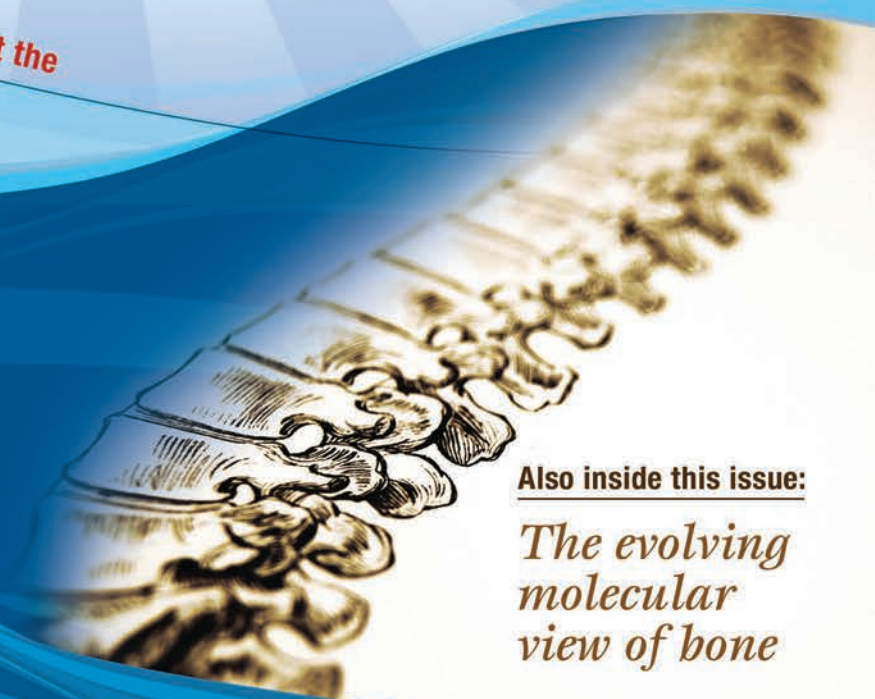
ASBMB today

October 2012

Find out about the thematic programming at the

2013 BOSTON ASBMB ANNUAL MEETING



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The evolving molecular view of bone

American Society for Biochemistry and Molecular Biology

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2013 annual meeting

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Catalytic Mechanisms
RNA Function & Protein Synthesis
Lipids & Membranes
Chemical & Systems Biology
Mechanisms of Gene Transcription & Regulation
Protein Modification, Trafficking & Degradation

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Submit to the ASBMB special essay series "Derailed But Undeterred" by Dec. 31. See Page 33 for details.

ASBMB today

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Being clear about transparency

BY JEREMY BERG

Shortly after I became a graduate student in the chemistry department at Harvard University, the great biochemist Jeremy Knowles assumed the department chairmanship. He instituted semiannual town-hall-style meetings with graduate students at which we could raise issues of concern and Knowles could describe ongoing and planned activities within the department. He attended to the issues that were easy to fix and at least acknowledged the harder problems. These meetings had a substantial positive effect on my morale and that of my colleagues. Although I was only slightly aware of it at the time, this practice made a big impression on my view of the power of transparency in leadership.

A decade later, I found myself in the unexpected position of being a department chairman. I remembered Knowles' lesson and met with the faculty, staff, postdocs and students regularly and encouraged them to bring their concerns to me. I also revealed as much as was reasonable about our department's finances so that the faculty and staff could understand both our capabilities and our limitations and help shape our priorities. Should we provide more resources to our departmental facilities or use the funds to hire new faculty or staff members? Without this information, staff participation in such decisions would have been difficult, and the potential level of frustration about why we were pursuing some actions and not others likely would have been higher.

Yet another decade later, I became director of the National Institute of General Medical Sciences at the National Institutes of Health. NIGMS is a substantially more complex organization than a basic science department, with more, and more diverse, stakeholders. Furthermore, I knew from my experience as an applicant, a grantee and a department chairman that NIH policies and procedures can be opaque. Why would a given percentile score result in funding in one year but not the next? Why had my budget been cut despite an outstanding score and a clear justification that I needed the full budget to complete the aims? Once I felt that I had mastered at least some aspects of the NIH's workings, I sought to share these insights with the scientific community, initially through periodic emails and later through a blog, the NIGMS Feedback Loop (1). These efforts were well received by the community, particularly posts that included data curves showing the probability of being funded as a function of percentile score and analyses of scientific output as a function of various parameters. I found the subsequent blog comments and emails from scientists and administrators useful for understanding the concerns of the community, collecting some creative ideas and shaping institute policies. I shared my experiences with others in the NIH leadership and have been pleased to see recently posted funding data from some other institutes (2, 3) as well as an informative blog written by Sally Rockey, the NIH deputy director for Extramural Research (4).

Transparency is particularly important for a taxpayer-funded enterprise. Aspects of this were formalized in the NIH Reform Act of 2006, which established the Scientific Management Review Board "to advise the NIH Director … on the use of … organizational authorities" (for example, adding, removing or transferring offices, centers and institutes) and to "identify the reasons underlying the recommendations" (5). When advising on "specific contemplated organization changes," the SMRB is charged with consulting with stakeholder groups both inside and outside the NIH. This was reinforced in the first report produced by the SMRB, "Deliberating Organizational Change and Effectiveness," which highlighted the importance of transparency and communication when considering substantial reorganizations (6).

After months of effort, I turned to another vehicle for promoting transparency in government operations, the Freedom of Information Act.

The SMRB embraced this approach in considering the potential merger of the National Institute on Alcohol and Alcohol Abuse and the National Institute on Drug Abuse. The SMRB and its working group evaluating this reorganization consulted extensively with stakeholders, including the advisory councils of the two institutes, scientific and patient-advocacy groups, and the public. Their comprehensive efforts culminated in the report "Substance Use, Abuse, and Addiction Research at NIH" (7). Not everyone agreed with the final recommendation to create a new, merged institute, but the SMRB and NIH leadership took into account considerable information and feedback, and all stakeholders had ample opportunity to provide input before the decision to pursue the merger was made.

The next major reorganization for which the SMRB was enlisted involved making "recommendations for organizing the agency's existing components to optimize a translational medicine and therapeutics program." In the course of its deliberations, the assigned working group decided to recommend the transfer of the Clinical and Translational Science Award program from the National Center for Research Resources to a new center focused on translational science. The CTSA program accounted for about 40 percent of the NCRR budget, with the remainder spread over programs focused on animal research resources, institutional capacity building, shared instrumentation and other areas.

Based on this pending recommendation, the NIH leadership decided to abolish the NCRR without further evaluation by the SMRB of the repercussions of doing so, ignoring the principles established by the SMRB only months before. Shortly after the translational medicine and therapeutics report (8) was presented to the full SMRB and approved by a 12–1 margin (I was the sole vote against), the NIH director sent a memo to the secretary of the U.S. Department of Health and Human Services urging her to recommend to Congress both that a new translational center be established and that the NCRR be abolished, as the secretary subsequently did.

Despite several attempts, I was unable to learn of any clear rationale for the abolishment of NCRR or what alternatives had been considered. After months of effort, I turned to another vehicle for promoting transparency in government operations, the Freedom of Information Act (9). In April 2011, I filed a FOIA request with Health and Human Services requesting information about the NCRR abolishment decision. After receiving an initial acknowledgment of my request, I waited a full year until I received the first materials. The emails and other communications were substantially redacted, and I have yet to receive all materials responsive to my request. The materials provided to date have not shed much light on the rationale for abolishing the NCRR. I did learn that the secretary of Health and Human Services and her staff were briefed by the NIH leadership about the likely SMRB working group recommendation, including the abolishment of the NCRR, before the SMRB had even met to discuss it and that legal staff at the NIH had objections to even attributing the recommendation for the creation of the new translational center to the SMRB. These discoveries further highlight the lack of transparency in considering these reorganizations.

Given the proposal to transfer a large program from the NCRR to the new translational center, was abolishing NCRR the best course of action? I do not know, but I would argue that neither did the NIH director. In bypassing the transparent, deliberative process established by the

In my experience, transparency almost always improves outcomes and has a positive impact on the perceptions and attitudes of even those who do not agree with a decision.

SMRB, the NIH director deprived himself and others of the input from different stakeholders that could have informed this important decision before it was made. Furthermore, the manner in which this significant reorganization was conducted substantially undermined the standing of the SMRB as a vehicle for transparency.

I am now examining other situations that would appear to benefit from greater transparency. One relates to indirect costs and facilities and administrative rates at different institutions. Surprisingly, there does not seem to be any available tabulation of such rates, and the ability to locate such information varies substantially from one institution to the next. Given that these costs are the topic of considerable discussion and affect the amount of research federal science agencies can afford to fund, I would argue that having such data readily available would only facilitate accurate analysis related to these issues. A second involves the new NIH program Discovering New Therapeutic Uses for Existing Molecules (10), which provides academic investigators access to study 58 compounds from eight pharmaceutical companies that were tested for safety but then abandoned for their initial therapeutic indication. Although the list of code numbers is available, the structures of the compounds are not, despite their importance for, among other things, computationally screening these compounds against potential targets. Some academic investigators have used creatively a variety of sources to prepare a partial list of these structures (11), but, again, the likelihood of success of the program would seem only to increase through the broad release of the structural information.

In my experience, transparency almost always improves outcomes and has a positive impact on the perceptions and attitudes of even those who do not agree with a decision. Certainly, some information is sensitive and cannot be shared widely without causing difficulties. Furthermore, achieving transparency is not always simple, even when desired, because effective communication and engagement can be quite challenging. Nonetheless, all will benefit if we encourage or even insist on greater transparency from organizations with which we are involved. A well-known part of Jeremy Knowles' scientific legacy involves wrestling with the concepts of efficiency and perfection in enzymatic catalysis. In the spirit of fostering a different component of his legacy related to the effective operation of organizations, I encourage you to come to me with any questions or suggestions you may have with regard to the operations of the American Society for Biochemistry and Molecular Biology.

Jeremy Berg (jberg@pitt.edu) is the associate senior vice-chancellor for science strategy and planning in the health sciences and a faculty member in the computational and systems biology department at the University of Pittsburgh.

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Geoff Hunt, public outreach coordinator: **@GoodbyeShoe**

In case you missed it

BY PUBLIC AFFAIRS STAFF

As Election Day grows nearer, the citizens of the nation are now inundated with political ads, making the case for and against certain candidates as parties and special interests work to frame this election in the most beneficial way. As a nonprofit organization, the American Society for Biochemistry and Molecular Biology is not permitted to engage in partisan activities. We are not permitted to donate to campaigns or political parties, and we are not permitted to endorse a candidate for office. We are, however, permitted to educate our members on the candidates' positions. Earlier this year, the ASBMB was invited to join 14 of the nation's top scientific societies to play an advisory role in the development of a science debate in an attempt to nail down the candidates' positions as they relate to science. The full responses from Democratic President Obama and Republican Mitt Romney can be viewed at www.sciencedebate.org.

Innovation and the economy: *What policies will best ensure that America remains a world leader in innovation?*

OBAMA

- says "we must create an environment where invention, innovation and industry can flourish";
- commits to doubling funding for key research agencies to support scientists and entrepreneurs; and
- set the goal of preparing 100,000 science and math teachers over the next decade to meet "the urgent need" to train 1 million science, technology, engineering and math graduates.

ROMNEY

- says the promotion of innovation "will begin on day one" by simplifying the corporate tax code, fixing job-retraining programs, reducing regulatory burdens and protecting U.S. intellectual property;
- emphasizes immigration reform to attract and retain skilled workers and says he'll raise visa caps for them and give permanent residence status to foreign students who earn advanced degrees in relevant fields; and
- credits federally funded basic research with moving the U.S. forward "in astonishing ways" and says funds should go to research programs that advance the development of knowledge and technologies with widespread applications and potential.

Research and the future: *Given that the next Congress will face spending constraints, what priority would you give to investment in research in your upcoming budgets?*

OBAMA

- says he strongly supports investments in research and development that spur innovation and proposed that the U.S. invest more than 3 percent of its gross domestic product in public and private R&D, "exceeding the level achieved at the height of the space race."

ROMNEY

- says "continued funding would be a top priority in my budget" and that policies must ensure "federal research is being amplified in the private sector and that major breakthroughs (can) make the leap" from the lab to the market.

Science in public policy: *We live in an era when science and technology affect every aspect of life and society and so must be included in well-informed public policy decisions. How will you ensure that policy and regulatory decisions are fully informed by the best available scientific and technical information and that the public is able to evaluate the basis of these policy decisions?*

OBAMA

- says policies should be based on "the best science available and developed with transparency and public participation" and that he appointed advisers "based on their credentials and experience, not their politics or ideology" and
- pledges to keep looking for new ways to improve transparency.

ROMNEY

- pledges to let the best science and information guide his administration's decisions and to "avoid the manipulation of science for political gain" and
- says "the costs and benefits of regulations will be properly weighed."

The ASBMB strongly encourages you to stay engaged, to read the full statements from the candidates on these and other issues of importance to you, and to make informed decisions. Above all else, we strongly encourage you to get out and vote Nov. 6!

Introducing myIDP: an interactive, online career-planning tool for scientists

BY JENNIFER A. HOBIN

It comes as no surprise to most graduate students and postdocs that, even after years of rigorous scientific training, landing a tenure-track academic position is not easy. Nor is it the norm. In fact, data show that less than half of all biomedical researchers are employed in academia, and less than 15 percent will wind up in tenure-track positions three to five years after they obtain their degrees. What may come as a surprise is the number of nonacademic career options available to those with doctoral-level scientific training. Now, a new interactive career and professional-development tool is available to help research trainees make sense of and prepare for the many career options available to them.

Called myIDP, the tool is designed to help graduate students and postdocs in the sciences create individual development plans, or step-by-step plans for identifying and reaching their career goals – whatever they may be. This free online tool walks users through the process of assessing their proficiencies in a host of science-related skills and knowledge areas, including research and technical skills, communicating to scientific and lay audiences, managing and leading people and projects, navigating peer review, and career planning. Because skills are only a part of the picture, myIDP also includes exercises to help users assess their science-related interests (Do you like designing experiments and reading papers in your field but hate writing grants and serving on committees?) and their career-related values (How important is it for you to work in a team? Be the boss? Have a stable salary and benefits?).

After a user has completed these self-assessment exercises, myIDP provides him or her with a list of 20 common scientific career options ordered from best fit to worst fit based on how the user's skills and interests match each career. The match is calculated by comparing the user's skills and interests to those that career advisers knowledgeable about job opportunities for scientists say are needed for each option.

myIDP also has an extensive list of resources for those interested in the different career paths, including traditional research positions in academia and industry as well as options with which trainees may be less familiar, such as research administration, regulatory affairs and science policy, just to name a few.

In addition to providing guidance on exploring these career options, myIDP helps users set career and professional-development goals. A summary report presents those goals in chronological order, and the application allows users to sign up for automated reminders to help them meet their goal deadlines. A series of articles providing a more in-depth explanation of each component of myIDP will be published in Science Careers and linked to the relevant pages of the Web module.

myIDP is based on the Individual Development Plan for Postdoctoral Fellows, a four-step career-planning framework developed by the Federation of American Societies for Experimental Biology in 2002. The goal of FASEB's IDP is to help scientists identify their short- and long-term career objectives and professional-development needs and to create, in conjunction with their mentors, written plans for meeting those goals.

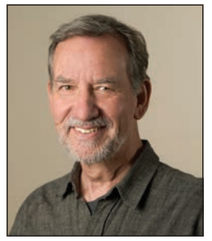
The process has received considerable attention in the research-training community: The National Postdoctoral Association recommended the IDP as a best practice in postdoctoral training; the National Institute of General Medical Sciences endorsed the IDP; and, most recently, the National Institutes of Health Advisory Committee to the Director's Biomedical Research Workforce Working Group recommended that the NIH require IDPs for all NIH-supported graduate students and postdoctoral researchers. In addition, the majority of postdoctoral offices surveyed by FASEB reported that they recommended that postdocs develop IDPs.

Perhaps most importantly, postdocs who develop IDPs benefit. A FASEB survey revealed that it helped postdocs assess their skills and abilities and identify the skills they need to advance their careers. Reflecting on

Continued on page 32

Three members receive Lasker awards

In early September, the Albert and Mary Lasker Foundation announced seven winners of the annual Lasker awards. Three members of the American Society for Biochemistry and Molecular Biology were among the recipients.



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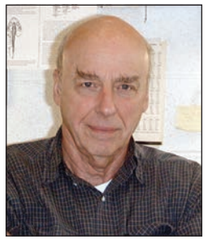
VALE



BROWN

Members James Spudich of the Stanford University School of Medicine and Ronald Vale of the University of California, San Francisco, won the basic medical research prize for laying the foundation for the study of cytoskeletal motor proteins. Also a co-winner was Michael Sheetz, who, with Spudich, developed the first biochemical assay to reconstitute myosin motor activity in vitro and showed that myosin and ATP were enough to direct transport along actin filaments. Vale and Sheetz later looked into transport along a microtubule in giant squid axon extracts and discovered a new molecular motor — kinesin — that runs along that track. Ultimately, the trio set the stage for figuring out how motor proteins drive transport of a host of molecules that play roles in many cellular processes and unveiled key aspects of how molecular engines convert chemical energy into mechanical work.

Member Donald Brown of the Carnegie Institution for Science in Baltimore won his prize for exceptional achievement along with co-winner Thomas Maniatis. The foundation lauded Brown's "leadership and citizenship in biomedical science, exemplified by fundamental discoveries concerning the nature of genes, by selfless commitment to young scientists and by disseminating revolutionary technologies to the scientific community." Brown established the biological function of the organelle known as the nucleolus and co-discovered gene amplification. Those findings, along with his observations of how cells control gene activity, are credited with ushering in the recombinant DNA era. Outside the lab, Brown founded and led the Life Sciences Research Foundation, and Maniatis created the Molecular Cloning manual, which has been used all over the world. In a statement, the foundation said, "Through their relentless pursuit of the questions that fascinated them and their willingness to help their peers as well as students, they have achieved success and have set a high of exemplary behavior for members of the biomedical research community."

Each Lasker prize category carries a purse of $250,000. The award ceremony was in late September in New York.

ASBMB journal-sponsored lectureships

The Journal of Lipid Research sponsored six lipid research conferences around the world this year. Below are the researchers selected for award lectures:

- **Deborah M. Muoio, Duke University,** Keystone Symposium on the Pathogenesis of Diabetes: Emerging Insights into Molecular Mechanisms, January
- **Bruce Spiegelman, Harvard Medical School,** Deuel Lipid Conference, March
- **Ruth McPherson, University of Ottawa Heart Institute,** XIV International Symposium on Atherosclerosis, March
- **Robert Hegele, University of Western Ontario and Robarts Research Institute,** Kern Aspen Lipid Conference: Systems Biology, Lipidomics and Cardiometabolic Diseases, July
- **Julie Saba, Children's Hospital Oakland Research Institute,** FASEB Conference: Phospholipid Metabolism – Disease, Signal Transduction and Membrane Dynamics, July
- **Stephen G. Young, University of California, Los Angeles,** Frontiers in Lipid Biology, a joint conference by the American Society for Biochemistry and Molecular Biology, the International Conference on the Bioscience of Lipids, and the Canadian Lipoprotein Conference, September

The journal Molecular & Cellular Proteomics sponsored three meetings. Below are the researchers selected for those award lectures:

- **Angus Lamond, University of Dundee,** Keystone Symposium: Proteomics, Interactomes, May
- **Susan L. Lindquist, Massachusetts Institute of Technology,** The Human Proteome Organization's 11th World Congress, September

Please submit member-related news and accolades to asbmbtoday@asbmb.org.

Two more Tabor young investigators

At meeting in the Netherlands, Catherine Bell was lauded for project on T-cell-mediated drug-hypersensitivity reactions

BY ADITI DAS

BELL

Catherine Bell, a doctoral student at the Medical Research Council Centre for Drug Safety Science at the University of Liverpool, won a Journal of Biological Chemistry/Herb Tabor Young Investigator award in June at the 19th International Symposium on Microsomes and Drug Oxidations and 12th European International Society for the Study of Xenobiotics Meeting in Noordwijk aan Zee, Netherlands. Bell was acknowledged for her work on the role of metabolism in drug hypersensitivity reactions.

Drug-induced, T-cell-mediated hypersensitivity reactions are a cause of concern for clinicians and pharmaceutical companies. They are usually detected during late stages of drug development and occur at low frequency; however, they remain a cause of mortality.

"I am particularly interested in the drug abacavir," a nucleoside analog used to treat AIDS and known by the brand name Ziagen, Bell said. "This is quite a hot topic at the moment, and a lot of new data has recently emerged suggesting novel mechanisms of drug interaction with T-cells."

Bell explains that patients expressing the HLA-B*57:01 allele are at significantly increased risk of abacavir hypersensitivity reactions. In fact, the U.S. Food and Drug Administration recommends pretherapy screening for the presence of the HLA-B*57:01 allele and the selection of alternative therapies for patients who carry it.

"We have generated abacavir-specific T-cell clones from healthy individuals expressing this allele to study how they are activated," Bell said. "Our data suggest that both direct and processing-dependent pathways are involved."

Originally from Lincolnshire, Bell moved to Liverpool in 2005 to embark on her undergraduate studies in pharmacology under the mentorship of Kevin Park and Dean Naisbitt. She is now in her final year of doctoral studies and has used quantitative methodologies, such as mass spectrometry, to study drug metabolism fate in patient immune cells as well as bioinformatic analyses, such as those used to examine human leukocyte antigen haplotype relationships among the alleles associated with organ-specific human diseases.

At meeting in France, Tomé won award for work on muscular dystrophy and other triplet repeat expansion disorders

BY ADITI DAS

TOMÉ

Stéphanie Tomé, a postdoctoral fellow at the Hospital for Sick Children and the University of Toronto, won the Journal of Biological Chemistry/Herb Tabor Young Investigator Award at the 7th International Conference on Unstable Microsatellites and Human Disease in June in Strasbourg, France.

Tomé was recognized for her work to unravel novel mechanisms and factors that regulate the genetic instability and subsequent pathobiology of the trinucleotide repeat expansion disorder myotonic dystrophy type 1. Also known as Steinert disease, DM1 is the most common adult form of muscular dystrophy and one of more than 40 diseases caused by unstable repeating DNAs.

Tomé earned her doctorate in human genetics in 2009 at Paris Diderot University under the guidance of Geneviève Gourdon. She said she became "fascinated by genetic instability" initially during a stint in 2004 in Stockholm, where she worked with the lab of Ulf Rannug analyzing the instability of CEB1 (human minisatellites) in Swedish people exposed to ionizing radiation. Then she set out on a course "to understand the mechanisms of CAG/CTG repeat instability in DM1 patients using a transgenic mouse model of DM1," she explained.

She collaborated with Christopher Pearson's group in Canada, with whom she pursued a postdoc fellowship. She has investigated the role of the DNA mismatch repair proteins MSH2 and MSH3 in the formation of CTG expansions and identified the role of ligase I in the formation of maternal CTG repeat expansion in vivo. "I participated in the development of an efficient antibody specific to MSH3 with the laboratory of Dr. Glen Morris in the United Kingdom," she said. "This new tool was important for my subsequent studies and for other labs."

This semester, Tomé is revisiting her alma mater in Paris to team up with Gourdon again to identify the genetic factors causing repeat contractions, rather than expansions, observed in some patients. She said she is moved by the potential translational impact of their research, adding, "Reversing repeat expansions in the mutant genes to the shorter lengths present in the nondiseased population is a worthy therapeutic goal, as the DNA is a single target that is the basis for the multitude of downstream events and symptoms."

ASBMB young scientists head to Capitol Hill

On Sept. 11, 30 American Society for Biochemistry and Molecular Biology members conducted more than 70 meetings and met with legislators from 26 states to advocate for increased funding for biomedical research.

Top left: From left, Rebekah Bullard, David Coleman, Ben Corb, Mark Stewart
Top right: From left, Danny Miller, Robert Palazzo, Liz Andrews
Bottom left: From left, Matthew Evans, Rose Willett
Bottom right: From left, Bob Matthews, Emily St. Amant, Melissa Englert

Aditi Das (addas06@gmail.com) is a Washington, D.C.-based science writer and research consultant at the National Institutes of Health and Maryland Biotech Center. Connect with her on LinkedIn.

Robert L. Hill retires as JBC associate editor after five decades of service

BY THE JBC ASSOCIATE EDITORS*

Robert L. "Bob" Hill, a Journal of Biological Chemistry associate editor whose long tenure coincided with the journal's exponential growth and its ascent to become the best in its field, retired last month after almost five decades of editorial service. Hill is credited with overhauling how the JBC recruits editorial board members and with curating a popular series of JBC articles that highlight groundbreaking work found in the journal's archives.

Hill joined the editorial board of the JBC in 1965 and served a second term from 1972 to 1977. He became an associate editor in 1988. His tenure spanned 47 years and was one of the longest editorial services in the journal's history — and nearly as remarkable as that of former Editor-in-Chief and current Co-Editor Herbert Tabor, who first joined the editorial board in 1961.

A renowned scientist and respected mentor

Born in Kansas City, Mo., in 1928, Hill earned a bachelor's degree in chemistry in 1949 and a Ph.D. in biochemistry in 1954, both from the University of Kansas. He then went on, as a National Institutes of Health postdoctoral fellow, to work under Emil L. Smith, a pioneer in protein chemistry, at the University of Utah.

Hill's postdoctoral studies with Smith introduced him to protein chemistry and enzymology research, areas he has pursued over his entire career. Hill remained at the University of Utah as a faculty member of the biochemistry department until 1961, when he joined the faculty of the Duke University School of Medicine, where he remains.

After arriving at Duke, Hill established one of the most highly regarded protein/enzyme chemistry labs in the world and did work on a range of proteins: abnormal hemoglobins, blood-coagulation proteins, immunoglobulins, lysozyme, acyl carrier protein and, most notably, lactose synthase. His work on glycosytransferases and other glycobiology problems identified him as a glycobiologist.

Beyond Hill's research accomplishments, he also provided a fertile training ground for countless graduate students and postdoctoral fellows, many of whom have become leaders in biochemistry research.

A NATURAL LEADER

Bob Hill assumed many leadership positions in biochemistry and was recognized with numerous honors and awards:

- In 1969, he was named the James B. Duke professor of biochemistry and in 1974 the chairman of the biochemistry department at Duke University, a position he held until 1993. During the nearly 20 years of his chairmanship, the department became one of the best in the world.
- He was secretary of the American Society of Biological Chemistry from 1972 to 1975 and president in 1976.
- He served on the Federation of American Societies for Experimental Biology board from 1972 to 1978.
- He was elected to the National Academy of Sciences in 1975, the Institute of Medicine in 1978, and the American Academy of Arts and Sciences in 1974.
- He served as general secretary of the International Union of Biochemistry from 1982 to 1991.
- He chaired the organizing committee of the very successful 17th International Congress of Biochemistry and Molecular Biology in San Francisco in 1997.
- He received the William C. Rose Award from the American Society for Biochemistry and Molecular Biology in 1991, the North Carolina Gold Medal (for science) in 1985 and the Karl Meyer Award from the Society for Glycobiology in 2001.

A visionary and reformer for the journal

Hill's primary role at JBC was to review and manage the review of papers on all aspects of protein chemistry, blood coagulation and especially glycobiology. He brought good judgment, strong values and high standards to the editorial process and made the JBC a premier place to publish papers in these important research areas.

Beyond editorial work, Hill made many other contributions to the JBC. He recognized that the editorial board is the heart of the journal, and, as the size of the board began to increase to keep pace with the exponential growth in the number of papers submitted, he transformed the process of selecting new board members from what had largely been an ad hoc process to one with rigorous review of prospective candidates.

With a current board of about 800 members serving staggered five-year terms, it is necessary to identify and recruit about 150 new board members each year. Hill established criteria that required the collection of curricula vitae from candidates, thereby ensuring that each new member had the experience, accomplishments, respect and judgment to provide the credible peer review for which the JBC is known.

A serious conservator of science history

Importantly, Hill also helped initiate and sustain a popular JBC feature called Classics. In this feature, landmark papers published in the JBC, including many seminal contributions that led to Nobel prizes, are reprinted along with brief biographical information about the authors.

Thus far, nearly 250 Classics have been published featuring more than 500 papers published since the JBC began in 1905. These articles trace a remarkable history of biochemistry in which the JBC played a central role.

Hill's role with Classics was to identify appropriate research areas and the key JBC papers and to oversee the preparation of the description of the time and context of the research. Given Hill's own remarkable research career, he knew many of the authors of the Classics and was able to contribute behind-the-scenes and personal insights about the work, the authors and the times. All his insights were interesting, and a few were even suitable for publication!

Collections of JBC Classics are available online, and many biochemists have reported that they are useful for teaching biochemistry.

HISTORIAN AND HISTORY MAKER

Bob Hill was a co-curator of the JBC Classic articles for many years. In 2006, the feature highlighted three of his own papers:

- The complete amino acid sequence of α-lactalbumin (1970)
- The disulfide bonds of bovine α-lactalbumin (1970)
- The purification and properties of the A protein of lactose synthetase (1971)

See all the Classics at **http://www.jbc.org/content/by/section/Classics**.

A man deserving of our thanks and more

Hill's career as a scientist, science leader and journal editor has been remarkable. The JBC and the field of biochemistry owe him great thanks, and we will miss his wise counsel.

*This article was written by JBC Associate Editor Robert Simoni on behalf of and in consultation with the journal leadership, including Editor-in-Chief Martha J. Fedor, Co-Editor Herbert Tabor and Associate Editors Norma Allewell, Ruma Banerjee, Judith S. Bond, George M. Carman, Joan W. Conaway, Peter Cresswell, John Exton, Paul E. Fraser, Joel Gottesfeld, F. Peter Guengerich, Richard W. Hanson, Gerald W. Hart, Vincent Hascall, John M. Kyriakis, I. Robert Lehman, Jerry Lingrel, Kenneth E. Neet, Luke O'Neill, Charles E. Samuel, James Siedow, William Smith, Linda Spremulli, F. Anne Stephenson, James T. Stull, Thomas Vanaman and Xiao-Fan Wang. We thank Jeanne Gladfelter, a longtime JBC staff member, for gathering the data included in the article.

JOURNAL MAKES ITS MARK

During Bob Hill's long tenure, the JBC clearly established itself as the premier journal of biochemistry in the world.

- The number of papers published annually increased to a peak of 6,434 in 2004 from 600 in 1965.
- The size of the editorial board increased to 833 in 2012 from 41 in 1965.
- The number of associate editors increased to 28 in 2012 from three in 1965.

ASBMB ANNUAL MEETING

BOSTON, *April 20–24, 2013*

Genomic replication and repair

BY STEPHEN BELL AND LEI LI

Genome integrity is central to maintaining cellular and organismal identity and preventing the development of diseases including cancer. Although early studies focused on DNA polymerase fidelity and DNA repair mechanisms, it has become clear that many other events contribute to genome maintenance. For example, the replication fork not only replicates the DNA but also coordinates many other functions required for genome stability.

The speakers in the first session will address how the replication fork facilitates chromatin assembly, detecting DNA damage and eliminating potential roadblocks. The coordination revealed by these studies illustrates how replication forks are the focus of many aspects of chromatin function beyond simple DNA replication.

In addition, it has become clear that activation of the eukaryotic replicative helicase is a multistep event involving both DNA and protein remodeling. The second session will explore the mechanisms that drive these events and how higher chromatin order structure influences the temporal regulation of origin activation during S phase.

When DNA damage occurs, cells need to respond instantly to prevent structural alterations on DNA from converting into heritable mutations. This response involves complex signaling pathways that extend well beyond the enzymes that remove the DNA damage.

The third session will highlight current investigations of DNA damage-signaling mechanisms, including initiation and optimization of damage checkpoint signaling, regulation of recombination and threading of the damage-signaling cascade via ubiquitination.

The last session will cover mechanistic aspects of how compromised genome stability leads to cancer. Clearly, a large set of genetic alterations is required to render a cell cancerous. At the chromosomal level, tumor-suppressing mechanisms can be compromized by cumulative and selective deletion of regions encompassing antiproliferation genes, invoking the cancer gene island concept. At the DNA level, endogenous metabolites can be a major source of mutations when pathways countering their actions are defective. These recent advances are mechanistically informative and pertinent to cancer etiology.

Stephen Bell (spbell@mit.edu) is a professor at the Massachusetts Institute of Technology and a Howard Hughes Medical Institute investigator. Lei Li (leili@mdanderson.org) is a professor at the University of Texas MD Anderson Cancer Center.

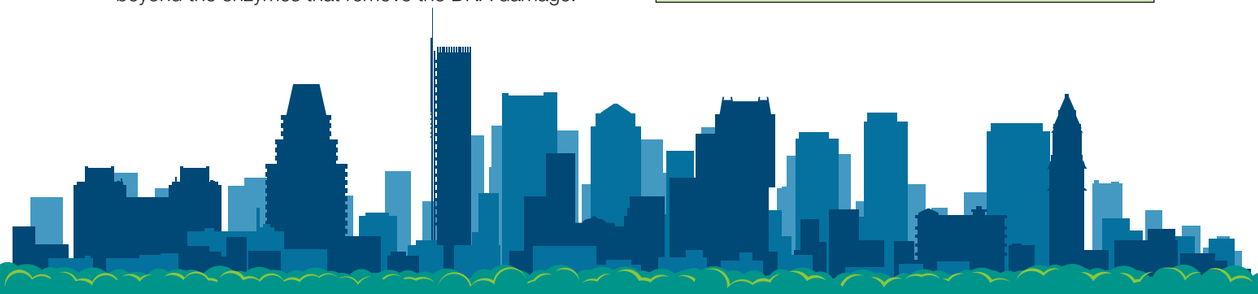
Genome Replication & Repair Thematic Sessions

Coordinating Functions at the Replication Fork

Mechanism and Control of Replication Initiation

Activation of DNA Damage Signaling

Mechanisms of Genomic Stability



Beyond template-driven control: glycans that regulate cell signaling

BY PAMELA STANLEY AND LANCE WELLS

A large body of evidence has demonstrated that post-translational modification of proteins by individual sugars or glycans composed of many sugars modulates key properties of glycoproteins. No post-translational modification is better suited for increasing functional diversity of proteins than glycosylation. During this program, the focus will be on how the non-template-driven addition of sugars to key proteins plays a critical regulatory role in modulating mammalian signal transduction and how aberrant glycosylation causes a variety of developmental diseases and promotes cancer progression.

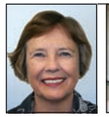
The first session will concentrate on how defects in the O-mannose glycosylation pathway are the underlying cause of multiple forms of muscular dystrophy. The O-mannose glycans on dystroglycan are essential for interactions of the cell with the extracellular matrix, and the pathophysiology of congenital muscular dystrophy can be attributed directly to enzymes and proteins that participate in the O-mannosylation pathway.

The second session will discuss glycans that regulate T-cell differentiation, cancer progression and spermatogenesis. These talks will illustrate the key roles that various classes of glycoproteins play in modulating both normal and disease-related signaling and differentiation.

The third session will center on the glycans of a single glycoprotein, Notch, and explore critical roles that various sugars play in Notch signaling pathways. Glycans on Notch modulate ligand binding and Notch activation. This session will focus on this one glycoprotein as a model for how glycosylation can increase functional diversity of proteins.

The final session will move inside the cell and focus on the nucleocytoplasmic O-GlcNAc transferase, functions for O-GlcNAc in CREB-mediated regulation of transcription in long-term memory, and the control of metabolism during oncogenic signaling via O-GlcNAc.

These talks, focused on a single sugar modification of nuclear and cytosolic proteins, will illustrate the wide variety of protein functions that can be modulated by nontemplate-driven glycosylation.



Pamela Stanley (pamela.stanley@einstein.yu.edu) is the Horace W. Goldsmith professor of cell biology at the Albert Einstein College of Medicine. Lance Wells (lwells@ccrc.uga.edu) is the Georgia Research Alliance Lars G. Ljungdahl distinguished investigator and an associate professor at the University of Georgia.

Glycobiology Thematic Sessions

O-Mannose Glycans & Muscular Dystrophy

Glycoslytransferases that Control Cell Growth & Differentiation

Roles for Glycans in Notch Signaling

Regulation of Gene Expression by O-GlcNAc

Transitions: We all go through them

BY PETER J. KENNELLY AND DORIT ZUK

No matter where you are today — student, postdoc, just starting out in your professional career or well into your chosen career path — sometime in the future, you'll be facing the prospect of a change. This could come about because you're moving on to the next step in your career or because you decide it's time to change direction. With change comes transition, the experience of moving from one situation to another, which can be exhilarating or challenging — and often both at the same time.

This year, the Education and Professional Development Committee decided to focus its program on those transitions we all go through during our careers and to try to answer some questions about these transitions. How do we decide to make a change and which change to make? When should we make it? How do we cope with the transitions we encounter along the way?

How do we train for a world in transition?

During these sessions, we will consider transitions from the perspectives of those making the changes and of those training others. Speakers will share their personal experiences as well as professional knowledge, providing insights and tips into transitioning into a variety of career paths away from the bench (e.g., law or high-school teaching) and transitioning at multiple career phases.

Everyone knows you have to transition through training — college to graduate school, graduate school to postdoc (typically but not always), postdoc to first "real" job. But those of us in midcareer positions make changes too and often aren't sure how to go about it. So we'll have a session that focuses on this type of transition and hear both from people who've done it and from a professional career adviser. We'll also discuss how to train students for a world in transition and hear about timeless skills we all should develop.

We hope you will attend these sessions and come away with some insights and tools you may be able to use when contemplating your next transition — be it exhilarating, challenging or both.


Peter J. Kennelly (pjkennel@vt.edu) is a professor and the head of the department of biochemistry at Virginia Polytechnic Institute and State University and chairman of the ASBMB Education and Professional Development Committee. Dorit Zuk (zukd@mail.nih.gov) is a science policy adviser to the National Institutes of Health deputy director for Extramural Research.

Health disparities in breast cancer

BY GLORIA THOMAS AND KITANI PARKER JOHNSON

At least five subtypes of breast cancer have been identified on the basis of their patterns of biomarker expression. Triple-negative breast cancer, or TNBC, is defined as breast epithelial cancer cells that lack the HER-2/neu receptor, the estrogen receptor and the progesterone receptor. TNBC patients have a high mortality rate, and, while breast cancer occurs in all races, the rate of TNBC is higher in black women.

The first session of this program will cover the basics of breast cancer, particularly the subtypes that affect black women. Stefan Ambs at the National Cancer Institute seeks to identify the racial/ethnic differences in tumor biology that influence the presentation of the disease or its response to therapy. Ambs will discuss novel targets in advanced breast cancer in black patients. Patricia Thompson of The University of Arizona Cancer Center will highlight ethnic differences and imbalances in outcomes of early-stage breast cancer. KiTani Parker–Johnson of Xavier University of Louisiana will discuss the role of the external microenvironment in recruiting breast cancer cells to proliferate, migrate and invade other tissues.

The second session will address an emerging breakthrough in TNBC: a concurrence that it is not one disease but instead a result of diverse genotypes. Matthew Meyerson of the Dana–Farber Cancer Institute has been involved in one of the most successful sequencing efforts that confirms this, and his group observed a fusion of MAGI3 and AKT3 in TNBC that presents a potential therapeutic target. Brian Lehmann, a postdoc in the lab of Jennifer Pietenpol at the Vanderbilt–Ingram Cancer Center, is working to elucidate molecular differences to identify targets and shape drug-discovery efforts. Eddie Reed of the University of South Alabama has had a successful career in research and clinical practice and will discuss the possible role of translational nucleotide excision repair in TNBC.

The third session will feature Chindo Hicks of the University of Mississippi Medical Center, who studies bioinformatics and genomics of complex human diseases. Hicks, who is developing and applying these tools to identify biomarkers and targets from gene-expression data, will focus on breast cancer in minorities. Rick Kittles of the University of Illinois College of Medicine at Chicago will present his use of genomewide association studies to identify common genetic factors that influence health and disease and to predict targets for cancer in black patients. He seeks to identify genetic and environmental factors to better understand the complex issues surrounding race, genetic ancestry and health disparities using GWAS and other -omics tools. Fatima Jackson of the University of North Carolina at Chapel Hill is using genetic mapping to link and predict black breast-cancer patient outcomes in the United States based on tribal roots in continental Africa.


Gloria Thomas (gthomas5@xula.edu) is an assistant professor at Xavier University of Louisiana and a member of the ASBMB Minority Affairs Committee. Ki Tani Parker–Johnson (kparker1@xula.edu) is an assistant professor at Xavier University of Louisiana.

Identifying Novel Biomarkers to Better Manage Breast Disease

Back to the Basics: the Biology of Breast Cancer

Breast Cancers that Elude Successful Treatments: Triple-Negative Breast Cancer

Genomics: Successes & Challenges in Identifying Novel Targets in Breast Cancer

Workshop: computational tools for assigning enzymatic functions

BY JOHN A. GERLT AND PATRICIA C. BABBITT

As of July, the nonredundant TrEMBL protein database contained 23,165,610 nonredundant sequences; a conservative estimate is that one half of these proteins have unknown, uncertain or incorrect functional annotations. Without correct annotations, the unlimited potential for medicine, chemistry and industry that could be obtained from functional and mechanistic understanding of nature's complete repertoire of enzymes and metabolic pathways cannot be realized.

The Enzyme Function Initiative (supported by NIH U54GM093342) is devising an integrated sequence/structure based strategy for predicting and assigning functions to previously unknown enzymes discovered in genome projects to meet this challenge.

To accomplish this goal, the EFI has brought together multidisciplinary expertise in bioinformatics, experimental structural biology and structural modeling/docking so that predictions of in vitro enzymatic functions can be made and experimental enzymology, microbiology and metabolomics studies can be pursued. The goal is to validate and confirm enzymatic functions found in vitro as the actual physiological functions of the enzymes in vivo.

This workshop will feature presentations describing the development and application of high-throughput computational tools to facilitate functional assignment of unknown enzymes:

1) Bioinformatic analyses can cluster sequences into probable isofunctional groups, thereby assigning tentative functions to be investigated by structure determination, structural modeling and docking, and biochemical experimentation.

2) Homology modeling methods can expand the use of structural modeling to guide function assignment to proteins without structures.

3) Computational docking methods can leverage structure to guide functional assignment by suggesting substrates for biochemical experimentation.

The presentations will be followed by a question-and-answer session to identify potential collaborations between the audience and the EFI.


John A. Gerlt (j-gerlt@illinois.edu) is a professor at the University of Illinois at Urbana–Champaign. Patricia C. Babbitt (Babbitt@cgl.ucsf.edu) is a professor at the University of California, San Francisco.

SPEAKERS
(all co-investigators in the EFI)

Patricia C. Babbitt, University of California, San Francisco

John A. Gerlt, University of Illinois

Matthew P. Jacobson, University of California, San Francisco

Andrej Sali, University of California, San Francisco

Brian K. Shoichet, University of California, San Francisco

From the lab to the kitchen table

Communicating science to a lay audience

BY GEOFF HUNT

The ASBMB Public Outreach Committee makes its debut at Experimental Biology 2013 with a wide array of formal and informal activities designed to get you fired up about taking your science out of the lab and into the streets!

Outreach buffet

Outreach can come in a wide variety of flavors. Come get a taste during our interactive roundtable session, "From the Lab to the Kitchen Table — Communicating Science to a Lay Audience," at 12:30 p.m. Monday, April 22, in Boston.

Daniella Scalice of the NASA Astrobiology Institute will discuss FameLab, the revolutionary science-communication competition, while Ann Merchant of the National Academy of Sciences will demonstrate how the Science and Entertainment Exchange works with Hollywood to get accurate science into movies and television shows.

If working at the grass-roots level is more your thing, take some time to talk with Cambridge Science Festival Director P.A. D'Arbeloff about Science on the Streets, or find Morgan Thompson of Harvard University, who will convey her experience running Science in the News, a student-run outreach group at Harvard.

For those who want to get your institutions involved with outreach, Hannah Alexander of the University of Missouri and Jon Dattelbaum of the University of Richmond will describe how outreach is incorporated into the courses they teach at their respective universities, and Tom Baldwin will share how he organized a public lecture series at University of California, Riverside.

Outreach and you

Do you have an outreach program that you would like to showcase for your ASBMB colleagues? Submit an abstract for our poster session, to be held during the Experimental Biology 2013 opening reception on the evening of Saturday, April 20, and take advantage of this special opportunity to share your activity with an energetic audience. Check out our abstract topic categories online.

Science cafés: the new social network

As the EB2012 Tweet and Meet demonstrated, events at science conferences are way better with beer. For EB2013, we will still have the beer, but we are changing the format: In conjunction with the team at sciencecafes.org, we will be hosting "Science Cafés: The New Social Network," a special, two-part science café for EB attendees on the evening of Monday, April 22.

For those of you who don't know, science cafés represent a rapidly growing, informal science-education activity, with more than 250 versions spread across 48 states and the District of Columbia. Cafés are typically held at local establishments (for example, bars, coffee houses or restaurants) on a regular basis (like the third Tuesday of every month), with scientists invited to participate in interactive discussions on their areas of expertise with crowds of dedicated followers and interested bystanders.

For our event at EB2013, we will start by having the team from NOVA ScienceNow present a how-to session that explains how to set up and run your own science café. Immediately following, we will host an actual science café! See what it is like to be part of the hottest trend in science outreach. Come, ask questions, learn a little something (and, of course, have some beer).

'What is a Germ?' Challenge

The annual meeting isn't till April. Why wait that long to get involved? Try out your outreach and communication skills right away! We are inviting ASBMB members to become part of the 2013 "What is a Germ?" Challenge.

This activity, co-sponsored by the Cambridge Science Festival and inspired by Alan Alda's Flame Challenge, invites ASBMB members to use any platform to submit their best explanation for answering the question "What is a germ?"

We want you to frame your response so that an elementary school student can understand it. Why? Because they are the ones who will be judging you! Schools from the greater Boston area will be grading the entries and letting our participants know which ones they like best. The best part: Finalists will be invited to present their submissions before a live audience during the 2013 Cambridge Science Festival's Curiosity Challenge on Sunday, April 21.

Our website goes live in November, so get your entry ready. Step up to the challenge!

Geoff Hunt (ghunt@asbmb.org) is the public outreach coordinator for ASBMB.

Mechanisms of signal transduction

BY KUN-LIANG GUAN AND CAROL LANGE

How do cells select and translate myriad signals into specific biological responses?

Understanding the full complexity of signal transduction is essential to understanding the many contexts for altered signaling, such as pathophysiological conditions related to stress or the development of cancer. Sessions within this broad theme will cover new findings in autophagy signaling, protein kinases and phosphatases, G-protein–coupled-receptor signaling and mechanisms of cell-signaling specificity in cell fate.

Highlights of the session on autophagy include details of the biochemical mechanisms and cell biology of autophagy machinery regulation, including novel aspects of the VPS34 lipid kinase complex function and regulation in response to nutrient signals.

Protein phosphorylation is a fundamental regulatory mechanism that affects nearly every aspect of cellular behavior. Recent findings from the Dixon lab (Tagliabracci et al., Science 2012) reveal that protein kinases are not confined to the cell interior: A family of Golgi-localized protein kinases are secreted and phosphorylate extracellular proteins implicated in bone biomineralization. The G-protein–coupled-receptor session will highlight not only the recent progress in the mechanistic understanding of GPCR signaling but also will cover the relevance of GPCR dysregulation to the development of human diseases.

Mechanisms of Signal Transduction Thematic Sessions

Mechanisms of Cell Growth & Autophagy Regulation

Protein Phosphorylation Networks

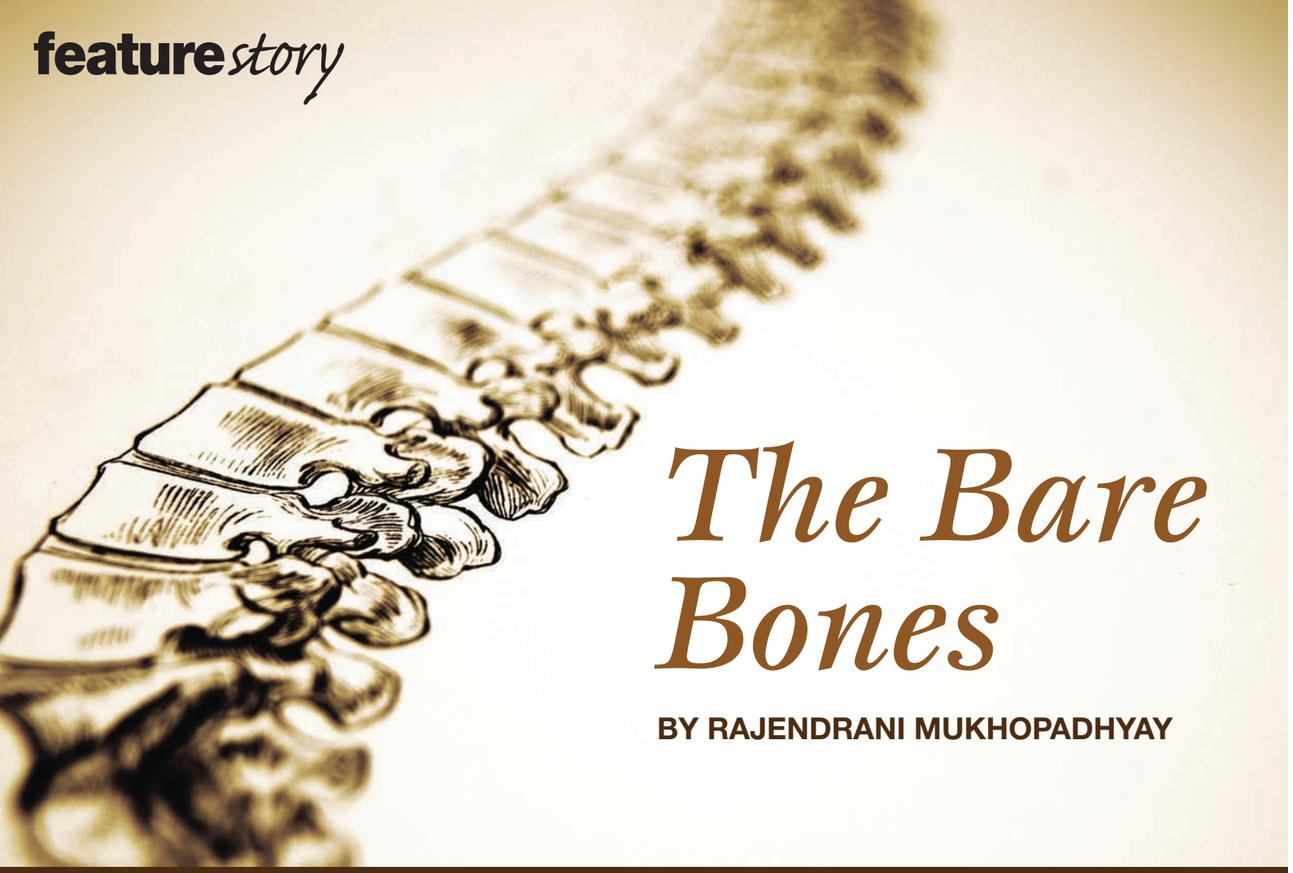
G-proteins in Cellular Regulation

Mechanisms of Signaling Specificity in Cell Fate: Growth, Proliferation or Death?

A final session will deal with mechanisms of signaling specificity and cell fate. The strength and duration of signaling can have profound effects on signaling output; cells reuse the same pathways in subtly different ways to regulate disparate biologies.

Related to this theme, the ser/thr protein kinase mTOR, the mammalian target of rapamycin, plays a critical role in many pathophysiological processes. The Blenis lab (Yu et al., Science 2011) has discovered a tumor-suppressive role for Grb10, a novel mTOR substrate that, when phosphorylated, inhibits both PI3K and ERK-MAPK signaling. Loss of Grb10 may contribute to the elevated signaling and altered cell fate that typify cancer.

Kun-Liang Guan (kuguan@ucsd.edu) is a professor of pharmacology at the University of California, San Diego. Carol Lange (lange047@umn.edu) is a professor in the departments of medicine and pharmacology at the Masonic Cancer Center at the University of Minnesota.



The Bare Bones

BY RAJENDRANI MUKHOPADHYAY

Our skeletons do more than just hold us upright

Most of us appreciate that if it weren't for our skeletons, we'd be bags of protoplasm oozing on the ground. But beyond that, a common perception of bone is that it's simply an inert mineralized tissue that does only a few things: protect delicate organs, help us to walk, act as a mineral store and house the blood-making machinery.

But that perception has started to shift over the past two decades. Thanks to advances in cellular and molecular biology tools, experts now say that bone is a dynamic tissue that sends out and receives messages from organs. It even tweaks the functions of organs and actively participates in maintaining mineral and energy homeostasis throughout the body.

OLD TO NEW

Bone constantly turns over. This process is called bone remodeling and rebuilds the skeleton bit by bit. Bone remodeling is the reason you don't have the same skeleton today as you did 10 or so years ago.

Understanding how bone remodeling happens at the cellular and molecular levels was a challenge for decades because the mineralized matrix of bone, containing calcium and phosphate, had made culturing bone cells by conventional methods difficult. But now a clearer picture is starting to come into focus. There are thought to be three types of bone cells: osteoblasts, osteoclasts and osteocytes. Osteoblasts build bone by putting down the mineralized matrix. Osteoclasts chew down bone. They are unique in that they are the only cells in the body designed to destroy their host tissue. Both cell types sit on the surface of the bone.

The challenge of studying bone is most evident when it comes to the osteocytes, cells derived from osteoblasts that make up 90 percent of bone. Because they sit deep inside the bone, studying them had been especially hard, and the difficulty led a number of researchers to ignore the cells. As Henry Kronenberg at the Massachusetts General Hospital quips, the conventional thinking used to be that osteocytes were just "stupid osteoblasts that got buried and stuck in bone."

Lynda Bonewald at the University of Missouri in Kansas City, an immunologist and hematologist by training, became intrigued by the osteocytes inside the bone matrix in the late 1980s because of their striking resemblance to neurons with dendritic protrusions. When she asked experts in the bone field what osteocytes did, "I was told they were just placeholders," she says. "I couldn't accept that explanation. I started thinking of ways to make cell lines."

Starting in 1997, Bonewald's group began to report osteocyte lines, such as MLO-Y4, which gave researchers a better idea of what the cells actually do. Osteocytes act as the mechanosensors of bone, probably sensing changes in fluid flow and how the skeleton is weighted during rest or exercise, a hypothesis Bonewald says histomorphologists proposed decades ago. She says osteocytes are probably not important as mechanosensors in the embryonic skeleton or very active postnatally during growth. But they are extremely important in adults. Osteocytes direct osteoclasts and osteoblasts where to degrade old bone and set down new material. They also secrete hormones. "Instead of being thought of as pitiful cells that got confused and stuck inside bone, they are now thought of as the master cells," says Kronenberg. "They are the brains of the outfit."

> **"Do what you love. Know your own bone; gnaw at it, bury it, unearth it, and gnaw it still."**
> – Henry David Thoreau

NOT INERT

Perhaps the biggest shift in how bone is perceived is in its function as an endocrine organ. Bone used to be thought of as a tissue that responded only to a couple of hormones, such as the parathyroid hormone sent out by the parathyroid glands and estrogen made by the ovaries. But findings in the past two decades have given indications that the bone doesn't just passively take orders from other organs: It makes its own hormones to modulate mineral metabolism and energy expenditure.

The role of bone in mineral metabolism came as a surprise less than 15 years ago when a hormone called fibroblast growth factor 23 was discovered. FGF23 "has potent effects on the proximal tubule of the kidney to regulate the reabsorption of phosphate," says Kronenberg. "It was interesting and surprising when it was first realized that the major source of FGF23 was the osteocyte." That osteocytes signaled to the kidneys when the body needed to hold onto phosphate alerted researchers to that fact that bone actively manages mineral metabolism.

The connection between bone and energy expenditure was first proposed by the group of Gerard Karsenty at Columbia University. His group used genetic approaches to show that leptin, the hormone released from fat tissue to regulate appetite and metabolism, inhibited bone formation through the nervous system. The work tied together appetite, energy metabolism and bone remodeling.

Osteocalcin was another surprise in the energy-expenditure picture. The protein has been cited in the literature for more than 40 years and is used as a marker for osteoblast activity. But "we didn't know what osteocalcin did," says Thomas Clemens at Johns Hopkins University.

In the 1990s, the Karsenty laboratory made a knockout mouse missing osteocalcin. The mouse was expected to have a bone phenotype, but, unexpectedly, it was a plump animal with only minor skeletal abnormalities. Around 2008, the Clemens group created a different mouse that lacked the insulin receptor on its osteoblasts. That mouse also became fat and looked just like the osteocalcin-null mouse that the Karsenty group had made a decade before. Like the Clemens group, the Karsenty group had made the mouse missing the insulin receptor in osteoblasts and had gotten the same phenotype. The mouse studies "linked insulin signaling in the osteoblasts to the production of osteocalcin," says Clemens.

The thinking now goes that insulin stimulates osteocalcin production by osteoblasts. The osteocalcin molecule gets stored

In 2002, President Bush proclaimed the decade to be the **National Bone and Joint Decade**. The Bone and Joint Decade recently renewed its mandate for another 10 years to 2020. Every October 12–20, the Bone and Joint Decade and US Bone and Joint Initiative recognize the week as their **National Action Week** to inform the public about musculoskeletal disorders.

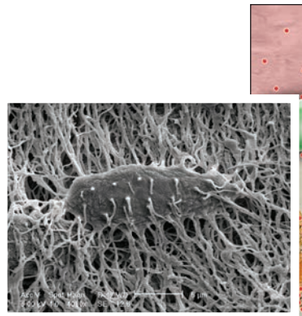
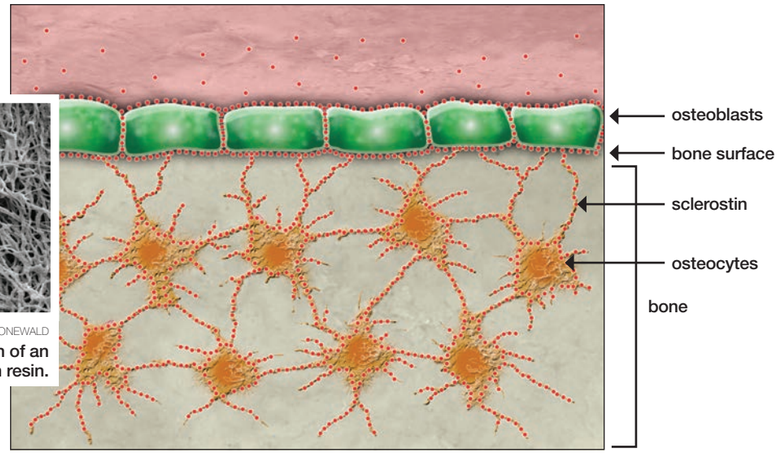


IMAGE CREDIT: LYNDA BONEWALD

Scanning electron micrograph of an osteocyte in resin.



Sclerostin inhibits osteoblast-mediated bone formation. IMAGE CREDIT: AMGEN

in the mineralized matrix. When osteoclasts dissolve bone, osteocalcin enters the bloodstream. From there, researchers have shown, one of the post-translationally modified forms of osteocalcin increases insulin secretion from the pancreas and enhances the ability of adipocytes to use glucose.

Because bone remodeling demands a lot of energy, "this new paradigm really allows us to think about the skeleton as the sensor for metabolic activity and also as a fine-tuner for insulin sensitivity," says Clifford Rosen at the Maine Medical Center Research Institute. "It takes a lot of energy to make bone. We don't know anything about the dynamics of how these cells use their energy."

The knockout mice have been critical in revealing osteocalcin's purpose, but there is a question mark hanging over the extent to which osteocalcin influences the insulin pathway in humans, say Clemens and Rosen. "The mouse has given us tremendous insights, but moving to humans, it's much more complicated," says Rosen. "We need to get a better idea of how important is osteocalcin in fine-tuning insulin secretion."

Clemens and Rosen explain that in some mouse models osteocalcin looks to be critical for regulating the insulin pathway. But mice aren't metabolic equivalents of us, because their metabolic rates are 100 to 1,000 times faster than ours. Both Rosen and Clemens say the differences in metabolic rates raise the question of whether the osteocalcin effects seen in mice come about simply because of the peculiarities of mouse metabolism. "It's a big challenge," says Rosen. "How do we apply what we see in mice to humans?"

And that is exactly what the next research steps should answer, says Clemens. He says that, while association studies in humans seem to suggest osteocalcin has an effect on insulin secretion, there haven't been any studies that show a clear cause-and-effect relationship. Those kinds of studies are begging to be done.

OSTEOPOROSIS DRUGS

Understanding fundamental bone biology has had great repercussions for one of the most recognized diseases of bone: osteoporosis. Osteoporosis appears in postmenopausal women, the elderly and people suffering from some diseases, such as anemia. The bones become fragile and easily snap. According to the National Osteoporosis Foundation, about 34 million Americans are at risk for the disease. By 2025, the foundation projects, osteoporosis will cost the American healthcare system $25.3 billion per year.

Osteoporosis happens when osteoclasts outstrip osteoblasts in performance. The reason postmenopausal women are more at risk is thought to be that estrogen indirectly inhibits the activity of osteoclasts. But after menopause, estrogen's protection disappears, and the osteoclasts start breaking down bone more quickly than osteoblasts can keep up. The speeding up of osteoclasts starts happening in the elderly for reasons yet to be deciphered. This causes elderly people to grow hunched, shrink in height and become more susceptible to broken bones.

But in the past 20 years, drugs have appeared to treat osteoporosis. Most of the ones on the market inhibit bone breakdown, or resorption, one way or another. One class of drugs is the bisphosphonates, which trigger apoptosis in osteoclasts. "The bisphosphonate category is probably about 80 percent of the osteoporosis drug use in the United States right now," notes Art Santora of Merck.

Another drug is a monoclonal antibody called denosumab, which is produced by Amgen. It is an inhibitor of RANK ligand, which was shown in the 1990s to be the key stimulator of osteoclast development through the Wnt/β-catenin pathway. By inhibiting RANK ligand, the drug prevents osteoclasts from maturing and chewing away the bone.

All these drugs are catabolic agents in that they stop the breakdown of bone. Given their numbers, Scott Simonet of Amgen says, "That area of the market is pretty saturated."

The excitement lies in drugs that can help build bone. The only anabolic agent on the market is a recombinant version of parathyroid hormone called teriparatide, marketed as Forteo by Lilly. The drug stimulates osteoblasts to put down new bone. Parathyroid hormone's classical role is to stimulate bone breakdown so that calcium is released to maintain serum calcium levels. But, for reasons not yet known, the hormone does the opposite and builds bone when injected once daily. The drug is effective for only 12 to 18 months.

Experts are excited about a drug that Amgen, in partnership with a company called UCB, has in phase III clinical trials. Simonet says that the drug is being developed for osteoporosis and fracture repair. The anabolic drug AMG 785 is a monoclonal antibody that targets a molecule called sclerostin.

The story of sclerostin best illustrates how molecular biology has been pivotal for bone therapeutics. In 1958, sclerosteosis was first described in two South African girls of Dutch-Afrikaner descent. Sclerosteosis patients have heavy, thick bones with large jaws and protruding foreheads; their thick facial bones pinch their facial nerves. Several research groups established that the gene involved was *SOST* and that sclerosteosis was a loss-of-function mutation of that gene.

"We didn't know where sclerostin was coming from, but, after several years of soul-searching, it became clear that it was coming from the skeleton," says Rosen. Coincidentally, at the same time, the Bonewald group's osteocyte lines were coming out. Those cell lines helped researchers establish in the mid-2000s that osteocytes were secreting sclerostin to stop bone formation. Amgen's AMG 785 shuts down sclerostin by blocking its inhibitory activity on osteoblasts.

Clemens and others take delight in pointing out that researchers had known about sclerostin's existence for many years. But once its molecular biology was established, it took less than a decade to get a drug against it in the pipeline. "It's really remarkable," says Clemens.

LOTS MORE TO DO

Experts interviewed for this story were unified in their upbeat enthusiasm for the future of molecular biology research into bone simply because there are so many rich hunting grounds in both basic and clinical endeavors. Experts are unrestrained in their enthusiasm when they say that new anabolic drugs will be developed in the next decade to help patients with postmenopausal, age- or disease-induced osteoporosis and skeletal fragility.

For basic researchers, there are many directions to pursue. For one, they need to understand how bone cells communicate and respond to mechanical and biochemical signals both at local and systemic levels. For example, "bone is an incredibly locally focused tissue," says Kronenberg. "If you break a leg, you want to fix that fracture right where it is. You don't want a systemic response to a fracture." How bone senses when to work locally and when to act globally is a question.

Another interesting idea that is emerging is that there is two-way communication between muscle and bone. "We always think of muscle affecting the skeleton" by pulling and pushing on the bones, says Rosen. "But there's the converse side: How does the skeleton regulate muscle?"

This is work Bonewald has undertaken in collaboration with the groups of Marco Brotto and Mark Johnson, also at the University of Missouri in Kansas City. "We took some of our osteocyte-conditioned media and put it on muscle cells. [Brotto] was absolutely blown away to see that the osteocytes secrete factors that support myogenesis," Bonewald says. "If you put the conditioned media on intact muscles that are contracting, it increases muscle force." She says the collaborators are working on figuring out the factors secreted by the osteocytes and how they affect signal-transduction pathways in muscle.

Indeed, factors secreted by bones are high on the exploration list. This is especially true for the relatively new discovery that bone senses and possibly influences metabolism. In Rosen's opinion, "the skeleton is secreting lots of endocrine factors. We know about FGF23, sclerostin and osteocalcin. We don't know enough about those, and my guess is there are also other substances being produced."

As schoolchildren, our earliest encounters with bone are with the jangling skeleton hanging in the back of the high-school biology laboratory. But with new findings emerging about the inner workings of the skeleton, bones can no longer be viewed as stiff and inert structures that simply hold us upright. Bone is truly a dynamic, living tissue that is constantly listening and responding to the way we live.

Rajendrani Mukhopadhyay (rmukhopadhyay@asbmb.org) is the senior science writer for ASBMB Today and the technical editor for the Journal of Biological Chemistry. Follow her on Twitter at www.twitter.com/rajmukhop.

MCP MOLECULAR & CELLULAR PROTEOMICS

Be sure to check out the MCP Journal News in this issue for a story on osteoblasts! *See Page 31.*

The Wyss Institute's pursuit of alternatives is gaining momentum

Biologically inspired innovation

BY CONNOR BAMFORD

At lab benches and computer desks throughout the Wyss Institute for Biologically Inspired Engineering in Boston, researchers are attempting to solve some of humanity's most pressing problems. The questions its scientists are asking are not uncommon: How can we discover more effective drugs? How can we solve the global energy crisis? But the possible answers they're developing are atypical, such as using autonomous microrobots to diagnose and treat diseases.

Part engineer, part biologist, researchers at Wyss (pronounced "Vees") are combining the power of synthetic biology, microfabrication technology and tissue engineering principally to understand how biological systems work and to manipulate and re-engineer them in the lab in a way we could never have done before. Researchers such as Pamela Silver and George Church, both synthetic biologists, hope that their work — and their colleagues' work — will have far-reaching health, environmental and economic benefits.

Silver and Church are among 17 full-time faculty members at Wyss whose research programs are supported in part by a more than $125 million institutional gift intended to foster a very special kind of environment. "The Wyss has been instrumental in bringing the right people together and providing the right atmosphere," Silver emphasizes. The institute allows the researchers the freedom to operate in entirely new fields, and this is at the heart of the institute's mission.

WHAT IS THE WYSS?

The institute emerged in 2008, when it was known initially as the Harvard Institute for Biologically Inspired Engineering. In a bid to blend the understanding of basic engineering and biological processes, fields that had a long and successful history at Harvard University, and apply them to the burgeoning number of medical and environmental issues in the modern world, a multidisciplinary team of Harvard-based faculty were convened by the provost to discuss the future of bioengineering in Boston.

Then, in 2009, Harvard business school alumnus and Swiss engineering magnate Hansjörg Wyss donated $125 million, and the story of the Wyss Institute began in earnest. That money from Wyss, who was then chief executive officer of the medical-implant manufacturing company Synthes, which recently was sold to Johnson & Johnson, allowed those at the institute to pursue high-risk scientific endeavors and to begin to realize the potential of a new research model, described in the institute's mission statement as one of "innovation, collaboration and technology translation."

ORGANS ON A CHIP

This capital injection has allowed one of Wyss' groups to confront, head-on, one major challenge facing modern drug-discovery programs: Why do animal models so often fall short of predicting the biological effects of drugs in humans?

"Animal models often fail to predict results in human clinical trials, and this has had a devastating effect on drug development," says Don Ingber, who is the leader of the biomimetic microsystems platform and founding director of the Wyss Institute as well as a professor at Harvard Medical School and Boston Children's Hospital. "Not only have costs skyrocketed, but fewer and fewer good drugs are in the pipeline, and so fewer good drugs are reaching patients."

Researchers need to model human biology accurately in the lab to develop new treatments. Think of heart disease or lung cancer: Scientists simply can't test novel drugs on human beings, yet the kinds of models they do use on a day-to-day basis (cell lines or rodents, for example) are the kinds of models that might lead them astray if they are not careful. But imagine if they were able to model human physiology without turning to rodents or nonhuman primates; this is where Wyss' researchers come in.

In 2010, the Ingber group reported in the journal Science the development of a human "lung on a chip." This in vitro model system was designed to mimic the functioning of a lung alveolus and uniquely showcases the group's focus on not just creating synthetic tissues but creating synthetic organs where multiple tissues types interact.

The team was able to co-culture the three major tissue components of the lung within a hollow channel in a single microfluidic chip composed of a clear, flexible silicone. Spanning the channel was a malleable and porous membrane coated with extracellular matrix. On one side resided human lung epithelial cells with air introduced above their surface to mimic the air sac, while on its underside grew human lung capillary endothelial cells with flowing culture medium representing blood within a pulmonary vessel. This channel was bordered on both sides by two additional hollow channels that experienced cyclic suction, which caused the neighboring tissue–tissue interface to undergo rhythmic stretching and relaxation, thus mimicking physiological breathing motions.

This device recapitulated pulmonary barrier functions normally seen only in vivo, and, when human immune cells were added to the flowing blood, they were able to respond to

BY THE NUMBERS

3: The number of years it took to generate initial funding for the institute

$125 million: Harvard's largest single philanthropic donation in its history – from alumnus Hansjörg Wyss

9: The number of universities and hospitals around Boston collaborating with the institute, including the Dana Farber Cancer Institute and the Massachusetts General Hospital

25: The number of open positions on the institute's recruitment page

$12.3 million: The amount received from the Defense Advanced Research Projects Agency to develop a spleen-on-a-chip device to diagnose sepsis rapidly

53: The number of peer-reviewed publications the institute produced in the first five months of 2012

1: The average number of Science or Nature papers published per month by the institute's 17 faculty over the first three years of its existence

17: The number of faculty members affiliated with the institute

The Wyss Institute aims to foster a friendly, collaborative research environment for scientists and clinicians.

the addition of pathogenic bacteria to the surface of the lung by adhering to the endothelium, migrating across the two tissue layers and engulfing invaders. Moreover, because the chip is clear, all of those processes could be visualized at high resolution and in real time. It is this system that is being pioneered to study the effects of novel treatments for lung disease.

For nearly three decades, Ingber and co-workers have been championing the idea that one of the most important factors in controlling the function of a particular organ or tissue is the mechanical forces that the cells experience in their natural microenvironments. "In the early days, biologists were skeptical or had no interest" in the role of tissue mechanics, Ingber says, but now this research is showing that it clearly has an effect that scientists can harness, in this case to create new in vitro assays.

The team has another nine systems in development (including the previously published gut on a chip) and is currently pursuing ways to connect them together to generate "an instrument that can probe, manipulate and analyze multiorgan system responses to replace animal testing," Ingber says. The group recently entered into a project with the Defense Advanced Research Project Agency worth up $37 million to develop an automated human-body-on-a-chip model leveraging its organ-on-chip technologies.

Still, Danny McAuley, a clinical professor in intensive care medicine with an interest in developing novel therapies for lung disease at Queen's University in Belfast, U.K., stresses the importance of not forgetting human testing. "[We] probably need better characterization of existing models to confirm data identified in models translates to human disease rather than new models," he says. He predicts that no in vitro model will completely replace human testing, but they "might be useful as a stop point in drug development."

Furthermore, Ingber's team is actively pursuing ways to combine its cell biology work with the other projects going on at the institute, such as those being done by synthetic biologists like Silver and Church.

A SYNTHETIC WAY OF LIFE

Silver's lab — along with colleagues James Collins and Church — focuses on the manipulation of both prokaryotic and eukaryotic genomes and on developing new ways to do so. These synthetic biologists seek to engineer and build novel, man-made alternatives to our genes and pathways to construct living organisms or cells with well-defined outputs and, hence, new or improved functions.

The Church lab has been at the forefront of developing easier and cheaper genomic technologies. "We've helped lower the cost of sequencing about a million-fold and of engineering genomes using DNA from chips by similar amounts," Church says. His lab, by helping to make genomics cheaper, faster and more accessible, has advanced fields ranging from ecology to medicine via chemistry and science policy.

There is no handbook for synthetic biologists to follow; they have had to develop their own sets of principles and rules, and those at the Wyss are at the leading edge of that work. As Silver explains, "Biology is not like electrical engineering in that it works in three dimensions — no wires — and over time scales that can be long. We seek new computational strategies and to move beyond trial and error in building complex biological systems."

Meanwhile, Silver and Church recently co-headed Harvard's International Genetically Engineered Machine — or iGEM — team, a group of biology students in an annual international synthetic biology competition aimed at the creation of devices to solve a particular issue. The team's project focused on the development of a system to engineer synthetic gene circuits in plants rapidly and easily.

The team altered existing plasmid vectors to accommodate DNA modules from the Biobricks parts registry, a standardized catalogue of genes, vectors and regulatory elements. As a proof of principle, they inserted a gene encoding the protein miraculin (a peptide that makes sour tastes become sweet) into Arabidopsis to alter the taste of a bitter plant significantly without altering sugar content.

Christina Agapakis, a postdoctoral researcher at the University of California, Los Angeles, and one of the researchers supervising the iGEM team, explains that the team wasn't allowed actually to taste their plants, so officially nobody knows for sure what it tasted like. However, she emphasizes, "We hope that these tools inspire and enable other iGEM teams to work with plants so that the toolkit can grow further."

BRINGING IT ALL TOGETHER

As Ingber looks to the future of his group's organs-on-chip model, he says, "Finally, we can start by building the simplest model that re-creates physiological functions of interest and then add back cells one by one to explore their relevance for any response of interest." But beyond cell biology, synthetic biology and genomics will have large parts to play as Wyss researchers come better to understand and manipulate human biology, which hopefully will pay off in terms of novel treatments for now-incurable diseases.

"We are collaborating with Don on enabling us to move from organs on chips to personalized and synthetic versions," Church explains. He is planning on aligning his work on personalized genomics with the Ingber group to uncover how our genetics influence cell or organ functioning. This fits nicely with Silver's vision of introducing her synthetic DNA into Ingber's systems in a way that truly reflects what the Wyss Institute is all about: innovation through collaboration.

Don Ingber, founding director of the Wyss Institute and a professor at Harvard Medical School and Boston Children's Hospital, leads the biomimetic microsystems platform that is engineering new human tissue models.

In attracting so many successful researchers and bringing them into close contact, the Wyss Institute has addressed one key problem with modern science: How do we make it easier to make important discoveries quickly?

"It is easier to do cutting-edge science when mixed in with developing — not just buying — the most cutting-edge engineering, and vice versa," Church underscores. This is made easier at a research institute fostering the development of life-inspired materials and medical devices that can anticipate disease and correct it before it gets out of hand.

The Wyss has aligned itself with a range of medical centers around the city of Boston, including the Dana–Farber Cancer Institute. "The opportunity to couple engineering expertise at the Wyss Institute with clinical investigation expertise at the Dana–Farber has dramatically accelerated the translation of exciting preclinical findings to testing in cancer patients," says Glenn Dranoff, associate faculty member at the Wyss Institute and professor of medicine at Dana–Farber, Brigham and Women's Hospital and Harvard Medical School.

We may never truly understand life until we are able to reconstruct it from scratch, and, as demonstrated by the Ingber, Church and Silver labs, the researchers at the Wyss Institute are trying to get us there with the great hope of answering some of our most pressing questions.

Connor Bamford (connorggbamford@gmail.com) is a Ph.D. student at Queen's University in Belfast, U.K.

FIT and fat

BY DAVID L. SILVER

The current view of the pathophysiology of the lipid droplet in adipocytes is that increased capacity or expandability of the adipocyte lipid droplet is beneficial to maintaining glucose and insulin sensitivity.

Natural selective pressure throughout evolution of the Eukarya has generated a staggering array of control mechanisms that maintain energy homeostasis, such as allosteric regulation of glycolysis, nutritional control of gene expression, and the nutritional control of triglyceride hydrolysis and oxidation. The latter process of triglyceride hydrolysis and oxidation provides a major source of energy for most eukaryotes, and, as such, triglycerides are deposited in a phylogenetically conserved, ubiquitous organelle called the lipid droplet. The lipid droplet plays an important role in storage of cellular triglycerides and has the capacity to expand and contract dependent on caloric intake and energy demand.

One unresolved issue in lipid droplet biology is determining the mechanisms for lipid droplet biogenesis. There is substantive new evidence that lipid droplets are formed from the endoplasmic reticulum (1). More recently, our research group discovered a two-gene family of endoplasmic reticulum membrane proteins having six transmembrane domains that we named fat-storage-inducing transmembrane (FITM1/FIT1 and FITM2/FIT2) protein. FIT proteins are phylogenetically conserved from yeast to human. Genetic evidence from overexpression and knockdown studies in mammalian cells indicates that FIT proteins play an important role in the generation of lipid droplets (2–4).

FIT2 is the anciently conserved FIT family member. Indeed, human FIT2 can complement several phenotypes found in an S. cerevisiae strain deleted for FIT2, SCS3, indicating conservation of function (5). How might FIT proteins mediate lipid droplet formation? Structural information on the FIT family is lacking, making it difficult to infer function based on sequence alone. Biochemical evidence indicates that FIT proteins do not mediate fatty-acid or glycerolipid biosynthesis but rather partition newly synthesized triglycerides into lipid droplets (2). Part of the biochemical mechanism appears to require direct binding of triglyceride (6), raising the possibility that FIT proteins might play a role in solubilizing membrane triglyceride to nucleate a de novo forming droplet within the endoplasmic reticulum membrane.

FIT1 and FIT2 have distinct tissue distributions in mice and humans — with FIT1 primarily expressed in skeletal muscle and in lower levels in heart and with FIT2 ubiquitously expressed at low levels in tissues but highly expressed in adipocytes of white and brown origin. The disparate tissue distributions of FIT1 and FIT2 and the observation that FIT1 produces small lipid droplets characteristic of skeletal muscle lipid droplets and that FIT2 produces large lipid droplets more akin to adipocyte lipid droplets indicate that each might have a unique physiological role in metabolism. Skeletal-muscle-specific overexpression of FIT2 in mice resulted in a marked increase in intramyocellular triglycerides but paradoxically a decrease in fatty-acid oxidation and expression of PPARalpha target genes and an increase in the utilization of glucose and branched-chain amino acids (4). These findings suggest that FIT2 produces lipid droplets that are not coupled to mitochondria fatty acid beta-oxidation.

FIT1 is more abundant than FIT2 in skeletal muscle. What might its physiological role be in lipid metabolism? It recently has been shown (7) that PGC1alpha, a major exercise-induced regulator of mitochondria biogenesis and function, can induce expression of FIT1 in primary human skeletal myocytes. Given this finding, it is tempting to speculate that FIT1 plays a causative role in the exercise-induced intramycocellular accumulation of triglycerides noted in the athletes paradox (8).

The current view of the pathophysiology of the lipid

Continued on page 32

jbc THE JOURNAL OF BIOLOGICAL CHEMISTRY

Prion and other amyloid diseases: Reed Wickner shares lessons from yeast cells

BY KAREN MUINDI

Bovine spongiform encephalopathy, commonly referred to as mad cow disease, and variant Creutzfeldt-Jakob disease, which (rarely) develops in humans who have eaten diseased tissue, are transmissible spongiform encephalopathies, or TSEs. While most TSE cases arise spontaneously, inherited genetic mutations also can cause these rapidly progressive, fatal and still untreatable neurodegenerative syndromes. The fear caused by the very mention of a case of mad cow disease has immediate effects across the globe and leads to bans on beef imports from the affected country, resulting in enormous socioeconomic consequences.

In the late 1960s, Tikva Alper presented evidence that the infectious agent of TSEs was not a nucleic acid, and John Griffith suggested it was self-propagation of a protein conformer. In 1982, neurologist Stanley Prusiner isolated the TSE infectious agent, finding that its main component was a protein, which he named PrP. He coined the term "prion" to mean "infectious protein." In 1997, he received the Nobel Prize for this important work. Many aspects, however, were still uncertain and difficult to clarify in experiments involving humans or animals. Surprisingly, the findings that permitted detailed studies and answers came from studies of proteins in yeast by Reed Wickner.

Wickner, who recently wrote a "Reflections" article for the Journal of Biological Chemistry, describes in his article how his background and skills positioned him to undertake these studies. He graduated with a mathematics degree from Cornell University in New York and then went on to study medicine at Georgetown University in Washington, D.C. Upon graduation, he honed his research skills studying enzymes and nucleic acids in postdoctoral fellowships with Herbert Tabor at the National Institutes of Health and Jerry Hurwitz at Albert Einstein College of Medicine. (Tabor was editor of the JBC for four decades and today serves as co-editor.)

In 1973, Wickner returned to the NIH and started working on yeast viruses. During that time, he came across research articles by Francios Lacroute and Michel Aigle that reported that mutations in the yeast protein ure2 affecting the regulation of the enzyme aspartate transcarbamylase had the same phenotype as a spontaneous, nonchromosomal mutant, [URE3], which requires ure2 for propagation. That a nonchromosomal element dependent on a certain gene for its existence could share the same phenotype as mutants of the very same gene got Wickner thinking: It struck him that it was just what one would expect of a prion of the URE2 gene product Ure2p. The lack of mammalianlike prion pathology might have kept others from drawing a similar conclusion, but Wickner had decided to focus on heritable features that would not depend on the particular phenotype produced by the prion.

Reed Wickner

Using then-new genetic approaches, Wickner showed that the [URE3] phenotype is indeed dependent on the gene ure2, confirming the findings of Lacroute and Aigle. He then went on to show that [URE3] yeast cells grown with low concentrations of guanidinium chloride lose the [URE3] phenotype. However, out of these cured cells, the [URE3] phenotype spontaneously arose again without its introduction from other cells. He also showed that overproduction of Ure2p resulted in a 100- to 200-fold increase in the frequency of [URE3]. This first demonstration of protein-based inheritance involving a protein unrelated to the mammalian prion protein was truly groundbreaking and was published in the journal Science in 1994.

Having broadened the prion concept beyond its restriction to mammals, Wickner went on to show that, at least for Ure2p, amino-acid content — and not amino-acid sequence — determines the ability to form a prion. He also has shown that, like mammalian prions, yeast prions are self-propagating amyloids (filamentous protein multimers) with in-register parallel beta-sheet architecture and has proposed a mechanism for how these prions may template the prion fold of the normal protein.

The highly genetically amenable yeast are well suited for these studies, which would not have been possible in mammals. Yeast have long been used to dissect complex problems in cell biology. They are uniquely amenable to the application of a large number of biochemical and genetic techniques. Their fully sequenced genome is easy to manipulate, they have a short life cycle, and they are inexpensive to grow and maintain. The discovery of the prion system in yeast is a major step forward in prion research, as we now have added to our arsenal the power of yeast genetics and biochemistry. Wickner's research underscores this, as he was able to confirm the concept that proteins can be infectious, extend this to show that protein conformation can be inherited, and study the mechanisms involved in the generation and propagation of yeast prions. Wickner's work has not only laid the groundwork for understanding the rare and very debilitating TSEs but also other more prevalent amyloid diseases, such as Alzheimer's and Parkinson's.

Wickner's studies are another example of how basic biochemical studies with no apparent relation to a human disease can lead unpredictably to insights into an important human disease. Wickner was able to carry out these studies only because of his extensive background in yeast genetics and yeast biochemistry.

Karen Muindi (Karen.Muindi@fda.hhs.gov) is a postdoctoral fellow at the U.S. Food and Drug Administration.

Everything is illuminated: 'Reflections' on light and life by Lubert Stryer

BY PUMTIWITT C. McCARTHY

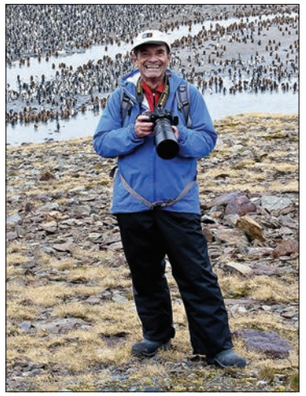
Lubert Stryer, professor emeritus at Stanford University, has spent his research career harvesting the power of light. Some of his most important work has used light to develop tools to explore the structure and function of biological macromolecules. In his recent "Reflections" article for the Journal of Biological Chemistry, Stryer recounts his life experiences and gives praise to many of the students, postdoctoral fellows and collaborators who have helped him produce a successful career. One common thread in his life has been his interest in trying to understand the "interplay of light and life."

Stryer's interest in light-catalyzed reactions was first piqued in an introductory biology course at the University of Chicago. Stryer writes in his "Reflections" essay that he can "vividly recall my excitement on seeing this graphic demonstration of key features of photosynthesis in a test tube." Conversations with Nobel laureate James Franck, an emeritus professor in chemistry at the University of Chicago, were just as important to his career path. Stryer worked as a waiter during his time at the university, and Franck was a frequent customer who always ordered the same thing. This left ample time for conversations about science. Stryer and Franck discussed Franck's initial research on energy transfer, which revealed that excitation energy can be transferred through direct electromagnetic interaction. At some point, Franck told Stryer, "One day, you too might work on energy transfer." This, in fact, turned out to be the case.

Stryer's first foray into studying fluorescence energy transfer came when he was a summer research student under Douglas Smith at Argonne National Laboratory. Smith introduced Stryer to photodynamic action, a process whereby light activates a photosensitizing dye in the presence of oxygen, leading to cellular damage. At Smith's urging, Stryer read the literature about Theodor Förster's theory of energy transfer. Stryer was intrigued by the theory's prediction of the absolute dependence on the distance of the two dipoles. Stryer viewed this as a potential way to develop new knowledge of biological macromolecules using energy transfer in proteins.

Stryer entered medical school at Harvard University under the mentorship of Elkan Blout. He performed research investigating polyglutamic acid and polylysine complexation with dyes and effects on optical rotation. Stryer devoted his career to basic research during his fourth year in medical school. Blout planned Stryer's postdoctoral research career, making sure Stryer boned up on his physics, chemistry and mathematics, and then Stryer headed off to the Medical Research Council Laboratory in Cambridge, England. It was an exciting time for Stryer, and he says his years in the two Cambridges were some of the best in his life.

Stryer's independent research career began at Stanford University. One of his major accomplishments there came while investigating how fluorescence energy transfer can serve as a way to measure the distance between two sites in a protein. Using the recently introduced solid-phase peptide synthesis technique, Stryer's group synthesized a series of polypeptides with



Lubert Stryer

chromophores at known distances and determined their transfer efficiencies. Their study demonstrated that energy transfer can serve as a "spectroscopic ruler." Much of the labeling work that is done today using FRET can be credited to the pioneering work of Stryer.

Another one of Stryer's significant accomplishments was offering a better understanding of the biochemical basis of visual amplification. Rhodopsin is a photosensitive membrane protein that undergoes a cis-to-trans isomerization in the presence of light. This isomerization starts the cascade of events leading to the eventual firing of the optic nerve and visualization. Stryer and his team were the first to elucidate successfully the components and mechanism of the cGMP cascade responsible for rhodopsin activation.

Stryer has had a number of fruitful collaborations that were born from his interest in light. These collaborations have led to the development of important light-based tools that have moved the field forward and are still in use today. Stryer and researchers from the University of California, Berkley, developed multicolor fluorescent probes conjugated to biological molecules for flow cytometry and fluorescence microscopy. Also, as a scientific adviser to what is now known as Affymetrix, Stryer directed efforts to produce light-activated combinatorial synthesis libraries on a solid support for peptides and oligonucleotides.

Now that Stryer's research career has ended, he explores his fascination with light in other ways. Since his retirement from Stanford, Stryer has spent much of his time enjoying his two interests: photography and adventure travel. He has traveled to Antarctica, the Arctic, the Galapagos Islands and Africa to take pictures. Although he is retired, science is still on Stryer's mind. He says, "Photography has heightened my awareness of color in the natural world and deepened my interest in color vision."

Pumtiwitt C. McCarthy (rancypc@od.nih.gov) is a research fellow in the National Institutes of Health Pharmacology Research Associate Program of the National Institute of General Medical Sciences.

How actin goes in new directions

BY RAJENDRANI MUKHOPADHYAY

The cytoskeleton protein actin plays a critical role in cell movement by assembling at cell protrusions. The assembly process involves actin-binding proteins, one of which is the actin-related protein 2/3, or Arp2/3, complex. This complex helps to form branched actin structures, which allow actin to push the membrane envelope forward and get the cell to migrate. But how Arp2/3 picks out specific actin networks is not well understood. In a recent "Paper of the Week" in the Journal of Biological Chemistry, a team led by C.-L. Albert Wang at the Boston Biomedical Research Institute demonstrated that caldesmon, an actin-binding protein, increased the Arp2/3-mediated branching activity at newly formed actin filaments. By using in vitro and imaging assays, Wang and colleagues found that caldesmon had no effect on branch formation at older actin filaments, but the younger, fresher actin filaments were twice as active in forming branches than the mature actin filaments. This suggested that caldesmon maintains freshly polymerized actin in a state with a higher affinity for the Arp2/3 complex. Wang explains the group is now working to determine if other actin-binding proteins have the same effect as caldesmon in modulating actin cytoskeletal dynamics and if caldesmon can affect cell migration and tumor metastasis by manipulating actin dynamics.

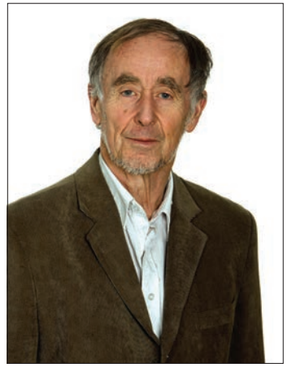
Rajendrani Mukhopadhyay (rmukhopadhyay@asbmb.org) is the senior science writer for ASBMB Today and the technical editor for the Journal of Biological Chemistry. Follow her on Twitter at twitter.com/rajmukhop.

THE JOURNAL OF LIPID RESEARCH

Late Swedish lipidologist Sven-Olof Olofsson remembered

BY MARY L. CHANG

The October issue of the Journal of Lipid Research includes a tribute to Sven-Olof Olofsson, a principal researcher at the University of Gothenburg's Sahlgrenska Center for Cardiovascular and Metabolic Research, who passed away suddenly in December at the age of 64.



Sven-Olof Olofsson

Though he was heavily involved as part of the medical faculty of the university, supervising 17 successful doctoral candidates, and was known to his patients as a knowledgeable yet empathetic cardiologist, his colleagues Jan Borén, Göran Bondjers and Olov Wiklund explain in their "In Memoriam" article that it was research that remained Olofsson's true passion.

His legacy includes his many studies on the assembly and secretion of apolipoprotein B100-containing very low-density lipoproteins, including elucidating the many steps of VLDL1 assembly. His more recent research included innovative exploration into lipid-induced inflammation and the development of insulin resistance, identifying the soluble NSF attachment protein-reception protein SNAP23 as a new link between how fat accumulates in cells and the development of diabetes.

He handily took the knowledge he learned from the bench to treat lipid disorders at the university's teaching hospital, where he was beloved by his patients. This human touch, along with his many scientific contributions, will be remembered for years to come.

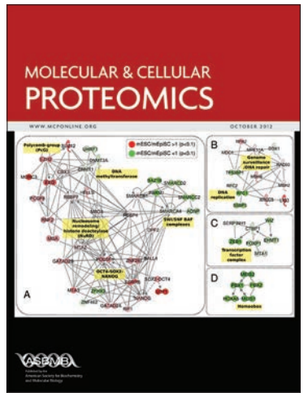
Mary L. Chang (mchang@asbmb.org) is managing editor of the Journal of Lipid Research and coordinating journal manager of Molecular and Cellular Proteomics.

MCP MOLECULAR & CELLULAR PROTEOMICS

Secretions of bone-forming cells

BY RAJENDRANI MUKHOPADHYAY

Osteoblasts secrete various proteins that make up bone as well as growth factors and cytokines that interact with organs outside of bone. Despite their critical role in bone formation and communication with other organs, the proteins that osteoblasts secrete are not very well understood. Osteoblasts evolve from stem cells in the bone marrow, which are called mesenchymal stem cells. "Mesenchymal stem cells are being introduced into clinical trials, and some of the putative beneficial effects of these cells are related to their secreted factors," explains Moustapha Kassem at the University Hospital of Odense in Denmark. "However, the nature of these secreted factors and their change during osteoblast differentiation are poorly documented and understood." So in a recent Molecular & Cellular Proteomics paper, a team led by Kassem and Jens S. Andersen at the University of Southern Denmark described a mass spectrometric analysis of the proteins secreted by osteoblasts over a period of two weeks as the cells developed and matured from mesenchymal stem cells in culture (1). The investigators used an isotope-labeling approach that allowed them to tell apart proteins that were secreted by the cells and contaminants in the culture media. One of the things the investigators established was that a hormone called stanniocalcin 2 behaved in an autocrine fashion to promote the differentiation of the mesenchymal stem cells into osteoblasts. The investigators also discovered nine novel factors that are secreted by mesenchymal stem cells. Kassem says they will now focus on these nine factors to better understand their role in mesenchymal stem cell biology.



Rajendrani Mukhopadhyay (rmukhopadhyay@asbmb.org) is the senior science writer for ASBMB Today and the technical editor for the Journal of Biological Chemistry. Follow her on Twitter at twitter.com/rajmukhop.

1. Kristensen, L. P, et al. Mol. Cell. Proteomics DOI: 10.1074/mcp.M111.012138 (2012)

MORE JOURNAL NEWS ONLINE

Minireviews about the ENCODE project

The National Human Genome Research Institute announced in September the results of a five-year international study of the regulation and organization of the human genome. The project is named ENCODE, which stands for the Encyclopedia of DNA Elements. In conjunction with the release of those results, the Journal of Biological Chemistry published a thematic minireview series entitled "Results from the ENCODE Project: Integrative global analyses of regulatory regions in the human genome," that focuses on several aspects of the findings.

Taking serine metabolism seriously

Do you think serine metabolism is important? If you study the brain, development or epigenetics, it may be of value to you. Serine is involved in all of these processes in addition to many others. In a recent Journal of Biological Chemistry minireview, Satish C. Kalhan of the Cleveland Clinic Lerner College of Medicine and Richard W. Hanson of the Case Western Reserve University School of Medicine argue that serine is underappreciated, and the authors make quite a case for it, underscoring the significance of serine metabolism.

washington **update** *continued*

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the transition from graduate school to postdoctoral training, one postdoc noted, "You are responsible for your own progress. An IDP helps outline key questions to answer and allows you to prioritize goals for the near future."

myIDP was co-developed by scientists at FASEB; the Medical College of Wisconsin; the University of California, San Francisco; the American Association for the Advancement of Science and Science Careers with support from the Burroughs Wellcome Fund.

FASEB is proud to have played a role in developing this important new tool and hopes that the resources provided through myIDP will encourage more graduate students and postdocs to develop career and professional-development plans.

"As a community, we must do more to help our trainees prepare for a broader range of scientific careers," said FASEB President Judith Bond. "It is our hope that training institutions and faculty advisers will encourage their graduate students and postdocs to use myIDP and that it will help trainees communicate with their mentors about their career plans."

To access myIDP, visit http://myidp.sciencecareers.org.

Jennifer A. Hobin (jhobin@faseb.org) is director of science policy in FASEB's Office of Public Affairs.

lipid *news* *continued*

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droplet in adipocytes is that increased capacity or expandability of the adipocyte lipid droplet is beneficial to maintaining glucose and insulin sensitivity. For example, PPARgamma activators improve glucose and insulin sensitivity but increase body weight, in part due to adipocyte differentiation and expansion (9). In light of these findings, it might be significant that mouse and human FIT2 are direct targets of PPARgamma (10), suggesting that enhancing FIT2 expression would be beneficial to improve metabolic parameters in obese, insulin-resistant people. These ideas await testing using mouse FIT1- and FIT2-deficiency models as well as the identification of human mutations in these interesting, anciently conserved fat-storing genes.

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Boston

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SPECIAL EVENTS

Professional Development for Graduate/Postdoctoral Trainees
Saturday, April 20

ASBMB Opening Reception
Saturday, April 20, immediately follows the Opening Lecture

Undergraduate Orientation: A Student's Guide to the ASBMB Annual Meeting
Saturday, April 20

17th Annual Undergraduate Student Research Poster Competition
Saturday, April 20

Beyond College: Coping with Some Common Challenges
Undergraduate workshop, Saturday, April 20

Undergraduate Breakfast with ASBMB Award Winners
Sunday, April 21, and Monday, April 22

ASBMB Welcome and Networking Reception
Sunday, April 21

ASBMB Thematic Fermentation Happy Hour
Monday, April 22

ASBMB Women Scientists Networking Event
Tuesday, April 23

Y.E.S. Mixer (Young Experimental Scientists)
Consult program for details