to aid in their decision-making processes. The group that assembled in San Francisco consisted of several past and present members of PAAC as well as several guests. The final document that was prepared by the PAAC and ASBMB Public Affairs Office staff focused on the three subgroups and their agendas, with a fourth group charged with developing a plan for evaluating proposals for joining with coalitions and organizations in the future. An executive summary of this document can be found following this article. Importantly, the evaluation process proposed has already been used to consider the invitation from the Coalition for the Life Sciences, and its positive recommendation was forwarded to the council (who has since voted to join).

The new organization of PAAC promises to allow (even demand) greater time of the Committee members, and there will be increasing pressure for greater involvement of new and interested people from the membership of the Society. Over the next several months, this urgency will become more evident as the new challenges offered by the change in administration manifest themselves. Apropos of this, at a second Council retreat in Tucson, AZ, several weeks after the PAAC retreat, a task force to increase the involvement of members in advocacy issues was formed under the leadership of past-president Heidi Hamm. PAAC will work closely with this group to help facilitate its goals. It is, of course, our hope that the considerable efforts that went into making these changes and plans will not have been for naught, and that PAAC, in its new form, will galvanize the membership to greater involvement while providing important and timely information to the leadership and membership of the ASBMB.

Executive Summary, Public Affairs Advisory Committee Strategic Plan

BY PETER FARNHAM

The Society's Public Affairs retreat occurred in early October in San Francisco, CA. The plan that came out of that retreat will be posted on the ASBMB website in the near future. For now, what follows is an executive summary.

The mission of the Public Affairs Advisory Committee (PAAC) is to monitor the relationship of the Society to the general public and to serve and advise the Society and its leadership on issues in which the membership has an interest.

In particular, it will organize and coordinate the advocacy efforts of the Society for increased support for research in the areas of interest to the membership, monitor the policies and regulations of government agencies with regard to their research priorities and mechanisms affecting the distribution of research and training funds, and generally consider and formulate recommendations and responses to issues related to science and society. The committee will also evaluate requests for Society participation in other like-minded organizations, with respect to both short and long term interactions, and make recommendations to the officers and Council on their merits.

The PAAC will be divided into three equal subgroups for managing the preliminary discussions on advocacy, funding, and other issues. Consideration of outside requests will be initially reviewed by the Executive Committee. All major decisions will be formulated by the full committee and presented to the Council for its consideration and possible adoption.

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Legislative Issues Subcommittee

The Legislative Issues Subcommittee will focus on monitoring legislation of interest to the Society and supporting or opposing such legislation through advocacy activities, including regular meetings with members of Congress and their staffs, both in Washington, D.C. and in the states and congressional districts.

The Subcommittee will plan visits by member scientists—both faculty and students—to Capitol Hill, in order to advocate for science. These visits will target key members of Congress and their staffs to maximize their impact. One weakness in previous Hill visits has been that mid-career scientists usually do not participate. PAAC plans to make a strong effort to increase participation from mid-career scientists in advocacy.

PAAC members are unanimous in their view that Hill visits were a very useful and appropriate activity for the ASBMB to engage in, and the Legislative Issues Subcommittee is charged with coordinating a schedule of events that reflects the importance of this activity. This will ensure that ASBMB continues to be a regular presence on Capitol Hill.

Research Funding Agencies Subcommittee

The Research Funding Agencies Subcommittee will ensure that the mechanisms for distributing available funds protect the excellence and future of biochemistry and molecular biology.

Topics of present importance are peer review of grant applications and the ongoing push at NIH for increased funding of translational research—often at the expense of basic research budgets. However, it is envisioned that the areas of focus may well change, possibly in the immediate future due to the change in administrations, and this group will have a continually changing agenda. In addition, the programs of other research funding agencies are also important, and the subcommittee wishes to monitor all agencies and departments that support ASBMB members' research.

Special Issues Subcommittee

The Special Issues Subcommittee will monitor, and act as needed, on topics of interest to biochemists and molecular biologists that are at the interface of life sciences and society. It will address topics that are not necessarily specific to pending legislation or regulation.

Foremost among the present items under consideration are the need to advocate for evolution in science education, defending the need for animals in research, the growing issue of financial conflicts of interest in research funding, and support for embryonic stem cell research.

Relationships with Outside Groups

The PAAC will evaluate requests for ASBMB to join or endorse outside organizations and coalitions. Such proposals will be circulated to the full committee for comment. The PAAC executive committee will then make a recommendation to the full committee, and the final decision of the full PAAC will be forwarded to the Council as a formal recommendation.

The full report, in addition to greater detail of the functions and activities of the PAAC and its subcommittees, also contains a history of the PAAC, a summary of U.S. political conditions at the time of the retreat, from which the plan was formulated (prior to the 2008 elections), a discussion of the Society's demographics, and a basic description of the PAAC's organizational structure.

A lengthy list of action items was prepared at the retreat, which serves as a guide for committee action and interest over the next five years. These items include maintaining the ASBMB Science Policy Fellowship and Local Advocates Network programs; arranging and coordinating regular visits to Capitol Hill for ASBMB members, students, and postdocs; focusing on peer review and training issues as we continue to monitor NIH, as well as increasing our advocacy on infrastructure issues; increasing our efforts to monitor and comment on activities at other science agencies; drafting proactive position statements on issues such as evolution education, use of animals in research, stem cell research, conflict of interest, misconduct in science, and indirect cost reimbursement of research conducted at academic institutions; and focusing increased attention to issues relevant to ASBMB's growing foreign membership.

This is by no means a complete list of committee intentions, and as with all five-year plans, the plan itself will evolve over time. However, it does represent a start. Of course, we strongly encourage all ASBMB members to participate in committee endeavors by providing us with feedback on public issues of interest to you: by volunteering to join our Local Advocates Network, by participating in a Hill Day if asked, and even by volunteering to serve on a committee task force when formed.

Please contact our director of public affairs, Pete Farnham, at pfarnham@asbmb.org, if interested in getting more involved in Society public affairs.

Retrospective: Irwin C. Gunsalus (1912-2008)

Former ASBMB President Irwin Clyde Gunsalus passed away at his home in Andalusia, Alabama on Oct. 25th. He was 96.

In a career spanning nearly eight decades, Gunsalus, also known as "Gunny," conducted research that led to many important discoveries on biological catalysis and regulation, the formation of essential metabolites, and mechanisms of chemical transformations and energy transfer critical to central metabolic reactions. His work drew upon many fields, including organic chemistry, physics, and genetics.

Gunsalus was born in South Dakota in 1912. After spending two years as a chemistry major at South Dakota State College, he transferred to Cornell University and received his B.S. in 1935. Intrigued by his undergraduate exposure to the sciences, Gunsalus stayed at Cornell to pursue graduate study in bacteriology with J. M. Sherman. He was awarded a Ph.D. in 1940 for a thesis titled, "The Chemical Nature of Enterococcus Group Antigen." Gunsalus was then invited to join the faculty of the department, where he remained for seven years.

In 1947, Gunsalus moved to Indiana University to become a professor of bacteriology. Three years later, he was enticed to move yet again. This time, he joined the newly developing Department of Microbiology at the University of Illinois in Urbana. In 1955, he became head of the Biochemistry Division in the Department of Chemistry at the university. After his mandatory retirement from Illinois at the age of 65, Gunsalus became an assistant secretary general of the United Nations, where he was the first director of the International Centre for Genetic Engineering and Biotechnology (ICGEB). Following that term of service, he became a senior scientist at the U.S. Environmental Protection Agency's National Health and Environmental Effects Laboratory, Gulf Ecology Division, where he studied the microbiological bioremediation of coastal ecosystems.

Gunsalus was a prime figure in the movement of bacteriology into modern microbiology using biochemistry, the physical sciences, molecular biology, and genetics. In his early research on bacterial growth factors, he discovered pyridoxal phosphate and lipoic acid (the active form of vitamin B-6) and showed how they each function in their co-enzyme forms to partner with enzymes during catalysis. During his time in Illinois, Gunsalus developed a genetic system for the study of *Pseudomonas*, dissected the 11-step pathway for terpene breakdown, discovered the first three-component microbial cytochrome P-450 system involved in this pathway, and purified and crystallized the hemoprotein component of cytochrome P-450. Later, Gunsalus and his colleagues published the sequence of bacterial cytochrome P-450 and solved its three-dimensional structure.

Gunsalus also held deep convictions about human rights, peace, and justice, as well as an ideal of global scientific cooperation. In 1967, he was one of four scientists who hand-delivered to President Lyndon B. Johnson a petition to halt the use of chemical and biological weapons in Vietnam. The petition was signed by 5,000 scientists, including 17 Nobel Prize-winners and 127 members of the National Academy of Sciences.

"Gunny was a charismatic leader of American science, being so obviously admirable that he provided an example that others felt inspired to follow," said Bruce Alberts, editor-in-chief of *Science* magazine and a former president of the National Academy of Sciences. "A born detective, he devoted his life to unraveling the chemical mysteries that make life possible. His pioneering, interdisciplinary approaches to deciphering the details of bacterial metabolism have helped to produce the vitality of modern biochemistry."

Greg Petsko, current president of the ASBMB, had this to add: "On many occasions, he committed small acts of kindness that meant a great deal to the recipient—usually a young scientist. I was the beneficiary of several of these over the years, despite our not knowing each other very well. I never forgot his generosity. His work on P-450 is a paradigm of microbial enzymology and biochemistry, and his record of service to the scientific and world communities is an example to us all."

asbmb member spotlight

Bissell Awarded Cancer Society Medal of Honor

The American Cancer Society presented its highest honor, the Medal of Honor for Basic Research, to Mina J. Bissell this past fall.

The Medal of Honor, originally called the American Cancer Society Award, was first given in 1949. The award honors Americans who have made outstanding contributions to the fight against cancer. Other winners of the 2008 Medal of Honor were Sen. Edward M. Kennedy, Susan Band Horwitz, and Jon M. Huntsman.

Bissell, a distinguished scientist in the Life Sciences Division of Lawrence Berkeley National Laboratory, is a pioneer in understanding the role of the microenvironment in cancer. For years, it was believed that gene mutation was the central cause of cancer until Bissell's work proved that a cell's environment plays a critical role in cancer formation.

Her current research focuses on the role of extracellular matrix, its receptors, and its degrading enzymes as central modulators of tissue-specific gene expression, signal transduction, apoptosis, and cancer. Using mammary glands from mice and humans, she and her colleagues study the above processes in breasts and breast cancer.

Ginsburg Receives AHA Distinguished Scientist Award

David Ginsburg, the James V. Neel distinguished university professor of Internal Medicine and Human Genetics at the University of Michigan Medical School, received a Distinguished Scientist Award from the American Heart Association at its 2008 annual meeting.

Ginsburg, who is also the Human Genetics Warner-Lambert/Parke-Davis professor of Medicine and an investigator at Howard Hughes Medical Institute, studies the components of the blood-clotting system and how disturbances in their function lead to human bleeding and blood-clotting disorders.

Specifically, he and his colleagues are looking at the blood-clotting protein von Willebrand factor (VWF) and how molecular defects in the protein are responsible for many of the less common subtypes of von Willebrand Disease. He also studies diseases involving coagulation factor V, a central regulator in the early phases of blood clot formation and plasminogen activator inhibitor-1 (PAI1) and PAI2, both of which regulate the fibrinolytic system that breaks down blood clots.

Kahn Named Manpei Suzuki International Prize Winner

C. Ronald Kahn, head of the Joslin Diabetes Center Section on Obesity and Hormone Action and the Mary K. Iacocca professor of Medicine at Harvard Medical School, has been named the first winner of the Manpei Suzuki International Prize for Diabetes Research.

According to the Manpei Suzuki Diabetes Foundation, Kahn was selected to receive the inaugural award in recognition of his many contributions to diabetes research over the past three decades—from the discovery of the basic mechanism of how insulin receptors produce a signal in cells to increase their metabolism, to alterations in this signaling process in diabetes and other disease states. He has also generated multiple strains of transgenic mice with alterations in insulin signaling in order to analyze insulin action, one tissue and pathway at a time.

Kahn will be formally presented with the award, which includes $150,000, at a ceremony in Tokyo in March 2009. He will also deliver a commemorative lecture at the event.

The newly established award, the largest for diabetes research and one of the largest in medicine, commemorates the 15th anniversary of the Manpei Suzuki Diabetes Foundation, which supports diabetes research through both grants and fellowships.

Mann Honored with Distinguished Achievement Award

Matthias Mann of the Max Planck Institute of Biochemistry received the Human Proteome Organization's (HUPO) Distinguished Achievement Award in Proteomic Sciences at the 2008 annual HUPO World Congress. The award was given to Mann in recognition of distinguished scientific achievements in the field of proteomic science.

Mann leads the Department of Proteomics and Signal Transduction at the Max Planck Institute. His research focuses on developing mass spectrometric methods to characterize protein modification with ubiquitin and small ubiquitin-like modifiers. In particular, he is analyzing the ubiquitin-modified proteome using stable isotope-labeling by amino acids in cell culture (SILAC). Using this method, Mann and his colleagues are quantitatively comparing the ubiquitination of total cellular protein following perturbations such as DNA damage. Mann is also developing streamlined methods to map ubiquitination sites on single, purified proteins present in small amounts detectable by Coomassie staining.

Mann also serves on the editorial board of *Molecular and Cellular Proteomics*.

Tabak Named NIH Principal Acting Deputy Director

Lawrence A. Tabak was appointed principal acting deputy director of NIH in November 2008. While serving in this capacity, Tabak will continue to serve as the director of the National Institute of Dental and Craniofacial Research, a position he has held since 2000.

As director of the National Institute of Dental and Craniofacial Research Institute, Tabak steered the Institute towards funding research on ways of preventing tooth decay, the use of adult stem cells to heal bone fractures and defects, the transfer of replacement genes into the salivary glands for therapeutic purposes, periodontal disease as a possible risk factor in premature birth, and pain management.

Tabak has published extensively on the structure, biosynthesis, and function of salivary mucins, the pathogenesis of salivary gland disease and dysfunction, and the use of saliva as a diagnostic fluid. His current research focuses on how mucin-glycoproteins—sugars that are essential for normal embryonic development—play significant roles in both innate and acquired immunity and also play important structural roles in membrane-bound proteins.

Valentine Awarded Glenn T. Seaborg Medal

Joan Selverstone Valentine, professor of Chemistry and Biochemistry at the University of California, Los Angeles, received the 2008 Glenn T. Seaborg Medal for her outstanding contributions to chemistry.

The Seaborg Medal was established in 1987 by the UCLA Department of Chemistry and Biochemistry to honor individuals for their significant contributions to chemistry and biochemistry. The medal is awarded annually, and the recipient is chosen by the UCLA Department of Chemistry & Biochemistry Executive Committee.

Valentine's research centers on transition metals, metalloenzymes, and oxidative stress. She is currently looking at the properties and biological functions of wild type copper-zinc superoxide dismutases (CuZn-SOD) in hopes of understanding why mutant human CuZn-SOD proteins cause familial amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease). She is also studying the roles of superoxide, hydrogen peroxide, metal ions, and small molecule antioxidants in *Saccharomyces cerevisiae* in order to study learn how redox balance is maintained in healthy eukaryotic cells.

Four ASBMB Members Elected to IOM

HORWICH

KUCHERLAPATI

MERCHANT

MOSES

This past October, the Institute of Medicine (IOM) announced the names of 65 new members and five foreign associates, four of whom are ASBMB members. Election to the IOM is considered one of the highest honors in the fields of health and medicine and recognizes individuals who have demonstrated outstanding professional achievement and commitment to service.

The ASBMB members newly elected to the IOM are:

Arthur Horwich, investigator, Howard Hughes Medical Institute; and Sterling professor of Genetics and Pediatrics, Department of Genetics, Yale School of Medicine, New Haven, CT;

Raju S. Kucherlapati, Paul C. Cabot professor of Genetics, Harvard Medical School; and scientific director, Harvard Partners Center for Genetics and Genomics, Brigham and Women's Hospital, Boston, MA;

Juanita L. Merchant, professor of Internal Medicine and Molecular and Integrative Physiology, Division of Gastroenterology, University of Michigan, Ann Arbor, MI; and

Marsha A. Moses, professor of Surgery, Harvard Medical School; and interim director, Vascular Biology Program, Children's Hospital Boston, Boston, MA.

The IOM was established in 1970 by the National Academy of Sciences. It has become recognized as a national resource for independent, scientifically informed analysis and recommendations on human health issues. With their election, members make a commitment to volunteer a significant amount of time as members of IOM committees, which engage in a broad range of studies on health policy issues.

A diversity of talent among IOM's membership is assured by the Institute's charter, which stipulates that at least one-quarter of the membership is selected from outside the health professions, for example, from such fields as the natural, social, and behavioral sciences; law; engineering; and the humanities. Current active members elect new members from among candidates nominated for their outstanding accomplishments. The newly elected members raise IOM's total active membership to 1,576 and the number of foreign associates to 89. With another 71 members holding emeritus status, IOM's total membership is now 1,736.

Modifications in the Mountains

BY RALPH A. BRADSHAW AND KATI F. MEDZIHRADSZKY

Against the majestic backdrop of the Sierra Nevadas and the deep blue of Lake Tahoe, the ASBMB hosted some 70 scientists at the Granlibakken Resort for three days of presentations and discussions on the nuances of the post-translational modifications (PTMs) of proteins. The focus of the meeting was two-fold: 1) technological advances in the determination of both old and new alterations, and 2) the evaluation of related physiological responses.

The meeting, organized by Kati Medzihradszky and Ralph Bradshaw of the University of California, San Francisco, was opened with a plenary lecture by Matthias Mann (Max Planck Institute, Martinsried), who provided a broad overview of the state-of-the-art, with many illustrations of extensive applications of mass spectrometry to the determination of PTMs. This was followed by sessions on glycosylation (featuring invited talks by Jim Paulson, Scripps Institute, La Jolla, and Jerry Hart, Johns Hopkins, Baltimore), phosphorylation (Pierre Thibault, Universite de Montreal), and oxidation (Cathy Costello, Boston University, and Judy Klinman, University of California, Berkeley) interspersed with sessions devoted to unusual modifications (Kati Medzihradszky, UCSF, and Jeff Gorman, Queensland Institute for Medical Research, Brisbane) and complex modifications (Yingming Zhao, University of Chicago) with one session on methodology (Andrew Alpert, PolyLC, Columbia, Josh Coon, University of Wisconsin, Madison, and Pavel Pevzner, University

LEFT: Emerald Bay, Lake Tahoe
ABOVE: Afternoon hike to Eagle Lake. Back row (L to R): Thomas Ringer (Innsbruck, Austria), Cathy Costello (Boston, MA), Kati Medzihradszky (San Francisco, CA), Eva Klement (Szeged, Hungary). Front row: Andy Alpert (Columbia, MO), Zsuzsa Darula (Szeged, Hungary), Eva Hunyadi-Gulyas (Szeged, Hungary), Jordane Biarc (San Francisco, CA), Patricia Ruperez (San Francisco, CA).

The success of the meeting was evident from the enthusiasm of the participants and the rigor of the discussions.

of California, San Diego). The invited speakers were rounded out by Frank Eisenhaber (A*STAR, Singapore), who discussed the state of *in silico* predictions of PTMs.

The five sessions were equally divided between these invited speakers and presenters selected from the submitted abstracts that expanded each of the sessions to include many additional paradigms and modifications. There were also a few dozen posters that were given in two evening sessions. All told, there were representatives from over a dozen countries.

This meeting, organized as a part of the revitalized ASBMB small meeting program, was also planned to emphasize an increased effort of the Society to expand its activities in the area of proteomics that has been anchored by the success of *Molecular & Cellular Proteomics*, which was launched in 2001. ASBMB also supports the now biannual Symposium on Mass Spectrometry in the Health and Life Sciences held in San Francisco and plans to expand the small meetings agenda in the off year are under discussion.

The success of the meeting was evident from the enthusiasm of the participants and the rigor of the discussions. Indeed, there was general agreement that it should be repeated, preferably in the same locale, in two years' time, as the ambience and location were quite conducive to additional discussions and exchanges of information. These took place at breaks, during meals, and certainly during the two open afternoons scheduled for hiking and relaxing (see accompanying pictures). There was (and is) no concern that the topic will not remain timely or current; indeed, the number of different modifications discussed was truly impressive. However, it was clear that all of the known modifications weren't covered, and it is equally clear that there are still a significant number of modifications to be defined, as was evidenced by the number of unidentified additional masses seen in MS/MS experiments. Of course, not all of these changes will prove to be either of physiological origin and/or significance, which is one reason why continued discussions of this topic are essential.

Ralph A. Bradshaw is a Professor of Chemistry and Pharmaceutical Chemistry and Deputy Director of the Mass Spectrometry Facility at the University of California, San Francisco. He can be reached at rab@cgl.ucsf.edu. Kati F. Medzihradszky is a Professional Research Chemist/Adjunct Professor of Pharmaceutical Chemistry at UCSF and can be reached at folkl@cgl.ucsf.edu.

The 2009 ASBMB/Schering-Plough Research Institute Award: Phillip Zamore

The 2009 Schering-Plough Research Institute Award will be presented to Phillip Zamore, Howard Hughes Medical Institute investigator and professor at the University of Massachusetts Medical School, at the ASBMB annual meeting. The Schering Plough Award was established to recognize young investigators for outstanding research at an early stage of their careers. Zamore will present his award lecture on Monday, Apr. 20 at 8:30 a.m.

Zamore did his graduate research with Michael R. Green at Harvard University and received his Ph.D. in Biochemistry and Molecular Biology in 1992. He then did a postdoctoral fellowship at the Whitehead Institute for Biomedical Research with Ruth Lehmann, also collaborating with David P. Bartel of the Whitehead Institute and James R. Williamson of the Scripps Research Institute. In 1999, he joined the faculty of University of Massachusetts Medical School as an assistant professor. He is currently the Gretchen Stone Cook professor of Biomedical Sciences at the University of Massachusetts Medical School, a position he has held since 2005.

Zamore's laboratory has played a role in nearly all of the major breakthroughs in the study of RNA silencing

A pioneer in the study of RNA silencing in eukaryotes, Zamore's laboratory has played a role in nearly all of the major breakthroughs in the study of RNA silencing. "Phil literally invented the study of the molecular mechanism of RNA interference (RNAi) when he and his collaborators developed in 1999 the first cell-free system that recapitulated RNAi in a test tube," says C. Robert Matthews, professor and chair of the Department of Biochemistry and Molecular Pharmacology at the University of Massachusetts Medical School.

This cell-free system was the result of a friendly argument between Zamore and fellow postdoc Tom Tuschl, who were debating how to recreate a type of double-stranded RNA gene regulation just discovered in flatworms. The pair decided to use components from fly cells to find out whether double-stranded RNA molecules could silence a gene in a test tube the way they did in worms. The experiment worked, and Zamore and Tuschl went on to show how short segments of RNA act as guides to ensure that the appropriate gene is silenced.

Since then, Zamore has used biochemistry, quantitative enzymology, genetics, and bioinformatics to learn how RNA silences genes. He and his colleagues provided the first evidence that small interfering RNAs (siRNAs) were produced by endonucleolytic cleavage of long, double-stranded RNA. This led to Zamore's proposal that siRNAs could be used to silence genes in mammals and as human therapeutics.

Zamore also showed that siRNAs guide protein complexes that slice their target mRNAs in two and that these small RNA-guided protein complexes are assembled by a complex, ATP-dependent pathway that sorts small RNAs into distinct functional pathways. Additionally, he united the RNAi and microRNAs pathways when he discovered that they are both made by the enzyme, Dicer. Subsequently, he developed siRNAs capable of distinguishing between two mRNAs that differ by only a single nucleotide, which has aided in the development of siRNA-based therapies for several prominent neurodegenerative diseases, such as Huntington Disease. More recently, Zamore and his colleagues have discovered that Piwi-interacting RNAs (piRNAs)—siRNA-like molecules that protect the animal germ line from transposons—form a distinct RNA silencing pathway that does not require Dicer.

"Zamore is one of the most brilliant biologists of his generation," says Victor Ambros, professor in the Department of Molecular Medicine at the University of Massachusetts Medical School. "Beginning almost immediately after becoming an independent scientist in 1999, he has consistently led the extremely competitive field of small RNA biochemistry and molecular biology. Zamore is unique; he is a gifted biochemist who thinks with the subtlety and rigor of a geneticist. The Zamore lab is remarkably productive, and even more remarkably, every one of his papers is important. It is fair to say that over the past six years, no other single scientist has contributed more than has Zamore to our understanding RNAi mechanisms."

The 2009 the Avanti Award in Lipids: Sarah Spiegel

Sarah Spiegel of the Virginia Commonwealth University School of Medicine will be presented with the 2009 Avanti Award in Lipids at the ASBMB Annual meeting in New Orleans. This award honors outstanding scientists whose research interests are in the field of lipids. Spiegel will present her award lecture on Sunday, Apr. 19 at 2:10 p.m.

Spiegel is one of the founders of the paradigm that sphingolipid metabolites serve as signaling molecules, and the sphingolipid signal that she discovered, sphingosine 1-phosphate (S1P), is now the most thoroughly characterized mediator in the field.

She received her B.S. in Chemistry and Biochemistry from Hebrew University in Jerusalem, Israel, and then went to the Weizmann Institute of Science in Rehovot, Israel to do graduate work with Meir Wilchek. After earning her Ph.D. in 1983, Spiegel moved to Bethesda, MD, to do a postdoctoral fellowship with Peter H. Fishman in the Membrane Biochemistry Section of the National Institute of Neurological and Communicative Disorders and Stroke at NIH.

Spiegel is one of the founders of the paradigm that sphingolipid metabolites serve as signaling molecules

In 1987, Spiegel joined the faculty of Georgetown University Medical School as an assistant professor in the Department of Biochemistry and Molecular Biology. In 1992, she became director of the graduate program in Biochemistry and Molecular Biology at Georgetown, and in 1996, she was promoted to professor in the Department of Biochemistry and Molecular Biology. Spiegel left Georgetown in 2002 to become professor and chair of the Department of Biochemistry and Molecular Biology at the Virginia Commonwealth University School of Medicine, a position she continues to hold today. She is also currently director of the Cancer Cell Biology Program at the Massey Cancer Center in Richmond, VA.

Speigel began working on sphingolipids as a graduate student, studying the role of gangliosides and other glycoconjugates in signaling. She continued working on gangliosides as a postdoctoral fellow and showed that ganglioside GM1 can cluster and signal—a concept that now has relevance for signaling through lipid rafts. As an independent researcher, she began to explore whether sphingosine might be a mediator of biological behaviors. In a series of experiments, she showed that sphingosine is rapidly converted to S1P and that S1P is a potent mitogen. She also worked out assays for the enzyme that produces S1P, sphingosine kinase, purified the kinase, and identified its gene. And finally, she discovered that not only is there an intracellular signaling pathway involving S1P, but there are also cell surface receptors for S1P. Hence, she proposed that S1P is not only an intracellular "second messenger" but is also secreted by cells as a "first messenger."

Speigel later demonstrated that S1P can suppress apoptosis, which led to her theory that the dynamic balance between S1P and its precursors, sphingosine and ceramide, functions as a cellular rheostat that determines whether a cell survives or dies. This was followed by several reports by her lab and many others that S1P controls important physiological and pathophysiological processes, including cancer, vascular maturation, angiogenesis, cardiac development, cardiovascular function, wound healing, atherosclerosis, immunity, and asthma. Speigel was also was the first to draw attention to S1P receptors as master regulators of cell motility.

"I have followed Sarah's work for two decades because of its relationship to my own interests in sphingolipid metabolism, and I have collaborated with her on many studies, which have given me the opportunity to see how she thinks, and deal forthrightly with findings that agree or disagree with her original hypothesis," says Alfred H. Merrill Jr., Professor of Biology, Chemistry, and Biochemistry, and Smithgall Institute Chair of Molecular Cell Biology at the Georgia Institute of Technology. "In every instance, I have been consistently impressed by her integrity, the high quality of her research, her concern for others, and her skill at leadership and organization."

ASBMB ROUNDTABLE: Osamu Hayaishi

BY NICK ZAGORSKI

Back in 1945, Osamu Hayaishi may not have dreamed of the great recognition he would achieve in science. The recent medical graduate had just made his fateful decision to pursue academic research at Osaka University, instead of going into clinical medicine, and now found himself working in a lab that had virtually no equipment, chemicals, or funds. It would be difficult enough to get even one experiment done, let alone try and start a career. But through perseverance, excellent colleagues, and a little luck, Hayaishi began to build up his scientific legacy, one that started with his discovery and characterization of oxygenase enzymes and later shifted to understanding the molecular mechanisms of sleep.[1] Born in Stockton, California in 1920—although he would spend most of his formative years in Japan—Hayaishi's scientific journey would see him continue his travels across the Pacific, from Osaka to Wisconsin, to Maryland, and back to Japan again. Considering this dual perspective, *ASBMB Today* decided to sit down with Hayaishi, currently director emeritus and chairman of the Board of Trustees at the Osaka Bioscience Institute, and get some insight into the scientific life of each country and how they compare.

ASBMB: *Relocating has been a big part of your career, both within and between Japan and the U.S. Which of your moves would you characterize as the most difficult? How did you manage to adjust?*

HAYAISHI: My return to the U.S. in 1949 was, thankfully, not so difficult for me, considering the conditions at this time right after the Second World War—most of my mentors and friends told me that I should have waited until the official peace treaty was signed and that Americans no longer thought of Japanese as enemies. I was initially discouraged after I arrived in San Francisco and stayed with my uncle's family for a couple of days, where I heard about their sad experiences in a relocation camp during the war. However, I was so lucky to have met two American post-doctoral fellows, Bernard Katchman and Ephraim Kaplan, when I landed at Madison. They were extremely kind and treated me as their own brother, and thanks to these and other great friends, I had no problem at all to get adjusted to the American way of life, scientifically, socially, or otherwise.

ASBMB: *Obviously, with today's interconnected world, traveling cross-country to study is a more common and less challenging task; given your experiences, have you encouraged your students to look across the ocean, and what advice do you give them?*

HAYAISHI: I have always encouraged my graduate students to go abroad for post-doctoral studies. I tell them it's important to have different training and the opportunity to have new experiences and meet different people. Interestingly, though, it has long been a tradition in Japan to be associated with the same school your whole career, and academic promotion was like riding on the escalator. For example, when I was appointed as chairman and professor of Medical Chemistry at the prestigious Kyoto University School of Medicine in 1958, I was the only non-Kyoto graduate among all the faculty members. Even today, many people still are hesitant to move to other laboratories either in Japan or abroad. However, the professor's appointment system in Japan has gradually been improving, so the trend has been slowly changing.

Incidentally, the sabbatical leave system does not exist in Japanese academia, and senior people have fewer opportunities to go abroad unless they are invited to foreign universities or institutes as visiting professors; that's another reason I encourage my students to go abroad if they can.

ASBMB: *While young Japanese scientists may see the U.S. as the epicenter of biological research, there is no denying that Japan's scientific enterprise has gone from almost non-existent to premier over the past 60 years. Having seen this progression, first-hand, to what do you attribute Japan's success in building up their research starting from such difficult times?*

HAYAISHI: I think Japan's enormous progress is due in part to Japan embracing the American research and medical systems. Before the Second World War, Japanese science,

as well as industry and military, were copied mostly from European models. For example, when I was a medical student, most of the professors had gone to study in Germany, and most of the text books were in German as well. However, after the Second World War, Japanese science became more influenced by the United States' system.

Of course, it is also true that because of the war, scientific growth in Japan was rather slow during the subsequent two decades or so, mostly due to economical reasons; when I came back to Japan in 1958, the general standard of living as well as science research was still far behind the U.S. My salary as a young professor at the most prestigious Kyoto University was only about one-thirteenth of my salary at NIH (Though this was an improvement over my first salary a decade earlier at Osaka University, which was not enough to even buy a bottle of Coca-Cola!).

Since then, I believe a combination of internal commitment and external support has helped spur progress. The Japanese government made a special effort to provide me with grants, and many Japanese foundations and pharmaceutical companies offered me generous support. In addition, NIH, the Jane Coffin Memorial Fund, the Rockefeller Foundation, the China Medical Board, and even several U.S. pharmaceutical companies contributed significant amounts of money to both research and to refurnish old buildings at the University; they even helped build a new library and building for radioactive experiments.

ASBMB: *Earlier, you mentioned Japan's lack of sabbaticals. With your perspective of academia in both the U.S. and Japan, what would you say are some other major differences in the sphere of research (i.e. obtaining grants, teaching responsibilities) between the two countries?*

HAYAISHI: It can be somewhat difficult to compare academic research in the U.S. and Japan because despite our progress, research funding, especially in the basic sciences, still lags in Japan compared to U.S. research. I have often talked to people at the Ministry of Education and explained the American system but in Japan, it takes time to improve or change some old traditional systems for various reasons, which are rather complicated to explain here.

For example, to review NIH grants in the United States, the so-called "study section" is a wonderful system. In Japan, only three reviewers review one application independently. This system has gradually been improved but is still not quite as good as the American system, partly because we don't have as many senior scientists who are qualified to review applications.

ASBMB: *On the other side of the coin, are there some aspects to being a researcher in Japan that are quite similar to the U.S. that people may not realize?*

HAYAISHI: One similarity, which I hope will change, is that Japan does place too much emphasis on publications in the top journals just like in the U.S. Sometimes, this even occurs in the selection of professors in clinical fields, rather than focusing on their clinical experience or ability.

"…the harder the problem, the more interesting it looks."

ASBMB: *What are some of the big biomedical issues on the minds of Japanese today? Do they mirror questions /concerns in the U.S.? For example, is stem cell research as controversial in Japan as it is in the States?*

HAYAISHI: Naturally, there will be social, racial, and historical differences in Japanese science, especially in the field of clinical medicine. However, as the world has been getting "smaller," I do believe all countries share many major problems and should collaborate more closely.

As to stem cells, there are some people who are concerned about their use on the grounds of ethical and religious views, but my guess is that, percentage-wise, the number of these people in Japan is probably much smaller than that in the U.S. And the Japanese government has also allocated a large amount of special funds for stem cell research. Personally, I believe that the entire stem cell controversy will begin to fade away over the next several years, and progress made along stem cells will contribute enormously to the better treatment of many so-called "incurable diseases" in the very near future.

ASBMB: *What are your thoughts on where Japanese science is headed in the next 10 to 15 years? Are there any specific fields that have become "hot" recently that you think will lead to major discoveries in Japan down the road?*

HAYAISHI: I don't mean to be selfish when discussing this question but neuroscience is certainly one field in which Japan might be able to accomplish something new, because brain science is such a complicated area that we need new ideas and fresh approaches from an entirely unexpected origin. For example, sleep is one of the most important and yet least understood physiological functions of the brain. We still cannot even answer simple questions such as, "What is sleep?," "Why do we need to sleep?," and "How are sleep and wakefulness controlled?" Also, the causes of most of the 88 known sleep disorders in the textbooks have not been scientifically elucidated. The World Sleep Congress is coming to Kyoto in October 2011, and we are eager to hear the hottest discussion in the most tranquil city in the world.

ASBMB: *Why do you think sleep and related research still has so many unanswered questions? Is it a matter of deficiencies in funding or eager scientists carrying out research in this area?*

HAYAISHI: The brain is the most complicated organ in the body, both structurally and functionally; other organs and tissues are relatively simple in comparison. And sleep is probably the most unique, global, and complex function of the brain, so adding that together makes it extremely difficult to understand its mechanisms of action, at this time. Not only sleep, but also other functions and dysfunctions of the brain such as memory, emotion, mental diseases, etc. still remain unsolved. I am afraid it might take a long time until we discover a big breakthrough. But, we scientists are a curious species, and the harder the problem, the more interesting it looks. I am confident more and more young ambitious scientists will challenge these formidable problems and hopefully, we will find some answers in the near future.

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

FOOTNOTE:

1. For more information about Hayaishi's career, see his *JBC* Reflection (2008 **283**, 19165-19175).

A Color-blind Crisis

BY MARCOS E. MILLA

By all accounts, we are living in exceptional times. The economic expansion of the second half of the 20th century had a tremendous impact on science that, combined with major victories for the cause of social equality, created a landscape of professional opportunities for an unprecedented number of scientists regardless of race, gender, creed, or nationality. Through a ripple effect, the U.S. attracted scientists and trainees from multiple countries. Even for individuals not interested in a long term stay in America, the likelihood of securing strong independent careers in their own countries was much improved with scientific training in the United States. All those factors were critical in establishing cultural attitudes towards diversity ranging from tolerance to proactive affirmation.

Fast forwarding to the close of the first decade of this 21st century, the U.S. stands at a very difficult junction in almost every sector of the economy. In the biomedical sciences, several signs make for a bleak outlook over the next years; one of the most unsettling: NIH suffers from a deep crisis both in funding resources and best practices for grant proposal evaluation and prioritization. Not surprisingly, less established faculty have taken the worst of the hit, as evidenced by the continuing upward trend in the age of first R01 awards. Even with a new government as well as new leadership at NIH, this trend will be difficult to revert any time soon. The situation is not any better in pharmaceutical industry, which is experiencing its biggest job losses in a generation. The ever-increasing costs of launching new drugs, combined with approaching patent expirations and pressures for price control, do not bear well for the future of the drug industry, unless something dramatic happens.

Where do we go from here? I call this a "color-blind crisis" because the present challenges of the whole scientific community go beyond any perceived or actual label. To put forward any preferred treatment in such times runs the danger of approaching the "what's in it for me" mentality that is in part to blame for the vast economic downturn that we are witnessing. Yet, we do need to keep on the radar opportunities for all and a research focus that includes the underserved, in order to protect what we have accomplished with regard to the inclusion of minorities in science.

How do we do that, exactly? Every crisis brings with it innovative solutions, just as any wildfire brings new life. This one may bring a dramatic redefinition of how biomedical research is approached by both academia and industry. The current model of basic research used in academia and drug discovery in industry may be discarded for a new model, in which pre-clinical and early clinical research and development occurs at the interface of academia and biotechnology companies; and late clinical research, development, and commercialization will be the turf of "Big Pharma." The government will likely retain a role in funding basic research, and perhaps in sparingly placing "earmarks" for programs of special interest to selected diseases/populations.

In a way, this change is already underway, with many pharmaceutical industry giants establishing incubator facilities for companies offering new, bold approaches to target identification, validation, and hit-to-lead activities. Several academic institutions are also sprouting drug discovery centers with diverse disease foci, with the objective of pushing home-grown therapeutic programs all the way from the bench to phase II trials to profitable deals with industrial partners. A few of those centers are already in operation, thanks to a variety of funding sources including private donors, many of whom are openly interested in addressing diseases deeply entrenched in underserved and minority populations. This approach adds a new and interesting ingredient to the mix: drug development for diseases lacking a profitable market, either because they are viewed as "Third World" indications with markets that cannot afford brand prescriptions, or due to a very limited number of patients likely to benefit from the therapy ("orphan" diseases). With time, these emerging, alternative ventures will hopefully become a substantial presence in the job market and, because of their roots and areas of interest, may actually aid in maintaining the diversity in biomedicine.

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Vision and Change in Biology Undergraduate Education

BY J. ELLIS BELL

During the past 18 months, the National Science Foundation has sponsored a series of "conversations" about biology education. The final step in this process was a summit meeting this past November about the roles scientific societies play in undergraduate biology education.

The two-day meeting was held at the Howard Hughes Medical Institute in Chevy Chase, MD and was hosted by the American Association for the Advancement of Science, the National Science Foundation and HHMI. Representatives from 14 societies (see sidebar), including ASBMB, as well as the National Research Council, Project Kaleidoscope, NIH, and the hosting organizations attended the summit.

At the beginning of the November meeting, Bruce Alberts, editor-in-chief of *Science* magazine, gave a presentation emphasizing the need for change in the undergraduate biology experience and the importance of inquiry-based science education. He summarized some of the key findings and diverse resources available from previous studies and ongoing programs including the Boyer Commission Report *Reinventing Undergraduate Education*, the *National Science Education Standards*, the Bio 2010 Project, the National Academies Summer Institutes on Undergraduate Education in Biology at the University of Wisconsin, and a NAS website for children on women's adventures in science. Despite broad recognition of the need for change and recommendations for best practices and numerous web-based resources, widespread implementation of inquiry-based undergraduate biology education has not occurred. However, through a variety of means, scientific societies can be an important force in promoting this change.

Next, each society presented a brief summary of their current activities in undergraduate education. Most societies have committees on education and sponsor a variety of activities spanning "K-to-gray" science education. Many societies encourage participation of undergraduates at their annual meetings (through special sessions, reduced rates, and travel awards), have undergraduate summer research fellowship programs, run programs for minority undergraduate students, include sessions or workshops on education at their annual meetings and/or convene special education meetings, and sponsor an award specific to education. Additionally, most societies publish articles on education in newsletters or society research journals, and some publish journals dedicated to education. Most have assembled open access teaching resources (images, videos, podcasts, laboratory modules, and curricula) that are available on society websites and/or through the BEN (BiosciEdNet) portal.

J. Ellis Bell, chair of the ASBMB Education and Professional Development Committee, summarized ASBMB activities that promote undergraduate research and active learning such as the undergraduate poster competition and platform talks at the annual meeting, the undergraduate affiliates network, and the XΩΛ Biochemistry & Molecular Biology Honor Society. He also described ASBMB activities aimed at promoting best practices in undergraduate education including curriculum recommendations for undergraduate biochemistry degrees, the ASBMB Award for Exemplary Contributions to Education, sessions on education at the annual meeting, articles on education in *ASBMB Today*, and the Teagle Report which examined undergraduate programs in biochemistry and molecular biology.

Small group sessions were also held at the summit and focused on how the community of biological science societies could collectively further improvement in undergraduate biology education. There was uniform consensus on a need to revitalize and refocus the introductory biology experience for science and non-science majors, emphasizing process rather than content through inquiry-based learning that imparts the skills and core knowledge that underpin all of biology. There was dissatisfaction with traditional teaching methods based on current textbooks and lectures, and there was a perceived need for a new or revamped, rigorously curated web portal for peer-reviewed resources with feedback from users. There was also discussion of strategies for altering academic culture, to ascribe more value to educational activities, as well as means to encourage faculty to adopt student-centered active learning pedagogy. Additionally, there was agreement that increased communication and collaboration between societies, as well as among members within societies, will facilitate progress on the above issues.

Teams from each society also developed and presented initiatives that could be implemented within their individual societies. The outcome reflected the extensive sharing of ideas that occurred during the summit, with most societies planning to broaden their activities to incorporate some of the strategies currently used by other societies. A couple of new themes emerged, specifically, strategies to more tightly integrate educational and research activities, and the intent of many societies to define a set of core concepts for their individual disciplines that might subsequently be used to develop a first-year biology experience for both science and non-science majors.

In the next several months ASBMB will introduce the following initiatives to assist teaching faculty:

1. ***Changing how we teach.***
   The Society will provide help to educators at various levels. We will organize a workshop at the annual meeting which will focus on designing a course and using "best practices" in teaching students. We are also considering developing an accreditation program that puts emphasis on effective (i.e. evidence-based outcomes) teaching and undergraduate research and outreach activities. As part of this initiative, some samples of "courses that work" will be posted on the education web site and we will show how they fit with the recommended ASBMB undergraduate curriculum. Finally, the Society will create a cadre of ASBMB Master Educators who will be available as mentors to those new to (or wanting to refocus) their teaching.

2. ***Changing what we teach.***
   As part of a national discussion on introductory science courses, the EPD will focus on courses that teach about what research is and how it is done with minimal factual content required. Such courses fit with early introduction of the skills from our recommended curriculum. In terms of the fundamental knowledge that students should have, the Society is already working with various groups to assist in the development of core concepts and concept inventories which will allow faculty to be more explicit about what students should know and be able to do at various points in their degree program.

3. ***Changing who we teach.***
   For a number of years, the Society has worked to increase the number of under-represented minorities in biochemistry and molecular biology and we will continue such collaboration to ensure best practices for institutions serving under represented minorities. These types of collaborations will also be extended to two-year colleges with the hope that this will facilitate transitions for students from two-year colleges to four-year degree granting programs. In terms of formal education, the Society has already announced plans for enhanced K-12 outreach through its Undergraduate Affiliates Network. Finally, through our education web page, we will focus on best practices in outreach to non-college learners to help foster life-long learning and interest in the sciences.

Together, these initiatives will offer increased support to those already involved in teaching biochemistry and molecular biology and proved guidelines and mentors for graduate students and postdoctoral fellows interested in developing their teaching portfolios.

Societies Represented at the NSF Education Summit

- American Institute for Biological Sciences
- American Physiology Society
- American Society for Biochemistry and Molecular Biology
- American Society for Cell Biology
- American Society for Microbiology
- American Society for Plant Biologists
- Biophysical Society
- Botanical Society of America
- Ecological Society of America
- Genetics Society of America
- National Association of Biology Teachers
- Society for Integrative and Comparative Biology
- Society for Neuroscience
- Society for the Study of Evolution

Ellis Bell is currently Professor of Chemistry and Chair of the Biochemistry & Molecular Biology Program at the University of Richmond. He is also Chair of the ASBMB Education and Professional Development Committee. He can be reached at jbell2@richmond.edu.

A Backwards Career in Biotechnology: *From Law to Human Embryonic Stem Cell Science*

BY ELIZABETH L. R. DONLEY

Donley

Elizabeth L. R. Donley is chief executive officer of Stemina Biomarker Discovery. She is a patent attorney who served as general counsel and director of business development for the Wisconsin Alumni Research Foundation for more than eight years. During her tenure at WARF, she also served as Managing Director of the WARF subsidiaries WiSys Technology Foundation (WiSys) and WiCell Research Institute (WiCell). Prior to joining WARF in 1998, Donley practiced law with the law firm of Quarles & Brady in the areas of intellectual property law, business transactions, securities, and corporate law.

Henry David Thoreau once said, "We must walk consciously only part of the way toward our goal and then leap in the darkness to our success." In late 2006, this statement inspired me to leave a well paid and prestigious position as general counsel and director of business development of the Wisconsin Alumni Research Foundation (WARF) for the unknowns of founding and running a biotech company with my scientific partner and co-founder, Dr. Gabriela Cezar.

Looking back upon the series of career choices and educational opportunities that led me to my current position as chief executive officer of Stemina Biomarker Discovery, one might conclude that I had no idea what I wanted to be when I grew up. That may be partly true, but upon closer examination, the somewhat circuitous route of my career path provides me with a wide variety of skills that I use every day. However, unlike many scientists who decide to leave the lab to pursue a career in law or business, I began my career as a businesswoman and lawyer and then became a scientist.

I didn't study science as an undergraduate; instead, I pursued a B.A. in advertising and public relations. I started my career in banking, working for a large Midwest-based bank. I worked my way up through the management training program into a commercial lending position making loans to small businesses. Eventually, I began pursuing an MBA in finance at night and obtained my securities and insurance licenses. But as I learned more about banking, investments, and finance, I found myself increasingly interested in the legal aspects of these transactions. After four years in banking, I decided to apply to law school.

After completing my law degree and finishing my MBA in the combined degree program at the University of Wisconsin, I began practicing business and securities law at a large Midwestern law firm. I had been with the firm for less than a year when a senior associate who was in charge of drafting patent license agreements for WARF, the patent and licensing organization for the University of Wisconsin, left the firm. The partner in charge of the client relationship with WARF asked whether I would be willing to take over the patent license drafting. I didn't realize it then, but this was a career-defining moment. Of course, as a first year associate in a law firm, the only thing one could say to any request was "Yes, I'd love to. What do you need me to do?" The next week, I was on a plane to Washington, D.C. to take a three-day course on patent licensing.

I began visiting WARF twice a week, meeting with the licensing staff and taking their requests for license agreements. Over the course of four years, I learned about patents, trademarks, copyrights, and an enormous variety of technology. I listened care-

fully to the inventors describing their inventions and to the licensing staff talking about the products and markets from which they hoped to capture royalties on intellectual property filed to cover those inventions. I was fascinated by both, but I realized that I didn't have a three-dimensional view of either from my perch as a scrivener hired from the law firm to memorialize these transactions.

In 1998, I was offered the general counsel position at WARF. This was another career-defining moment, but this time, I realized it. I was excited about the prospect of working in the tower located at the western edge of the University of Wisconsin campus, at the very crossroads of science and industry. In this new position, I not only continued to draft all of the patent licenses but I also became a member of the licensing team and became involved in structuring and negotiating the business deals. After I was asked to join the management team, I began to guide WARF from a business perspective.

During my career at WARF, I was also a member of the committee that reviewed and accepted invention disclosures submitted each month by scientists on campus for intellectual property protection and commercialization. I studied these disclosures and listened to the discussion by scientific staff. During these discussions, I often felt like a person traveling in a country where I only had a limited grasp of the language. I loved learning about science, but I knew that to be more effective in all aspects of my job, I really needed to be able to speak the language of science. This led to my decision to investigate the possibility of obtaining a degree in some aspect of the biological sciences.

When I was accepted into the masters program in bacteriology in the fall of 2000, I thought I knew what I would do with the degree, but I never could have guessed where it would lead me. I had chosen the bacteriology department at the University of Wisconsin for several reasons. Firstly, the department offered a part-time all-course-work-based masters of science program, and this fit my full-time work schedule. Secondly, I wanted to take the patent bar and in order to accomplish this, I needed 30 or so credits in specific course work. Basically, I figured that if I was going to take 30 or more credits, I ought to get a degree rather than just take the classes. Thirdly, I wanted to become fluent in the language of science, and the course-work approach offered me a chance to learn about a lot of different scientific disciplines. I optimistically set off for my first two classes along with the undergrads since I had only studied biology and chemistry as part of the breadth requirements for my B.A. I soon learned that this was not going to be a walk in the park for someone who hadn't taken a science class since 1984.

I have to credit my father with getting me through that first year. I spent a lot of time studying, and I was struggling. My husband was very supportive as we juggled two careers, two kids, as well as my course load. One particularly bad day, after failing a biochemistry exam, I began weighing my options. I wondered whether I had made a mistake, when I remembered something my father had said. As a high school student or an undergrad, whenever I would come to him and make my case for dropping a class, he would listen and then tell me, "We're not quitters in this family—redouble your efforts!" I used to get angry with him for his never-give-up attitude, but apparently, he made his mark on me; as I struggled with classes for which I had not taken the required prerequisites, I knew I could not quit—it just wasn't a choice. So, I redoubled my efforts. I dropped biochemistry, went backwards, and took organic chemistry. I took the prerequisites and then I went forward. It took me four and half years, taking one or two classes at a time year-round to finally finish that masters degree, but I learned the language of science, and I fell in love with it.

During my final summer in the

> *"…the somewhat circuitous route of my career path provides me with a wide variety of skills that I use every day."*

masters program, I worked a couple of hours a week in a lab growing human embryonic stem (hES) cells. At WARF, I had the dubious privilege of managing the patent portfolio covering the hES cells. WARF had taken a lot of criticism for the management of these patents, and I was grateful for the opportunity to think about the amazing scientific potential of these cells, rather than fight another battle over them. I did not know it then, but working in the lab that summer turned out to be yet another career-defining moment.

I finished my directed research, wrapped up my degree, and passed the patent bar. I had planned to use these tools to take over the managing director's position at WARF when my boss retired. I was eager to lead a business based on science using the experience I had gained in banking, law, and technology. It was at this time, however, that I was asked to serve as interim managing director of WiCell Research Institute (WiCell), WARF's stem cell research subsidiary.

I was continuing to learn a lot from the stem cell research community when I met Dr. Cezar, an assistant professor at the University of Wisconsin. She had developed an interesting technology using hES cells and metabolomics to test whether drugs would cause birth defects in the developing human embryo. I was intrigued by both her technology and her energy. We talked about forming a company together around her technology, combining hES cells and metabolomics to identify biomarkers of drug toxicity, efficacy, and human disease.

In mid 2006, Wisconsin's Gov. Jim Doyle announced an initiative to provide funding to stem cell companies located in Wisconsin. This was an economic development initiative designed to leverage the significant scientific expertise in the Wisconsin stem cell research community in response to California's $3 billion Proposition 71. Dr. Cezar and I met again and decided the time was right to build the business plan for Stemina Biomarker Discovery around her technology. At our next meeting, we decided that I would take the business leadership role and leave WARF and WiCell. Dr. Cezar would stay at the University and take the scientific leadership role at Stemina as chief scientific officer.

> "I was eager to lead a business based on science using the experience I had gained in banking, law, and technology."

In October 2006, I gave notice that I would be resigning my positions at WARF and WiCell. It was a leap of faith, as Thoreau would say, but I haven't regretted it for a minute. We built our business plan, obtained a $1 million start-up package from the state of Wisconsin under Gov. Doyle's initiative, raised $1.6 million in angel capital, built our facility at the UW Research Park, and opened our doors on Nov. 1, 2007.

With our one-year anniversary now behind us, I can truthfully say that I have never done anything that I enjoy more. Our scientific team is tremendous, and I'm proud to say that I not only attend the science meetings every Friday, but I participate fully in the discussion of our results and planning our next experiments. Meanwhile, I run the business and legal aspects of the company every day.

I never would have anticipated that I would run a hES cell research company one day, but looking back, it seems that every stop along the way in my career and education was specifically designed to prepare me for this opportunity. I use the financial knowledge I learned from banking and my MBA to monitor our finances and maximize our funding. I use the legal knowledge in business, securities, and intellectual property law gleaned from my experience in private practice and at WARF to set up our company, draft our financing documents and stock option plan, negotiate our licenses from WARF, and prosecute our patents. And finally, I use my scientific knowledge to help plan experiments. Career-defining moments are difficult to recognize, but in hindsight, they are hard to miss.

Mastering Media Matters

BY SARAH CRESPI

Your science is good, but what about your PR skills? Although most scientists sigh and look heavenward at the mere mention of networking and glad-handing, there are several compelling reasons to let others know what you're up to in the lab.

Why participate? One very good reason: your institution will be pleased with the thought of receiving good press and a higher profile. The journal publishing your work will be very happy with the positive attention as well. And probably the most rewarding reason: your family will clip it out.

More substantially, communicating research, especially the fruit of government grants, is the duty of all members of the scientific community. It also demonstrates to the paying public the importance of funding scientific research.

"Try to provide some perspective on the human impact of your work"

Getting it Done

OK, so now you've signed up for an interview. Here are a few things to think about: who is the target audience? Other scientists, specialists, or the general public? The first two types of readers may make your life easier, in terms of not having to define a protein, but be prepared for complex questions; ask if the journalist can send some in advance.

During the interview, feel free to interrupt yourself and start a quote over. You don't need to speak in complete paragraphs. Take a breath; the journalist isn't always waiting for you to talk more—they might have to take notes or compose a question.

An interview aimed at the last group, the general public, requires a different kind of preparation.

Think about metaphors for the specifics you work with; is there something you can compare it to that will help non-scientists understand? Make numbers easy by using reference points in laymen's terms, like pennies, pin heads, inches, and pounds. Provide the practical implications of your research. How will it really affect people's lives?

The journalist will be looking to include this information whether you supply it or not. Try to provide some perspective on the human impact of your work.

And lastly, ask to review the accuracy of the science included in the piece, even if the journalist has a science editor.

However, don't expect to get to rework your quotes or overhaul the entire article. What's most important is the accuracy of the science.

What are your peeves and praises when it comes to journalists and science writing? Let us know at Tekkie@asbmb.org.

Sarah Crespi is a Multimedia Communications Specialist at ASBMB. She can be reached at screspi@asbmb.org.

Science Journalists Speak Out*

Peeves

- "Everyone has deadlines. Sometimes a swift 'no' from you will allow the journalist to move on to another source. Be honest about your time and your interest in participation."
- "Scientists who lapse into jargon. We're writing for a general audience and need to know about their research in the most basic and understandable terms possible."
- "One word answers to questions."

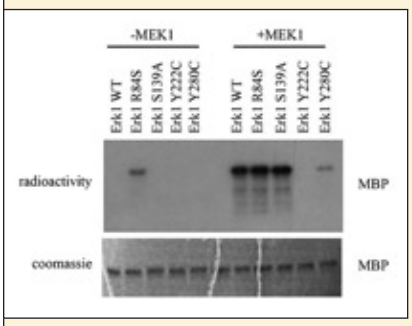
Praises

- "A good interview is one that flows like a casual conversation and is one in which you can hear the scientist's enthusiasm about their research."
- "A researcher who has thought about their subject from a number of different perspectives—as a scientist, as a citizen, and as a human—and helps convey that broad view to the public."
- "I love anecdotes that bring readers into the lab or thought process of the researcher."

From an informal poll of science journalists and communication officers.

Active and Always ERKing

Mitogen-activated protein kinases (MAPKs) are highly conserved signaling proteins that require dual phosphorylation of a threonine and tyrosine residue for their activation. Multiple MAPK proteins and isoforms are present in all eukaryotic cells and are typically activated concomitantly in response to a given stimulus. As such, it can be difficult to pinpoint the role of individual MAPKs. Creating mutant, constitutively active forms of MAPKs is one approach to delineate individual function, but this strategy is problematic as phosphorylated tyrosines cannot be mimicked accurately. In this paper, the authors used yeast genetics to develop intrinsically active forms of the Erk MAPK family. They first identified six variants of the yeast Mpk1/Erk enzyme that were active despite the absence of the upstream MAPK kinase; one variant altered a conserved arginine residue, which they then mutated in mammalian Erk1 and Erk2. Both mutant mammalian Erk kinases displayed high intrinsic activity *in vitro*, and the Erk2 mutants were also active in human embryonic kidney cells; this activity was a result of acquired autophosphorylation and could be increased even further by the *sevenmaker* mutation that prolongs kinase activity. As these arginine residues are conserved in multiple MAPKs, they should point the way toward generating other active mutants.



The R84S Erk1 mutant displays *in vitro* activity even in the absence of its activator (MEK1).

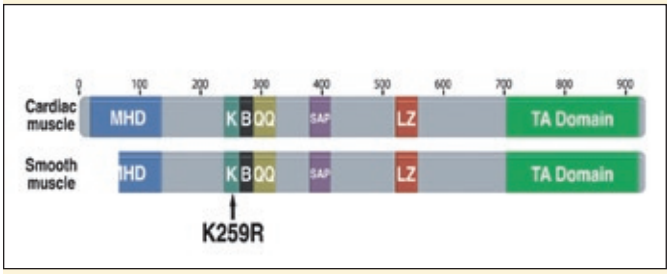
Isolation of Intrinsically Active (MEK-independent) Variants of the *ERK* Family of MAP Kinases

Vered Levin-Salomon, Konstantin Kogan, Natalie G. Ahn, Oded Livnah, and David Engelberg

J. Biol. Chem. 2008 **283**, 34500–34510

Myocardin's Missense Mutation

Myocardin (MYOCD) is a transcriptional co-activator that binds to myocyte-enhancing factor (MEF2) or serum response factor (SRF) to activate cardiac or smooth muscle gene programs. The MYOCD smooth muscle isoform, however, lacks the amino-terminal MYOCD homology domain (MHD) and as a result has higher activity. In this study, the researchers explore the role of MHD in regulating activity with the aid of a rare missense mutation they identified: MYOCD K259R, a variant with impaired SRF binding in cardiac cells but normal smooth muscle activity. The researchers assayed MYOCD along with MHD and found that the amino terminus exerts an autoinhibitory effect by binding to MYOCD; this binding disrupts SRF activation and could inhibit the conversion of fibroblasts into smooth muscle cells. The inhibitory effect was exaggerated with the K259R variant, indicating that this is a gain of function mutant that leads to cardiac hypotrophy. These elegant findings should provide fresh insight into the biology of myocardin.



Comparison of the cardiac and smooth muscle isoforms of myocardin.

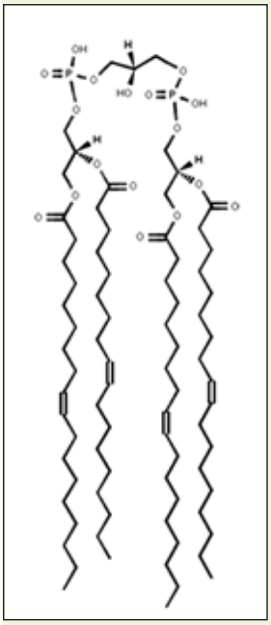
A Rare Human Sequence Variant Reveals Myocardin Autoinhibition

Joshua F. Ransom, Isabelle N. King, Vidu Garg, and Deepak Srivastava

J. Biol. Chem. 2008 **283**, 35845–35852

Warburg Revisited

Over 75 years ago, Otto Warburg first proposed that cancer originated from irreversible injury to mitochondrial respiration. Since then, however, the structural basis for impaired respiration has remained elusive, and much controversy remains surrounding the Warburg effect. In this study, the researchers evaluated the composition of cardiolipin (CL), a phospholipid found almost exclusively in the inner mitochondrial membrane that is intimately involved in maintaining mitochondrial integrity and function. They used shotgun lipidomics to analyze CL content in purified brain mitochondria from mice, as well as several subcutaneously grown brain tumors derived from those strains, including an astrocytoma, ependymoblastoma, a stem cell tumor, and two microgliomas. Major abnormalities in CL were observed in all of the diverse tumor samples; the compositional abnormalities involved an abundance of immature lipid species and lack of mature CL molecules, suggesting major defects in CL synthesis and remodeling. The tumor abnormalities were also associated with significant reductions in both individual and linked electron transport chain activities, thus providing an evidentiary link between mitochondrial defects and cancer.



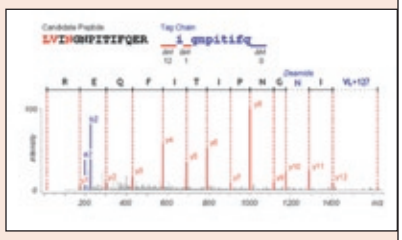
Structure of 1,1',2,2'-tetraoleyl cardiolipin, one of the over 100 CL molecular species present in mouse brain mitochondria.

Cardiolipin and Electron Transport Chain Abnormalities in Mouse Brain Tumor Mitochondria: Lipidomic Evidence Supporting the Warburg Theory of Cancer

Michael A. Kiebish, Xianlin Han, Hua Cheng, Jeffrey H. Chuang, and Thomas N. Seyfried

J. Lipid Res. 2008 **49**, 2545–2556

An Eye for Modifications



MOD^{i} uncovers an uncharacterized mass of 12 Da at the N terminus of the ^{67}LVINGNPITIFQER^{80} peptide of GAPDH, which may represent a novel modification.

Most proteins undergo a variety of post-translational modifications (PTMs) that can significantly affect their cellular functions. Procedures for identifying PTMs, such as mass spectrometry, are therefore critical to understanding protein biology. However, because examining all possible PTM combinations can be exhaustive, most existing search tools for MS analysis are restrictive and only take a few types of PTMs as input, which might overlook important modifications. In this study, the researchers describe a new algorithm, called MOD^{i} ("mod eye"), which rapidly searches for all known types of PTMs at once without limiting the number of possible modified sites in a peptide. MOD^{i} does so by introducing the notion of a tag chain, a structure made from multiple sequence tags that effectively localizes modified regions within a spectrum and overcomes *de novo* sequencing errors common in tag-based approaches. With this creative approach, MOD^{i} effectively manages the computational complexity of peptides with multiple PTMs and can even identify novel PTMs. As a proof of principle, the researchers tested MOD^{i} performance in an analysis of PTM-rich proteins such as glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and lens protein.

Unrestrictive Identification of Multiple Post-translational Modifications from Tandem Mass Spectrometry Using an Error-tolerant Algorithm Based on an Extended Sequence Tag Approach

Seungjin Na, Jaeho Jeong, Heejin Park, Kong-Joo Lee, and Eunok Paek

Mol. Cell. Proteomics 2008 **7**, 2452–2463

Browsing Molecules by the Bay

BY NICK ZAGORSKI

The nondescript building housing the SSRL belies the impressive technology contained within.

"Never judge a book by its cover." It's an old saying but often an apt one. That's certainly the case with the complex that houses the Stanford Synchrotron Radiation Lightsource (SSRL). Standing in front of the nondescript aluminum-sided building and nearby trailer where the offices are housed, nestled among some of California's picturesque golden-brown hills just west of the main Stanford campus, one gets the feeling of being at an industrial warehouse or construction site, as opposed to one of the world's leading scientific resource centers.

While wandering the interior of the building, accented with a maze of pipes and instrumentation that surrounds the circular core of the synchrotron, a visitor may start to wonder why Clyde Smith, a jovial Kiwi who has been a staff scientist with SSRL's Macromolecular Crystallography (MX) group since 2003, seems so excited about the place. "I first visited here 10 years ago, and ever since then, I've wanted to work here," he says.

Smith then explains that the somewhat haphazard appearance of the synchrotron enclosure stems from its place in history—the SSRL happens to be the oldest synchrotron X-ray scientific user facility in the world, having started operations in 1973. Initially, this large, electromagnetic donut (80 yards in diameter) was built specifically as an electron-positron collider for particle physics experiments, but in the early 1970s, some enterprising Stanford faculty realized that they could leech off the radiation produced by accelerating the electrons for other applications, including X-ray crystallography. Thus, many beam lines, radiating out like spokes on a wheel, have been constructed around the synchrotron over the years to harness the energy and make it available for scientific discovery.

With funding from NIH's National Center of Research Resources (NCRR), the first instruments aimed at biology studies were developed at SSRL in 1980, and today, NCRR, with additional support from NIGMS and the DOE's Office of Biology and Energy Research, supports SSRL's structural biology enterprise. Currently, the SSRL houses 13 operational beam lines, although quite a few branch out further, resulting in nearly 30 actual experimental stations. Of these, the MX group has six beam lines at their disposal, with a seventh in construction, that serve around 1,000 scientific users from academia, national labs, and industry each year in experiments that span from understanding the relationship of biological structure and function to designing new drugs.

Then, as Smith proceeds to one of the workstations, the wonder starts to sink in. And it's not just the giant automated X-ray beam, which is reminiscent of many a laser present in the lairs of Bond villains. For in the middle of this device, affixed to a thin fiber loop and continually blasted by super-cool nitrogen gas, is the object of the machine's affection. It's a tiny crystal, no bigger than a pinhead, which holds within it the structural secrets of a protein—that is, the precise location of every one of its thousands of individual atoms. And for the dedicated staff of the MX group, their job is to make sure those secrets become unlocked.

A Man and a Mission

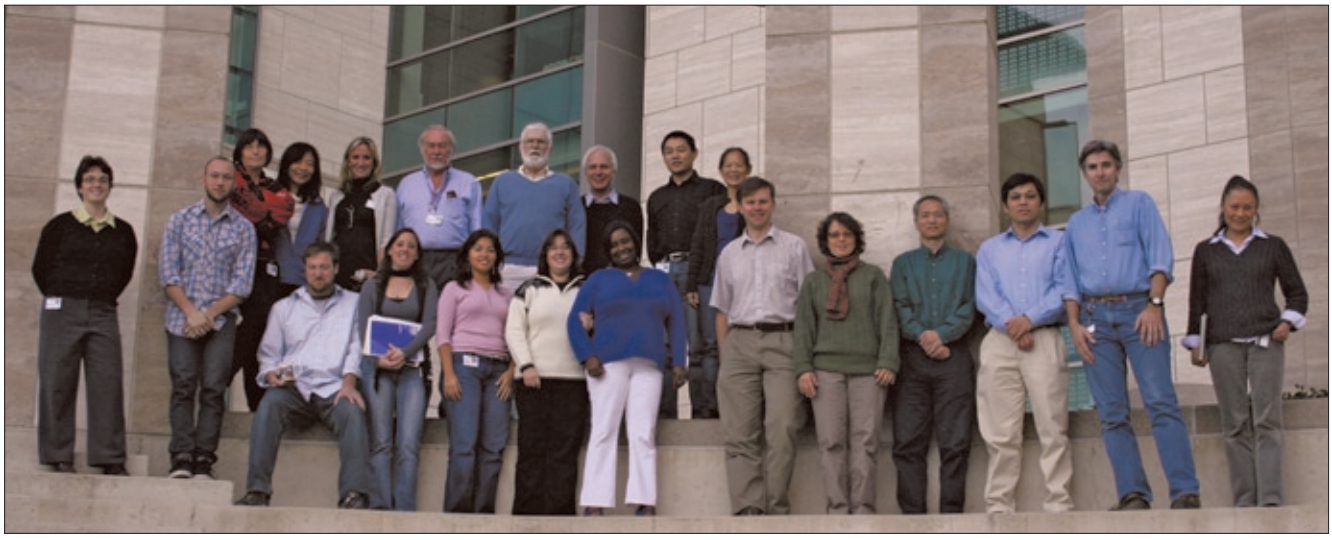
Approximately 35 miles up Highway 280, the new Mission Bay campus of the University of California, San Francisco, located right near the waterfront, offers up a different aesthetic perspective. Distributed around a spacious tree-lined quad, the newly built buildings of Mission Bay provide a sense of urban luxury—well exemplified by the modern, fully equipped fitness room in Mission Bay's community center (named for William J. Rutter, former chair of Biochemistry and one of the prime movers in creating the Mission Bay campus).

And inside one such building, Genentech Hall, there is a workroom that houses its own share of impressive equipment used in protein analysis. Known by monikers such as MALDI and Orbitrap, the 10 machines present here are mass spectrometers, instruments that offer their own take on structural determination. By separating and fragmenting protein samples, mass spectrometers can yield insights into individual proteins, such as the presence of modifications like phosphorylations or identify the individual components of complex protein samples, making mass spec an intimate necessity for proteomics.

As Al Burlingame, a professor of pharmaceutical chemistry and director of this Mass Spec facility, points out some of the different spectrometers available for use, he recounts the somewhat unusual origin of this facility. Back in 1970, he was quite removed from biology, instead working on the organic geochemistry of moon rocks; with the lunar programs winding down, though, Burlingame needed a new research direction and found one while studying biomedical mass spectrometry on a Guggenheim fellowship in Sweden (see sidebar story).

Realizing the immense potential of this application, Burlingame wrote up his own grant to NIH's, NCRR to set up a mass spec resource back in the U.S. The grant was approved in 1973, the same year crystallography began at the SSRL. The Mass Spec resource was initiated at the University of California, Berkeley, where Burlingame was a research chemist, then relocated to nearby UCSF in 1978, where prominent scientists like Bruce Alberts, Stan Prusiner, and J. Michael Bishop offered a strong biology presence to support this fledgling operation.

Initially, the Resource's work was primitive, by Burlingame's own account: "We analyzed DNA adducts, oligosaccharides, small molecules like that." In the 1980s, though, mass spec entered the big time. "Back then, everyone was working on two-dimensional gels and Edman degradation to identify proteins," Burlingame says, "and I knew that tandem mass spec could beat the snot out of Edman degradation." And, he was right. Burlingame recalls getting a sample of rat sialyltransferase required for synthesis of Sialyl Lewis X antigen from UCLA colleague Jim Paulson, who had spent nearly 15 years trying to sequence it. "We obtained about 25 percent of the sequence within a week. That set the stage for what would eventually emerge as proteomics."



Members of the Mass Spectrometry Facility. Back row (*L to R*): Katalin Medzihradszky, Feixia Chu, Ana Gago Martinez, Al Burlingame, Ralph Bradshaw, Ralf Schoepfer, Yi Guo, Nancy Wang. Front row (*L to R*): Gigi Knudsen, Sam Myers, Mike Trnka, Jordane Biarc, Paty Salas Castillo, Patricia Ruperez, Ronde Stephens-Pitts, Robert Chalkely, Kris Casler, Shenheng Guan, Frank Li, David Maltby, Kathy Li.

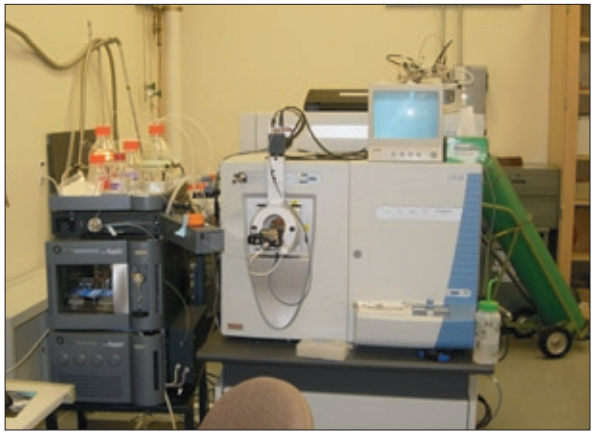
PHOTOGRAPH COURTESY OF AENOCH LYNN.

Two of a Kind

While the SSRL MX Group and UCSF Mass Spec Resource may differ a bit in style, their substance is much alike. As National Research Resources, both centers share the common goal of providing their technologies as a service to researchers from across the world (these services are generally free, although at SSRL, users who do private sector research are charged full cost recovery, around $250/hr). These facilities on the San Francisco peninsula are just two of about 60 such NCRR-supported U.S. resource centers nationwide, which include other crystallography and mass spectrometry centers, as well as centers for other technologies such as NMR, cryo-electron microscopy, and computational biology.

Of course, while X-ray macromolecular crystallography and mass spec can be expensive (a state-of-the-art spectrometer runs for over $1 million while a complete X-ray workstation can be over $5 million) and technically demanding, these applications are not beyond the reach of individual research institutions. Says Burlingame, "The commercial mass spec instrumentation is pretty easy to use these days; scientists only need minimal training to undertake most standard applications." Likewise, relatively routine structures can be done by in-house X-ray sets. So why, then, do scientists from all corners of the globe still apply in droves—Burlingame typically works with around 100 collaborators at any given time, with topics spanning plant biology to stem cells—to utilize these resources?

On the mass spec side of things, a resource hub like UCSF helps counter the rapid cycle time of spectrometer technology. "Right now, the time that a certain machine remains 'cutting edge' is two years or less," Burlingame notes. While X-ray beam lines are somewhat universal (the MX Group has tweaked their six stations to try and make them as identical as possible to avoid long queues on customer favorites), one requires different methods of fragmenting and analyzing protein samples, depending on their strategy. Therefore, it may be more economical for a research group to use a shared central resource that always has the top-of-the-line equipment, instead of continually recycling their spectrometers.



An Orbitrap mass spectrometer with electron transfer dissociation (ETD) connected to a high pressure liquid chromatography system from Waters, one of UCSF's new machines that will tackle post-translational modifications in histones and chromatin.

As for crystallography, the SSRL does offer quite a bit more than the norm. Having a giant synchrotron as a radiation source allows for much higher-resolution structure determination, and in cases where the protein crystals are small (well, small for a crystal) or scatter X-rays poorly, this additional brightness is a must.

"The majority of structural challenges being undertaken today, like large complexes or molecular machines, can only be done with the brightness available at a synchrotron; it's why the demand is so great, not just here, but at all 45 MX beam stations spanning the six operational U.S. synchrotrons," notes Keith Hodgson, Stanford Professor and creator of the structural biology program at SSRL. As testament, he highlights that 82 percent of all new structures deposited in the Protein Data Bank (PDB) in 2007 were done using synchrotron radiation.

And then there's the automation. "It's an area of immense pride for us," Smith says, pointing to the robotic arm attached to the workstation. "We've set up our robot to load crystals almost exactly like a human would. They were a bit temperamental in the past, but now are extremely efficient and even self-correcting." The robot holds three 96-well cylinders, so each beam can run 288 crystal samples in one run, which is ideal for screening large data sets to identify crystals that provide the best resolution.

In fact, the whole workstation is fully automated, and with the aid of a computer program called Blu-Ice and control and video that are network distributed, beam line users can access the machines from the comfort of their own lab, home, or favorite internet café. All they have to do is send their materials over to the SSRL, then log on during their scheduled beam time, and collect data remotely. The Mass Spec Resource offers a similar no-hassle system; researchers can send their protein samples over to UCSF and into the capable hands of facility manager David Maltby, and then sit back until they receive an email with their results.

That convenience certainly increases the appeal of these resources, though it may not be so exciting for the staff. "Back in the day we would have visitors from all over come to the building and work with us," Smith says, "but now hardly anyone comes in anymore."

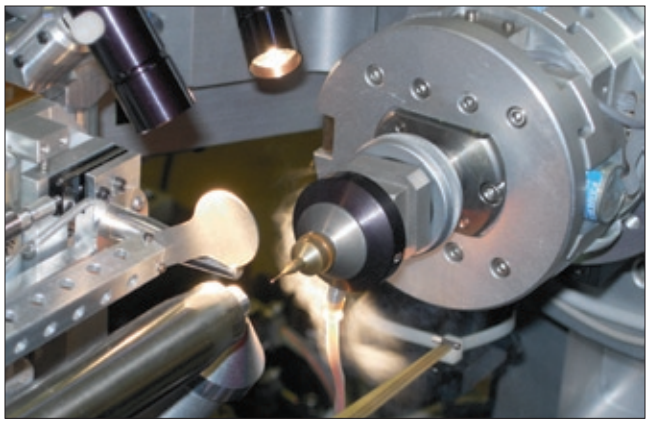
It's a shame too, because remote users are missing out, and it's not just the generally fantastic Bay Area weather—"Our previous location on

Parnassus Hill in the center of the city could get a bit foggy," says Robert Chalkley, an assistant professor at the mass spec facility, "but at Mission Bay, not only are we less isolated from our colleagues than before, but it's always sunny."—No, the real loss is that despite their speed and power, these high-tech machines are still just pieces of equipment. The true heart of these two resources, and the real reason behind their success, is the people.

Covering a Full Spectrum

Shannon Eliuk had heard many great things about the UCSF Mass Spectrometry resource while a graduate student at the University of Alabama at Birmingham. "Dr. Burlingame is regarded as a leader in the field, and his center is pretty well known," she says. "It was definitely one of my top choices for a postdoc and I'm excited to have been offered the position."

And in the three months since joining the UCSF group, Eliuk, whose main project focus is analyzing changes in histone modifications during stem cell differentiation, has been more impressed. "Everyone here is really bright, and among them we have experts in every aspect of mass spectrometry, be it the chemistry, biology, or programming," she says. "It's almost like having an encyclopedia around you."



A protein crystal (affixed to the fiber loop, (*center*) prepares to be blasted by an X-ray beam.

Currently, this living encyclopedia comprises 18 people, headed by Burlingame and Deputy Director Ralph Bradshaw (the two are also co-editors of *Molecular & Cellular Proteomics*), who moved to the Bay Area a couple of years ago after 25 years at UC Irvine. The remaining team consists of four junior faculty members, assorted postdocs, and specialists (the UCSF nomenclature for non-tenure track research scientists), who work on both independent projects and group efforts with external collaborators.

While the projects run a wide path, and include areas like neurobiology and parasitology, the main thrust of the UCSF Mass Spec Resource is post-translational issues, particularly phosphorylation and chromatin remodeling. (Bradshaw and Kati Medzihradszky, another professor at the facility, recently co-organized an ASBMB meeting on this topic at Granlibakken in the Sierra Nevada (see story on p.14)). This specialization helps UCSF carve out a unique niche to draw in interested investigators; Burlingame points out that there are several NIH Mass Spectrometry Resources across the U.S., each one with a slightly different bent. For example, Catherine Costello leads a resource at Boston University that concentrates on glycobiology, while the resource at Washington University at St. Louis, a noted medical institution, focuses on clinical applications.

"Mass spectrometry becomes invaluable in this area because it's really the only unbiased method to analyze post-translational modifications," notes Chalkley, who works extensively on a sugar modification known as O-GlcNAc. "With other approaches, you have to make assumptions as to where a modification might be." Mass spectrometry also proves its worth when studying combinatorial modifications like histones, where multiple side chains can be modified by several different chemical groups. The UCSF center has, in fact, just received its first instrument that uses electron transfer dissociation (ETD) technology. "It's the next wave in terms of defining epigenetic changes," says Burlingame.

But even the most sophisticated spectrometer can be rendered useless if one cannot properly prepare and interpret the data. "People don't appreciate how sensitive and universal a mass spec is," Burlingame says. "It's not like identifying a protein with antibodies, where it doesn't matter that there are 1,000 other molecules around the protein of interest. Contaminants like cytokeratins," he says as he rubs his hair, "ionize perfectly well. It just takes a tiny bit of dust and hair to settle on a sample to produce a spectrum of total garbage. And that leads to another common issue; many people do not know the difference between a good spectrum and bad spectrum."

Fortunately, this resource shines at training. For the past 15 years, Burlingame has offered a yearly (formerly every two years) hands-on course on proper mass spectrometry use. The course includes a series of lectures that discuss the latest buzz-words in the field, as well as a laboratory portion where participants can bring their own biological samples and learn about sample handling, extracting protein from gels, and data analysis. At the end, everyone presents a lecture on their project so everyone in the group can be filled in.

For scientists who know a little more about what they're doing,

the UCSF Resource still has much to offer. Most notable is a software package called Protein Prospector. As Aenoch Lynn, a specialist whose expertise lies with computer programming and data management, notes, data analysis is still the name of the game. "For a given experiment, you're most likely looking at one week of preparation, one day of running the sample through the machine, and then one month of looking over the results."

Prospector looks to make that final and most important portion more bearable. This research suite, first developed at UCSF in 1996 by programmer Peter Baker and graduate student Karl Clauser (now at the Broad Institute), features numerous aids, most notably protein database search programs that allow you to easily identify your protein samples. Lynn and Chalkley have been continually modifying and updating Prospector over the years and have a brand new version available for public use (prospector2.ucsf.edu), which they believe is the best spectrum analysis software out there.

As Cool as Ice

When it comes to X-ray crystallography, data analysis is a serious business as well. "It would be great if a researcher could just place a crystal into a beam line, press 'Start' and get a nice PDB image sent to them a few hours later," says SSRL staff scientist Ana Gonzalez, "but that's not the case." Well, at least not yet; Gonzalez, head of the MX group's User Support Team, has been using her programming skills to make interpreting all that X-ray scattering data less painful.

Her most recent endeavor has been developing a program called Web-Ice that integrates data analysis into the data collection process. Web-Ice calculates some basic parameters of an X-ray scatter plot and then produces a score that determines whether that plot is worth looking at. This program works great for individuals interested in large-scale crystal screenings, as they can quickly identify their best samples. "You still have to make some decisions about the sample, but we definitely make the screening process as easy as possible," Gonzalez says.

"I think our efforts at improving the user experience provide a great example of why we believe that, support-wise, our beam lines are the best in the country," states Irimpan Mathews, another MX staff scientist. In his case, Mathews aims to improve the pre-beam line portion of crystallography, namely generating the crystal. He notes that crystallization is easier now than in the past due to the availability of numerous pre-made solutions, but the process remains tricky and time-consuming (see sidebar). "For example, we still don't have an easy way of mounting crystals," he

Ahead with Axel

Photon Science faculty member Axel Brunger (who happens to be a former protégé of current society president Gregory Petsko), has always been forward thinking; his knack for seeing emerging problems and trends in structural biology helped him devise the widely used X-PLOR and CNS programs that refine atomic models to match the observed diffraction data and led him to be one of the first researchers to integrate both computation and "wet-lab" biology in his work.

That foresight would make Brunger, also a professor in the Departments of Molecular and Cellular Physiology, Neurology and Neurological Science, and Structural Biology (by courtesy) at Stanford University as well as an HHMI investigator, an ideal person to ask about the current and future challenges facing crystallography. Interestingly, though, the answer he gives is timeless.

"Getting good crystals remains the biggest obstacle, especially with some of the trickier biological systems like large protein complexes or membrane proteins," he says. "Due to mobility, these proteins simply won't produce crystals that diffract to high-resolution."

Solving this 'low-resolution challenge' will require both direct and indirect strategies, he notes. The direct approach involves new microcrystal beam lines (SSRL is commissioning one right now) that will raise the bar on diffraction. "On conventional beam lines, the beam diameter is often larger than some of the crystals being studied," he says, rendering small crystals essentially useless due to background noise and radiation damage. But, while previously a crystal size of several hundred microns would be considered 'good,' new microcrystal beam lines allow high-resolution structure determination for crystals as small as 10 microns.

That number might get even smaller. "Eventually, you're going to run out of unit cells, but I'm curious as to how far we can push it."

Brunger himself is exploring the possibility of side-stepping low-resolution problems by means of 'super-resolution,' a computational approach that takes advantage of the more than 30,000 available structures of individual domains in the PDB. "After we acquire a low-resolution image of a structure, we plan to use this vast resource to enhance the structure and exceed the nominal diffraction limit of the crystal."

Of course, in the future, crystals may be removed from the equation entirely. Brunger notes that the SLAC (where SSRL is housed) is constructing a new, extremely intense beam called the Linac Coherent Light Source (LCLS). This powerful laser will act like a high-speed molecular camera and could have several macromolecular applications, like time-resolved studies of cellular reactions. "And though it's still an open question, in theory, the LCLS could allow the time-resolved imaging of proteins in a non-crystalline state."

says, "so I've been looking at methods to directly crystallize a protein on the mounting loop to save time and resources." Another area of concern is radiation damage from the X-rays that eventually wears down a crystal, and Mathews has been looking at ways to reduce radiation damage while still retaining resolution.

It's all in a days work for the tireless staff in the SSRL MX Group. Under the guidance of group leader Michael Soltis, the 30-odd team members keep the workstations in tip-top shape and provide assistance in the set-up, running, and analysis of all crystals (the facility is up and running nine months of the year, 24-7, while the summers are reserved for maintenance and improvements to the synchrotron and instruments). The staff are divided into two principal groups, beam line scientists who primarily work in user support and maintenance and staff scientists like Gonzalez, Mathews, and Smith who split time between support duties and independent research projects (though as staff they often don't write up their own grants and instead collaborate with other investigators).

So, when he's not helping a Japanese researcher figure out why his crystal isn't diffracting well, Smith is solving structures of antibiotic deactivating enzymes like aminoglycoside phosphotransferases. "I'm fascinated by the continual evolutionary battle between bacteria and antibiotics," he says, adding that he could go on all day talking about this topic. "But to think, we haven't been using beta-lactam drugs like penicillin very long, and we're already on the fourth generation of these antibiotics. It's a fight we can't win, but I'm going to do my part to try and keep up."

The MX group also runs training workshops a few times each year to familiarize users with all the intricacies of the SSRL beam line environment. These courses cover all aspects of running a sample, whether locally or remotely, such as how to prepare and ship samples, run large sample sets with the automated robot, and use interface programs like Blu-Ice and Web-Ice. In addition, Mathews and other staff participate in a summer internship program that provides enterprising high school or college students a thorough introduction to the wonders of crystallography (Mathew's most recent student has been helping him work out new crystal mounting applications).

With such dedicated and knowledgeable staff, it's no surprise the MX group receives its own share of accolades. "The facility is outstanding," says noted biologist and biophysicist Axel Brunger, a member of the Stanford faculty who works with the team on development issues, from his office on the main campus of Stanford. "It's one of the main reasons I took a position at Stanford, since I had the ability to be right next door to such a tremendous resource."

Back with Burlingame

Looking back, all the researchers who have benefitted from the UCSF Mass Spectrometry Resource during the 35 years it's been running should be thankful Al Burlingame didn't have as much exuberance for the space program as some of his peers.

Back in 1968, Burlingame became involved in the project to analyze the lunar samples that were going to be brought back from the Apollo missions. "There was a lot of initial excitement in that," he says. "Some people thought that the moon would be composed of carbonaceous meteorites, though it became clear after first material was studied that this was not the case." And though his group carried out some valuable experiments, like analyzing solar wind chemistry, by 1970, Burlingame knew that the program was quickly coming to an end—he notes that President Nixon had tried to shut it down once already.

"And while some of my colleagues began looking forward to the forthcoming Mars missions, I had become fed up with the space sciences by then," he says. And that led him to his fateful sabbatical at the Karolinska Institute in Solna, Sweden.

"The use of mass spectrometry in biomedicine is really intertwined with Sweden, from work at both the Karolinska and the University of Gothenburg," Burlingame says, citing the pioneering mass spec analysis of tuberculosis lipids in the 1950s and as part of the Nobel-winning studies of prostaglandins carried out by Bengt Samuelsson and Sune Bergstrom in 1959–1962. "I grew up on the other side of the fence, having used mass spectrometry in natural product research and drug development, but after seeing the Swede's perspective on this technology I reached a turning point in my career."

Upon Further Review

On second glance, it appears the SSRL MX Group and UCSF Mass Spec Resource may not be so different after all. Sure, one center gives you the chance to irradiate proteins in the quiet California countryside, while the other lets you vaporize them amidst the hustle and bustle of downtown San Francisco, but both house top of the line equipment, excellent support staff, and abundant training opportunities for applications that are becoming more and more essential for almost any biochemical, molecular, and cell biologist out there. So, if you need to conduct some protein crystallography or mass spectrometry in your research, you can't go wrong paying either place a visit… or a virtual one at least.

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

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Monica Burney
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Maricelis Camacho
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THE HAVEL LECTURE

"Adventures In Lipid Metabolism"
Stephen Young, University of California, Los Angeles, CA

Session 1: Transcriptional Regulation of Lipid Metabolism

"Macrophage Subtypes and Diabetes Mellitus" Chris Glass, University of California, San Diego, CA
"Transcriptional Control of Hepatic Lipid Metabolism" Marc Montminy, Salk Institute, La Jolla, CA
"PGC-1 and SIRT1 Interactions" Pere Puigserver, Harvard, Boston, MA
"Functional Roles of Nuclear Receptors in the Adipocyte" Mitch Lazar, University of Pennsylvania, Philadelphia, PA

Session 2: Protein–Lipid Interactions

"Phospholipids and Protein Folding" William Dowhan, University of Texas Health Science Center, Houston, TX
"Sterol Binding to INSIGS and Regulation of Cholesterol Metabolism" Arun Radhakrishnan, Cornell Medical School, New York, NY
"ANGPTL Proteins" Jonathan Cohen, UT Southwestern Medical Center, Dallas, TX

Session 3: Lipid Metabolizing Enzymes

"Metabolite Profiling to Identify New Lipid Metabolizing Enzymes" Benjamin Cravatt, Scripps Research Institute, La Jolla, CA *JLR* 50th Anniversary Lecture
"Crystal Structures of Bile Acid Biosynthetic Enzymes" Trevor Penning, University of Pennsylvania, Philadelphia, PA
"Intestinal Bile Acid Transport Mediated by OST"

Session 4: New Drugs Affecting Lipid Metabolism

"CETP Inhibitors" Molly Ranaletta, Merck Research Laboratories, Rahway, NJ
"Development of Lipid Lowering Therapeutics" Margrit Schwarz, Amgen, South San Francisco, CA
"Liver-Selective Thyroid Hormone Agonists as Cholesterol Lowering Agents" David Linemeyer, Metabasis Therapeutics, La Jolla, CA
"RNAi Approaches to Modifying Lipid Levels" Kevin Fitzgerald, Alnylam Therapeutics, Cambridge, MA

scientific meeting calendar

JANUARY 2009

Gordon Research Conference: Glycobiology
JANUARY 18–23, 2009
VENTURA, CA
www.grc.org/programs.aspx?year=2009&program=glycobio

Keystone Symposium–Obesity: Novel Aspects of the Regulation of Body Weight
JANUARY 20–25, 2009
BANFF, ALBERTA, CANADA
www.keystonesymposia.org/Meetings/ViewMeetings.cfm?MeetingID=997

Sanibel Conference on Mass Spectrometry: Lipidomics and Lipids in Mass Spectrometry
JANUARY 23–26, 2009
ST. PETERSBURG BEACH, FL
www.asms.org/Default.aspx?tabid=70

The 22nd Biennial Conference of the Australian & New Zealand Society for Mass Spectrometry
JANUARY 27–30, 2009
SYDNEY, AUSTRALIA
www.mmb.usyd.edu.au/ANZSMS22

FEBRUARY 2009

Gordon Research Conference—Plant Lipids: Structure, Metabolism, & Function
FEBRUARY 1–6, 2009
GALVESTON, TX
www.grc.org/programs.aspx?year=2009&program=plantlipid

Molecular Targets for Cancer Prevention Conference
FEBRUARY 4–5, 2009
BETHESDA, MD
http://web.ncifcrf.gov/events/cancerprevention/2009/default.asp

The 14th Annual Proteomics Symposium
FEBRUARY 6–8, 2009
LORNE, AUSTRALIA
www.australasianproteomics.org

Pacific Lipid Association 3rd Annual Scientific Forum
FEBRUARY 20–22, 2009
SALT LAKE CITY, UT
www.lipid.org

US HUPO 5th Annual Conference
FEBRUARY 22–25, 2009
SAN DIEGO, CA
www.ushupo.org
E-mail: ushupo@ushupo.org
Tel.: 505-989-4876

Keystone Symposium–Complications of Diabetes and Obesity
FEBRUARY 24–MARCH 1, 2009
VANCOUVER, BRITISH COLUMBIA
www.keystonesymposia.org/Meetings/ViewMeetings.cfm?MeetingID=998

2nd International Conference on Advanced Technologies & Treatments for Diabetes (ATTD)
FEBRUARY 25–28, 2009
ATHENS, GREECE
www.2.kenes.com/attd/Pages/home.aspx

Biophysical Society 53rd Annual Meeting
FEBRUARY 28–MARCH 4, 2009
BOSTON, MA
www.biophysics.org/2009meeting

MARCH 2009

Deuel Lipid Conference
MARCH 3–6, 2009
BORREGO SPRINGS, CA
www.deuelconference.org

Enabling Technologies for Structural Biology
MARCH 4–6, 2009
BETHESDA, MD
meetings.nigms.nih.gov/?id=4931

Gordon Conference on Oxidative Stress & Disease
MARCH 8–13, 2009
TUSCANY, ITALY
www.grc.org/programs.aspx?year=2009&program=oxidat

ACS Spring National Meeting & Exposition
MARCH 22–26, 2009
SALT LAKE CITY, UT
www.acs.org/meetings

APRIL 2009

3rd International Congress on Prediabetes and the Metabolic Syndrome—Epidemiology, Management, and Prevention of Diabetes and Cardiovascular Disease
APRIL 1–4, 2009
NICE, FRANCE
www.kenes.com/prediabetes

ASBMB Annual Meeting
APRIL 18–22, 2009
NEW ORLEANS, LA
www.asbmb.org/meetings.aspx

Keystone Symposium—Complex Lipids in Biology: Signaling, Compartmentalization, and Disease
APRIL 22–27, 2009
OLYMPIC VALLEY, CA
www.keystonesymposia.org/Meetings/ViewMeetings.cfm?MeetingID=961

Arteriosclerosis, Thrombosis, and Vascular Biology Annual Conference
APRIL 29–MAY 1, 2009
WASHINGTON, D.C.
www.americanheart.org/presenter.jhtml?identifier=3057022

2009 NLA Scientific Sessions
APRIL 30–MAY 3, 2009
MIAMI, FL
www.lipid.org

MAY 2009

American Thoracic Society International Conference
MAY 15–20, 2009
SAN DIEGO, CA
www.thoracic.org

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

Cancer Proteomics 2009
JUNE 8–12, 2009
DUBLIN, IRELAND
www.selectbiosciencies.com/conferences/files/Agendas2009/CP2009_Agenda.pdf

3rd EuPA Meeting—Clinical Proteomics
JUNE 14–17, 2009
STOCKHOLM, SWEDEN
www.lakemedelsakademin.se/templates/LMAstandard.aspx?id=2529

VII European Symposium of the Protein Society
JUNE 14–18, 2009
ZURICH, SWITZERLAND
www.proteinsociety.org

XV International Symposium on Atherosclerosis
JUNE 14–18, 2009
BOSTON, MA
www.isa2009.org

International Conference on Cytochrome P450
JUNE 21–25, 2009
OKINAWA, JAPAN
www.p450meetings.com

Gordon Research Conference: Atherosclerosis
JUNE 21–26, 2009
TILTON, NH
www.grc.org/programs.aspx?year=2009&program=athero

SEB at Glasgow 2009
JUNE 28–JULY 1, 2009
GLASGOW, SCOTLAND
www.sebiology.org/meetings/Glasgow/glasgow.html

JULY 2009

Gordon Research Conference: Molecular & Cellular Biology of Lipids
JULY 19–24, 2009
WATERVILLE VALLEY, NH
www.grc.org/programs.aspx?year=2009&program=lipids

23rd Annual Symposium of the Protein Society
JULY 25–29, 2009
BOSTON, MA
www.proteinsociety.org

Protein Lipidation, Signaling, and Membrane Domains
JULY 26–31, 2009
SAXTONS RIVER, VT
src.faseb.org

AUGUST 2009

ACS Fall 2009 National Meeting & Exposition
AUGUST 16–20, 2009
WASHINGTON, D.C.
www.acs.org/meetings

Kern Aspen Lipid Conference
AUGUST 22–25, 2009
ASPEN, CO
www.uchsc.edu/kernconference

18th International Mass Spectrometry Conference
AUGUST 30–SEPTEMBER 4, 2009
BREMEN, GERMANY
www.imsc-bremen-2009.de

SEPTEMBER 2009

World Congress on Oils and Fats and 28th ISF Congress
SEPTEMBER 27–30, 2009
SYDNEY, AUSTRALIA
www.isfsydney2009.com

OCTOBER 2009

3rd ESF Functional Genomics Conference
OCTOBER 1–4, 2009
INNSBRUCK, AUSTRIA
www.esffg2008.org

Bioactive Lipids in Cancer, Inflammation, and Related Diseases (11th International Conference)
OCTOBER 25–28, 2009
CANCUN, MEXICO
www.bioactivelipidsconf.wayne.edu

APRIL 2010

ASBMB Annual Meeting
APRIL 24–28, 2010
ANAHEIM, CA
www.asbmb.org/meetings.aspx

JUNE 2010

8th International Conference on Hyaluronan of the International Society for Hyaluronan Sciences
JUNE 6–11, 2010
KYOTO, JAPAN
www.ISHAS.org

AUGUST 2010

14th International Congress of Immunology
AUGUST 22–27, 2010
KOBE, JAPAN
www.ici2010.org