ASBMB today

July 2010

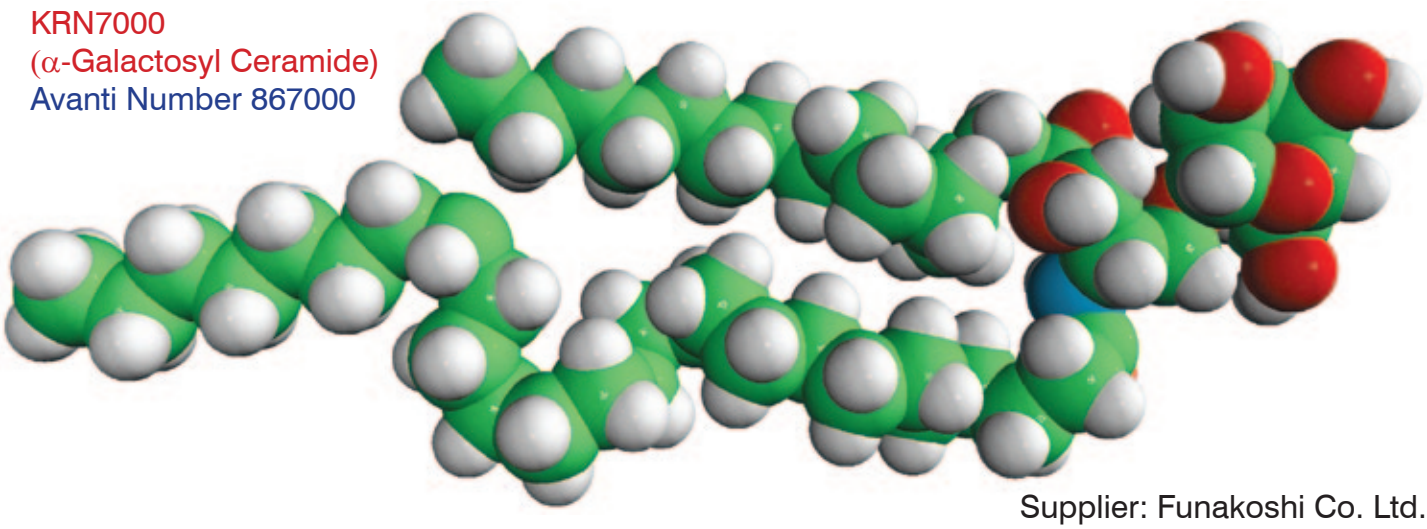
ASBMB PRESIDENTIAL PRIMER:

Suzanne Pfeffer

American Society for Biochemistry and Molecular Biology

Adjuvant Immunotherapy using KRN7000

KRN7000
(α-Galactosyl Ceramide)
Avanti Number 867000



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Hepatic metastasis is a major clinical problem in cancer treatment. We examined antitumor activity of alpha-galactosylceramide (KRN7000) on mice with spontaneous liver metastases of reticulum cell sarcoma M5076 tumor cells (spontaneous metastasis model). In this model, all mice that were s.c. challenged with one million tumor cells developed a solid s.c. mass by day 7 and died of hepatic metastases. In the current study, we administered 100 microg/kg of KRN7000 to the model mice on days 7, 11, and 15. This treatment suppressed the growth of established liver metastases and resulted in the prolongation of survival time. Fluorescence-activated cell sorter analysis of phenotypes of spleen cells, hepatic lymphocytes, and regional lymph node cells around the s.c. tumor revealed that CD3+NK1.1+ (NKT) cells increased in hepatic lymphocytes of the KRN7000-treated mice. Cytotoxic activity and IFN-gamma production of hepatic lymphocytes were augmented in comparison with those of spleen cells and regional LN cells. At the same time, interleukin (IL)-12 production of hepatic lymphocytes was markedly enhanced. Neutralization of IL-12 using a blocking monoclonal antibody diminished the prolonged survival time. These results showed that the *in vivo* antitumor effects of KRN7000 on spontaneous liver metastases were dependent on the endogenous IL-12 production, where NKT cells in the liver are suggested to be involved. Adjuvant immunotherapy using KRN7000 could be a promising modality for the prevention of postoperative liver metastases.

Fuji, N., Y. Ueda, H. Fujiwara, T. Toh, T. Yoshimura, and H. Yamagishi. (2000).
Antitumor effect of alpha-galactosylceramide (KRN7000) on spontaneous hepatic metastases requires endogenous interleukin 12 in the liver. *Clin Cancer Res* 6:3380-7.

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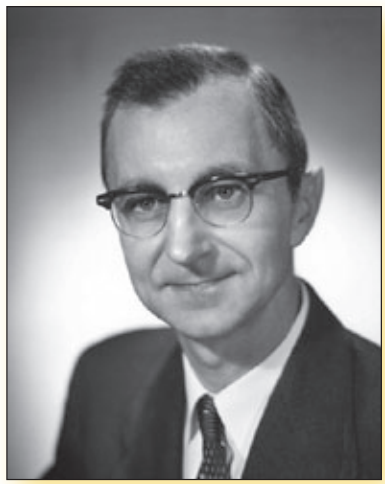

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Last month we ran a story on biochemistry rap artist Tom McFadden. Now, you can view a follow up videocast with McFadden at http://bit.ly/b6Spsl.

ASBMB today

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

letters to the editor

Basic versus Translational Research

Dear Greg,

In your May President's Message, discussion continues on the apparent lack of support of "basic research" versus "translational research" by the National Institutes of Health. I'm concerned because this affects our research into the molecular basis of lectin-carbohydrate interactions in cellular recognition (glycobiology), which, until recently, was supported by the National Cancer Institute for 30 years.

So, let's examine the linguistic claims that basic and translational research are separate efforts. In the present context, let's define "basic research" as studies of biological processes and the molecules involved. "Translational research" can be defined as studies that target the molecular basis of disease, with the hopeful goal of a "cure." However, finding cures for diseases such as cancer requires understanding the alteration of normal cellular processes to the transformed state and then changing the latter to the former. Thus, both the disease state and normal state need molecular definition, which requires research into both. In other words, you can't fix something unless you understand what the differences are. (Automobile mechanics know this well.) Thus, both basic and translational research need NIH support because they are interlocked scientifically.

It follows that care needs to be given in defining basic research as something without evident translational components. This is the base line required for translational research. We need much more data on the molecular mechanisms associated with normal homeostasis in human biology, as well as the change involved in the disease process. In this regard, our "basic research" has led to new models of the interactions of lectins with cell surface glycans of pathogens in innate immunity (1) and cellular homeostasis in metazoans (ground state for health) (2). These findings are a result of more than 30 years of basic research!

For future discussion, you may consider the effects on NIH funding of having predominantly one sector of science define equilibrium and nonequilibrium chemical interactions in humans.

Sincerely,
Fred Brewer
Albert Einstein College of Medicine

REFERENCES

1. Tadano-Aritomi, K, Kubo, H., Ireland, P., Hikita, T., and Ishizuka, I. (2010) Isolation and Characterization of a Unique Sulfated Ganglioside, Sulfated GM1a, from Rat Kidney. *Glycobiology* **20**, 270 – 278.
2. Glycobiology, in press.

The President's Farewell

Dear Editor,

Our outgoing (in both senses) president penned a lovely farewell in the June issue of ASBMB Today. He was as engaged and creative as any ASBMB leader in recent years. I wish to add my view that his monthly col-

continued on page 7

Your ASBMB

BY SUZANNE PFEFFER

It is a special honor and a privilege to begin my term as president of the American Society for Biochemistry and Molecular Biology. Our outgoing president, Greg Petsko, deserves an enormous thank you from all of us — for guiding the society so ably and for making us feel that we really are a part of ASBMB by writing such engaging, thought-provoking and humorous columns. He has been a terrific role model, and his shoes will be impossible to fill. Luckily, for all of us, Greg will continue to serve as an officer of the society for an additional year, in the role of past-president. I am especially grateful that I will be able to rely on his wise counsel during my term.

I hold a special place for ASBMB in my scientific heart. I had the privilege of starting my life as a biochemist while still an undergraduate student, first during a brief summer stint with Don Lightfoot at Virginia Polytechnic Institute and State University and then returning to my undergraduate University of California, Berkeley, campus and the lab of Mike Chamberlin, where I worked on Escherichia coli RNA polymerase for two years. My project culminated in a first author paper in the Journal of Biological Chemistry. At the time, several of the Berkeley faculty members were JBC editorial board members, and I remember asking Clint Ballou for guidance on how to prepare a figure on a day when Chamberlin wasn't around. Teasing me, he took out a giant pair of scissors as if to slice my artwork — I almost died. This was, of course, at a time when figures were drawn by hand — computers were not yet tools at every desk. Publishing that first paper in JBC and receiving those reprints with my name in print for the first time made me feel like an ASBMB member for life. Being elected president is thus a special honor for me, and I will do my best to serve you, our members, during my term.

In preparation for my presidency, the past year has included my participation in many of our society's committee meetings. This has provided me with a chance to learn first-hand about many of the important activities in which ASBMB is currently involved. Thanks to the work of all of our committees, under the guidance of the council leadership and outstanding staff, ASBMB is in very good shape.

Under the watchful eye of Merle Olson, our finance committee has done a wonderful job of shepherding the society's reserve funds that have now recovered to pre-economic downturn levels. These funds support all of our activities, including staffing and production of our journals, as well as enabling the Undergraduate Affiliate Network Committee, Minority Affairs and Education and Professional Development Committees (UANC led by Neena Grover, MAC led by Craig Cameron and EPD by Ellis Bell followed by Peter Kennelly) to offer 316 travel or child care fellowships for students, postdocs and faculty to attend our 2010 annual meeting. Thanks to all of the members of these committees for excellent program contributions during the meeting in Anaheim.

The Public Affairs Advisory Committee, led by Bill Merrick, has dedicated itself to forging new relationships with members of U.S. Congress, as well as with representatives of all of the institutes at the National Institutes of Health and with key program directors at the National Science Foundation. The committee's main focus this year has been to work to ensure the continued prioritization of investigator-initiated research. Peter Farnham, our director of public affairs, joined this past year by Kyle Brown, our science policy fellow, have led the charge and guided the committee's activities with great leadership and enthusiasm.

Herbert Tabor, editor of the Journal of Biological Chemistry, Ralph Bradshaw and Al Burlingame, co-editors of Molecular and Cellular Proteomics and Ed Dennis and Joe Witztum, co-editors of the Journal of Lipid Research, are doing wonderful jobs of overseeing their publications. Indeed, all of the editors and editorial board members deserve our thanks for their dedicated service to the society and the scientific community overall. The Publications Committee, under Toni Antalis, has provided guidance to JBC, MCP and JLR and has helped to adjudicate ethical issues that arise from time to time. Thanks to the ASBMB council, starting this month, ASBMB members will be eligible for page charge and color figure discounts, and JBC no longer requires a fee to submit manuscripts. This, together with the excellent quality of the review

process, should encourage our members to continue to support our society publications. ASBMB publishes these journals to serve you, our members. We have been leaders in the use of electronic publishing and will continue to excel in the electronic journal world. (Check out one of our most recent additions — the ability to rotate three-dimensional images with just the click of a mouse in our journal article PDFs.)

The 2010 program chairs and the ASBMB Meetings Committee (chaired by Joan Conaway) deserve hearty congratulations for assembling an incredibly successful annual meeting in Anaheim. And, during 2010, ASBMB will sponsor four small meetings, the majority of talks for which will come from submitted abstracts. This means that more students and postdoctoral fellows will have a chance to speak, and the sessions will not be dominated by the same names that always seem to appear on speaker lists that we all peruse in popular science journals. Thanks to Ali Shilatifard for overseeing the Small Meetings Subcommittee. And, finally, the Nominations Committee assembled an excellent slate of candidates to lead the society moving forward.

> "One of my top goals for the next two years is to try to address the needs of our youngest members."

Just because the ASBMB is doing well doesn't mean that we can't do even better. One of my top goals for the next two years is to try to address the needs of our youngest members. Graduate student representatives polled from 50 different biochemistry departments all indicated strong enthusiasm about the possibility of ASBMB sponsoring local meetings for students and postdoctoral fellows. These meetings would offer an opportunity for participants to share their research in the form of short talks and posters and also would include panel discussions on topics including career options and how to apply for jobs, be it an academic, industrial or legal setting or a consulting or teaching position. We already have started to plan two regional pilot workshops — one at Rutgers University and one at Northwestern Medical School, with Raleigh-Durham and Seattle to follow soon after. I will keep you posted on our progress and would love to hear from you if you would like our help in creating and sponsoring a one-day ASBMB graduate student/postdoc event in your city.

We also hope to include more mentoring events during the annual meeting. I will return to the question of graduate training in a future column. We need to be thinking about whether our current curricula adequately train students to work on a genome-wide and/or systems-wide level — should we be teaching students to handle large data sets and make full use of statistics? Can they program in MATLAB? Are we helping them learn to identify the most important scientific questions rather than just how to carry out the next experiment? And, are we providing them with leadership skills that will carry over into the jobs they likely are to assume, including biotech, teaching, law and advocacy? ASBMB will try to facilitate discussion of these critical issues and ways to address them in the months to come.

So, why should you be an ASBMB member and support this society? ASBMB is devoted to promoting the discipline of biochemistry and molecular biology. This means using all of our resources to expand and improve scientific training and mentorship at all levels, to provide venues for our members to share their findings — whether in person, print or online — and to establish important contacts to facilitate scientific exchange and collaboration. Our society works hard to fight for research dollars for its members and to keep them informed about science policy matters that will affect them both as scientists and as citizens. ASBMB can help bring us together to make our science better and to keep it collegial in the true Merriam-Webster sense of that word, "…marked by camaraderie among colleagues." So, thank you for your continued support, and please don't hesitate to let me know what you think will make us even better. XXX

FASEB Advocates for Improved Research Funding and Training Opportunities

BY JENNIFER A. HOBIN AND KAREN R. MOWRER

Seventeen Federation of American Societies for Experimental Biology Board of Directors and Science Policy Committee members from 14 states and Canada came to Washington, D.C., in May to participate in FASEB's annual Capitol Hill Day. Led by FASEB President Mark Lively, the scientists talked to members of Congress about the importance of sustaining support for biomedical research, and presented FASEB's fiscal 2011 federal funding recommendations of $37 billion for the National Institutes of Health and $7.68 billion for the National Science Foundation.

"Fiscal year 2011 is a critical year for science. Our goal is to continue the pipeline of innovative medical and technological advancements," stated Lively. By the end of the day, FASEB members had attended a total of 40 congressional meetings, including breakfast events with U.S. Sens. Tom Harkin, D-Iowa, and Patty Murray, D-Wash., and visits to the offices of six other Senate Appropriations Committee members.

The response to FASEB's mission largely was positive. Congressional staff members appreciated the rationale behind FASEB's funding recommendations, and many were grateful to receive specific information about the impact that NIH funding has on their state. Nearly all who met with FASEB acknowledged the importance of biomedical research, and many expressed support for boosting funding to the agency.

Nonetheless, the difficult fiscal environment left some offices less than optimistic about the ability to provide significant funding increases. For many members of Congress, the top priority continues to be economic recovery and job creation. This was evident when staff inquired about the short-term economic impact of biomedical research funding, the number of jobs retained and created by the American Recovery and Reinvestment Act and the number of grants and positions that would be lost if NIH does not receive the full $37 billion appropriation FASEB recommended.

FASEB's advocacy for increased research funding did not end with Hill Day. FASEB also sent letters to the House and Senate Labor, Health and Human Services Appropriations subcommittee leadership urging a fiscal 2011 increase in the NIH budget, and signed a letter supporting a strong 302(b) allocation (the top-line budget number) for the subcommittee.

In addition to advocating for increases to the federal research budget, FASEB has been promoting improvements in scientific training. As part of an effort to develop a strategic plan for training and career development, the National Institute of General Medical Sciences solicited community input on its training portfolio this past spring. In a letter on this issue, FASEB urged the institute to broaden scientific training opportunities. FASEB believes that the goal of NIGMS training programs should be to prepare trainees for a range of scientific careers, and that scientific training should be broad-based and incorporate training in teaching and mentoring and preparation in professional skills.

FASEB noted that NIGMS could encourage training in all of these areas by expanding programs to help both trainees and established investigators acquire teaching and mentoring skills, requiring institutions to provide educational training to students and postdoctoral fellows supported on training grants and providing funding for institutions to develop professional skills workshops. In addition, NIGMS policy should allow all trainees to devote time to these activities in the course of their research training. NIGMS hopes to complete its strategic planning effort in early 2011.

Jennifer A. Hobin (jhobin@faseb.org) is associate director for scientific affairs in the Office of Public Affairs at FASEB and Karen R. Mowrer (kmowrer@faseb.org) is the legislative affairs officer at FASEB OPA.

For more information:

- FASEB's fiscal 2011 recommendations: http://tinyurl.com/2ax5e9g
- FASEB letter to leadership urging a fiscal 2011 increase in the NIH budget: http://tinyurl.com/25rxbbx
- FASEB's letter urging NIGMS to broaden scientific training opportunities: http://tinyurl.com/28ag3vz

House Panel Considers Risks, Rewards of Synthetic Genomics

BY KYLE M. BROWN

On May 27, in response to the recent announcement that scientists had created the first microbe with a man-made genome, the U.S. House Energy and Commerce Committee heard expert testimony on the scientific and ethical implications of synthetic biology. During the hearing, representatives sought to understand the emerging technology's benefits and risks.

A Cell Reprogrammed

"It is the first cell whose parent is in a computer," said J. Craig Venter, founder of the J. Craig Venter Institute and one of the first to sequence the human genome.

Starting with only "four bottles of chemicals" and a genetic blueprint encoded into the files of their computers, Venter and his team synthetically created an organism's genetic code, spelling out a genome with more than 1 million letters of DNA. They even encoded into the organism's DNA their names, quotations from literature and other identifying markers.

After synthesizing the genome, the scientists replaced the DNA of the bacteria Mycobacterium capricolum with their man-made set of genetic instructions, just as one might install a new operating system on a computer.

The revamped cell took on the characteristics encoded in its new set of genes.

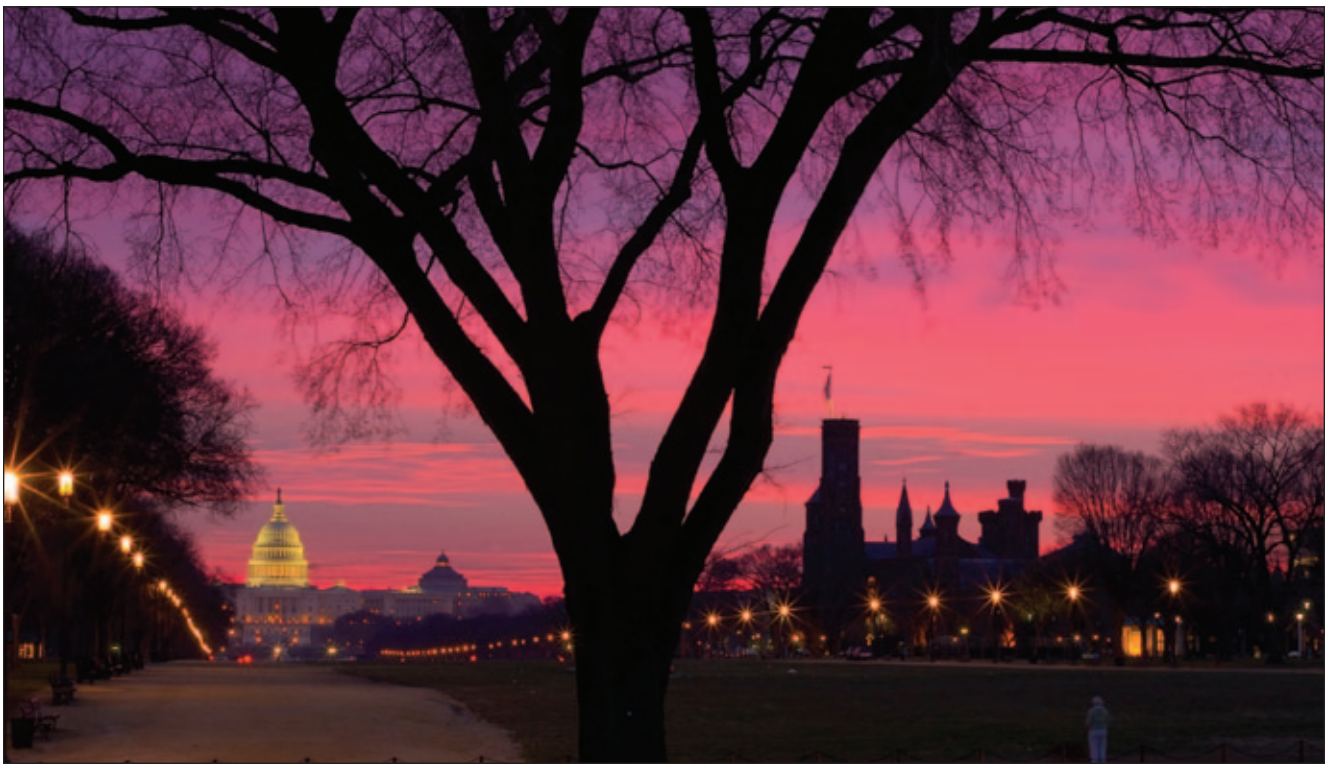
"It's not life from scratch," Venter said, "but now we can write new software of life."

New Possibilities

Members of the committee expressed excitement about the potential benefits of synthetic genomics.

"Synthetic biology will be a major frontier in the 21st century," said U.S. Rep. Bart Gordon, D-Tenn.

U.S. Rep. Henry Waxman, D-Calif., chairman of the committee, agreed. He said that genetic engineering research has had amazing effects over the decades, noting that it has been used to make insulin, vaccines and other important medical advances.



"Whereas most research involves one-celled organisms like bacteria or yeast, the results are far reaching," Waxman said.

Committee members also were encouraged by the research's potential applications for clean energy technologies.

U.S. Rep. Kathy Castor, D-Fla., asked Jay Keasling, acting deputy director of the Lawrence Berkeley National Laboratory, about research that uses yeast to produce diesel fuel from sugar cane.

The process is "akin to brewing beer," said Keasling, who anticipates his team soon will be able to produce fuel in this manner at competitive prices.

"We can innovate our way out of this problem," said U.S. Rep. Edward Markey, D-Mass., referring to issues surrounding the continued use of fossil fuels.

But Venter was more cautious. "I am an optimist and a scientist," he said, emphasizing that that new applications will need to be proved and may be a decade away from the marketplace.

Weighing the Risks

Meanwhile, several members of the committee expressed concern about the potential misuse of the technology.

"Advancements in science must be balanced by strict ethical guidelines," said U.S. Rep. Frank Pallone, D-N.J.

Pointing to a "culture of responsibility," Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases at the National Institutes of Health, outlined some of the oversight mechanisms that exist for similar research.

Fauci said that, although current regulations don't specifically address synthetic biology, the NIH recently drafted new guidelines and is soliciting public feedback. He also noted that the private sector has created best practices that are implemented almost universally.

"People with nefarious motives don't need synthetic biology," Fauci said, noting that it would be much easier to cause harm using other methods. He cautioned against creating new and restrictive regulations.

Synthetic biology "doesn't add much to the ability to do bad stuff" and has "much greater applicability to do something really good," Fauci said.

Driven by Basic Science

Keasling and other experts agreed the breakthroughs by Venter's team, and others underscored the importance of basic science.

The technologies that made those discoveries possible were based on basic science research and funding, Keasling said, noting how difficult it is to get funding to carry out foundational research.

Venter said that research investments would continue to be "one of the most important economic drivers for the future."

Challenging the government to play a more active role in creating innovative technologies, Venter said the federal government needs to rethink the way it funds research.

"Federal funding follows innovations; it seldom leads them," Venter said.

Kyle M. Brown (kmbrown@asbmb.org) is an ASBMB science policy fellow.

For more information:

- Learn more about the hearing and read written testimony from the witnesses: http://bit.ly/9M1RXh
- Venter's article in Science Express: http://bit.ly/b2e0le

letters *to the editor* *continued from page 2*

umns were "sui generis." They were so, and not only because he writes beautifully. They had more traction because of the sweep of his attentiveness to major issues and a willingness to think outside the box. Greg's columns were not focused narrowly on our shop, thus their value. He looked beyond the guild, and we are fortunate that he did so, with such eloquence. His monthly columns have given these pages, and his audience, an enormous intellectual lift.

Thoru Pederson
University of Massachusetts Medical School

REPLY: I fear Thoru gives me far more credit than I deserve. If my columns had the wit and eloquence that he exhibits in his letter, they might be worthy of his praise. But it's incredibly gratifying that someone of his stature and style enjoyed my little efforts. This made my day— and probably, my month. *Gregory A. Petsko*

2010 ASBMB Special Symposia

Deadlines Approaching

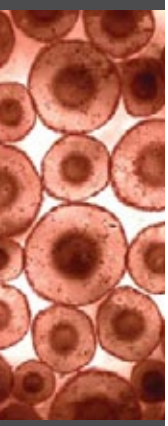
Calendar of EVENTS

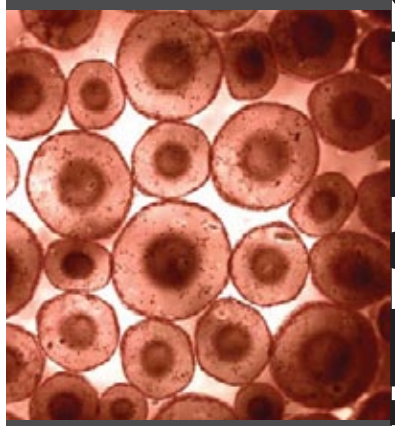
September 30 – October 4, 2010

Transcriptional Regulation by Chromatin and RNA Polymerase II

Granlibakken Resort, Tahoe City, CA

Organizer: Ali Shilatifard
Stowers Institute for Medical Research





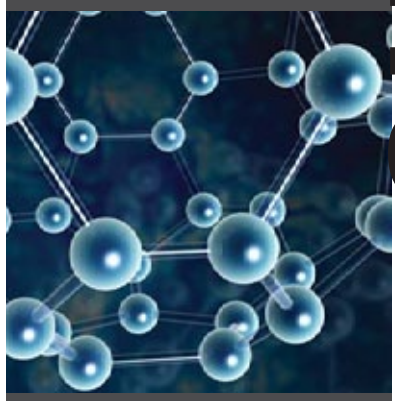
October 14 – October 17, 2010

Biochemistry and Cell Biology Of ESCRTs in Health and Disease

Snowbird Resort, Snowbird, UT

Organizer: James Hurley
National Institute of Diabetes and Digestive and Kidney Diseases

Phyllis Hanson
Washington University School of Medicine



October 21 – October 24, 2010

Post Translational Modifications: Detection and Physiological Evaluation

Granlibakken Resort, Tahoe City, CA

Organizer: Katalin Medzihradszky
University of California, San Francisco

Gerald Hart
Johns Hopkins University School of Medicine

October 28 – October 31, 2010

Biochemistry of Membrane Traffic: Secretory and Endocytic Pathways

Granlibakken Resort, Tahoe City, CA

Organizer: Suzanne Pfeffer
Stanford University School of Medicine

Vivek Malhotra
Center for Genomic Regulation, Barcelona, Spain

www.asbmb.org/meetings

ASBMB Announces New Council and Committee Members

Starting July 1, 2010 several new American Society for Biochemistry and Molecular Biology council and committee members will start their terms. Karen Allen, Michael A. Marletta and Jonathan Weissman will join the ASBMB council; Scott D. Emr and Anna Marie Pyle will become members of the Nominating Committee; Ronald R. Bach, Michael Gelb, Rachel Green, Laura Kiessling and Keith R. Yamamoto will join the Public Affairs Advisory Committee; Paul F. Cook, Ann Marie Pendergast and Frances Sharom will join the Publications Committee and Mark Lemmon will remain as the society's secretary. All newly elected members began serving their terms on July 1, 2010.

Nominating Committee

Scott D. Emr

is director of the Weill Institute for Cell and Molecular Biology at Cornell University. He received his Bachelor of Science degree from the University of Rhode Island and his doctoral degree in molecular genetics from Harvard University. The Emr lab studies the regulation of cell signaling pathways by phosphoinositide kinases, vesicle-mediated transport reactions and selective ubiquitin modifications.

Anna Marie Pyle

is a professor in the department of molecular biophysics and biochemistry at Yale University. She received her bachelor's degree from Princeton University and her doctorate in chemistry from Columbia University. Pyle uses the group II intron as a model system for studying ribozyme catalysis, RNA folding and RNA-protein interactions. She also studies the mechanisms of RNA helicase enzymes. She has been an ASBMB member since 2007.

ASBMB Council

Karen N. Allen

is a professor of physiology and biophysics at the Boston University School of Medicine. She earned her Bachelor of Science from Tufts University and her doctorate from Brandeis University. Her research is concerned with diverse aspects of protein structure, function and design. Her lab employs a multidisciplinary approach involving state-of-the-art X-ray crystallography and spectroscopy, molecular modeling, enzymology and molecular biology to address fundamental problems at the interface of enzymology and structural biology.

Michael A. Marletta

is the Aldo DeBenedictis distinguished professor of chemistry and a professor of biochemistry and molecular biology at the University of California, Berkeley. He earned his bachelor's degree in biology and chemistry from the State University of New York at Fredonia and his doctorate degree from the Massachusetts Institute of Technology. Marletta's primary research interests lie at the interface of chemistry and biology with emphasis on the study of protein function and enzyme reaction mechanisms. He has made fundamental discoveries concerning the biological action of nitric oxide. He has been an ASBMB member since 1988.

Jonathan S. Weissman

is a Howard Hughes Medical Institute investigator and a professor of cellular and molecular pharmacology and of biochemistry and biophysics at the University of California, San Francisco. He received his undergraduate physics degree from Harvard College and his doctorate in physics from the Massachusetts Institute of Technology. Weissman's research looks at how cells ensure that proteins fold into their correct shape, as well as the role of protein misfolding in disease and normal physiology. He also is developing experimental and analytical approaches for exploring the organizational principles of biological systems.

Publications Committee

Paul F. Cook

is the Grace B. Kerr centennial professor of chemistry and biochemistry at the University of Oklahoma. He earned a bachelor's degree from Our Lady of the Lake College and a doctoral degree from the University of California, Riverside. Cook's research interests center around the application of kinetic, spectroscopic and recombinant techniques to the elucidation of mechanism of enzyme action. He has been a member of ASBMB since 1982.

Ann Marie Pendergast

is James B. Duke professor of pharmacology and cancer biology at Duke University Medical Center. She graduated from the University of Michigan with a bachelor's degree in chemistry and the University of California, Riverside with a doctorate in biochemistry. The goal of her research is to define the role of the Abl family of tyrosine kinases and their targets in normal development and pathological conditions including cancer, bacterial pathogenesis, muscular dystrophies, neurodegenerative disorders and immune deficiencies. Pendergast has been a member of ASBMB since 2006.

Frances Sharom

is a professor in the department of molecular and cellular biology at the University of Guelph. She also is a professor and Canada research chair in membrane protein biology and director of the biophysics interdepartmental group graduate program. Sharom received her bachelor's degree from the University of Guelph and her doctorate in biochemistry from the University of Western Ontario. Her research group takes a multidisciplinary approach, using the tools of biochemistry, biophysics, molecular biology and cell biology, to explore how membrane proteins work at the molecular level. Sharom has been a member of ASBMB since 1984.

Public Affairs Advisory Committee

Ronald R. Bach

is an associate professor in the department of medicine at the University of Minnesota Medical School as well as a research health scientist at the Minneapolis Veterans Affairs Medical Center. He earned both his bachelor's and doctorate degrees at Yale University. Bach's research looks at biomarkers of Gulf War Illness and the molecular mechanisms of tissue factor-initiated blood coagulation. He has been an ASBMB member since 1990.

Michael H. Gelb

is the Harry and Catherine Jaynne Boand endowed professor of chemistry in the department of chemistry and department of biochemistry at the University of Washington. He studied chemistry and biochemistry as an undergraduate at the University of California, Davis and earned a doctoral degree at Yale University. His current research looks at structure, function, and regulation of interfacial enzymes including phospholipases A2; the structure-based design and combinatorial chemistry of inhibitors of drug targets from parasites that cause tropical diseases and biochemical studies of protein prenylation. Gelb has been an ASBMB member since 1986.

Rachel Green

is a Howard Hughes Medical Institute investigator and a professor in the department of molecular biology and genetics at the Johns Hopkins University School of Medicine. She earned a bachelor's degree in chemistry from the University of Michigan and a doctorate in biological chemistry from Harvard University. She currently uses biochemical approaches to study the mechanism of translation by the ribosome, and its regulation, in bacterial and eukaryotic systems.

Laura L. Kiessling

is a MacArthur Foundation fellow and Hilldale professor of chemistry and biochemistry at the University of Wisconsin-Madison. She received her Bachelor of Science from the Massachusetts Institute of Technology and her doctorate from Yale University. Her group develops and implements synthetic methods that provide access to biologically active compounds for hypothesis- and discovery-driven research. Areas of current focus include chemical glycobiology, multivalent binding in protein-carbohydrate interactions and signal transduction. She has been an ASBMB member since 1994.

Keith R. Yamamoto

is a professor in the department of cellular and molecular pharmacology and executive vice dean of the school of medicine at the University of California, San Francisco. He earned a bachelor of science degree from Iowa State University and a doctorate in biochemical sciences from Princeton University. The Yamamoto lab is interested in mechanisms that regulate gene transcription in different cell types and physiological settings. The central focus of their studies is the intracellular receptor superfamily of regulators – metazoan factors that include receptors for steroid and thyroid hormones in mammals. Yamamoto has been a member of ASBMB since 1977.

Secretary

Mark A. Lemmon

is a professor and interim chairman in the department of biochemistry and biophysics at the University of Pennsylvania School of Medicine. He earned his Bachelor of Arts from the University of Oxford and his doctorate degree from Yale University. His research looks at the biochemistry and structural biology of membrane targeting by phospholipid-binding domains.

Thanks

We thank the following outgoing council and committee members for their service to the society:

Kathleen M. Beckingham, Publications Committee

Ralph A. Bradshaw, Public Affairs Advisory Committee

H. Alex Brown, Publications Committee

Alma Burlingame, Public Affairs Advisory Committee

Elizabeth A. Eipper, Publications Committee

Judith Klinman, Nominating Committee

Robert J. Lefkowitz, Nominating Committee

Judith S. Bond, Public Affairs Advisory Committee

Joan A. Steitz, Council Member

Christopher T. Walsh, Nominating Committee

James A. Wells, Council Member

Robert D. Wells, Public Affairs Advisory Committee

Adrian Whitty, Council Member

ASBMB Receives NSF Award

The American Society for Biochemistry and Molecular Biology was awarded a National Science Foundation Research Coordination Network Undergraduate Biology Education (RCN-UBE) grant worth $370,000. The grant will support a five-year project that will bring hundreds of life scientists together to develop a rich central resource for biochemistry and molecular biology educators.

The online hub will include biochemistry and molecular biology core concepts, assessment tools and effective pedagogical approaches.

The project will be led by J. Ellis Bell, a professor of chemistry at the University of Richmond and past chairman of the ASBMB Education and Professional Development Committee; Cheryl Bailey, an assistant professor of biochemistry at the University of Nebraska-Lincoln; Hal White, a professor at University of Delaware; Duane Sears, a professor at the University of California, Santa Barbara; Margaret Johnson, an associate professor at the University of Alabama; and Carla Mattos, an associate professor at North Carolina State University.

ASBMB will bring together educators and researchers across the country this fall to participate in a series of one-day workshops designed to develop and evaluate biochemistry and molecular biology foundational concepts.

For more information about NSF RCN grants, visit: http://bit.ly/cEQ3sl.

Retrospective: Leon A. Heppel (1912–2010)

BY JERARD HURWITZ

Leon A. Heppel, who carried out pioneering work in the areas of physiology and nucleic acid biochemistry, passed away on April 9 at the age of 97 in Ithaca, N.Y.

Heppel, born to a poor Mormon family in Granger, Utah, received his doctorate in biochemistry from the University of California, Berkeley (1937) and his medical degree from the University of Rochester (1941). His research efforts during this period revealed that Na^+ and K^+ ions were capable of crossing animal membranes, contrary to the entrenched belief that the lipid cell membrane prevented the passage of hydrophilic metals. He often mentioned that, years later, he enjoyed being asked if he was the son of the Heppel who discovered the Na^+/K^+ membrane permeability.

After completing his medical internship at Strong Memorial Hospital in Rochester, N.Y., in 1942, Heppel and his medical school classmate, Arthur Kornberg, joined the U.S. Public Health Service during the early part of World War II. Heppel was assigned to the National Institute of Health, where, under orders from the Navy, he carried out toxicology research. During this period Leon, together with Herbert Tabor, Bernard Horecker (the only trained enzymologist in the group) and Arthur Kornberg (who, due to Heppel's efforts, was reassigned to the NIH from sea duty) jointly organized a self-educating luncheon club to learn enzymology. By 1948, this effort matured into a new enzyme section at the NIH, headed by Kornberg, which included Horecker and Heppel.

In the early 1950s, in collaboration with his longtime colleague Russell Hilmoe, Heppel focused on enzymes that hydrolyzed RNA, particularly spleen phosphodiesterase. The nature of the products formed and the phosphodiester bond hydrolyzed by this enzyme were elucidated by Heppel during a sabbatical period at the Molteno Institute in Cambridge, England (1953) in collaboration with Roy Markham and John D. Smith. Their laboratory had developed cutting-edge methodologies that separated and identified RNA fragments using paper chromatography and paper electrophoresis. These studies demonstrated that the natural configuration of the internucleotide linkage in RNA was 3'-5' rather than 2'-5'. In collaboration with Paul Whitfield, a graduate student in Markham's laboratory at that time, Heppel demonstrated that the hydrolysis of RNA by pancreatic RNase occurred through a cyclic oligonucleotide, which was isolated and elegantly characterized.

In 1955 (soon after I joined the enzyme section at the NIH as a postdoctoral fellow with Bernie Horecker), Severo Ochoa presented a seminar on the work he and Marianne Grunberg-Manago carried out on the isolation of polynucleotide phosphorylase (PNPase) from Azotobacter vinelandii, the same enzyme independently discovered in Escherichia coli by Uri Littauer and Kornberg. Ochoa presented evidence that the enzyme catalyzed the production of long polymers from ribonucleoside diphosphate, but the nature of the phosphodiester bond formed was unclear. As Heppel was the premier expert in analyzing the structure of oligoribonucleotides, Ochoa proposed a collaborative study with Leon to define the nature of the products formed by PNPase. These joint studies (which included Maxine Singer, a young postdoctoral fellow in Leon's laboratory at that time) rapidly elucidated the mechanism of action of PNPase.

In retrospect, many of us had no idea that these efforts would lead to the isolation of RNA polymers that helped define the interactive properties of RNA, DNA and RNA-DNA hybrids, as well as the polynucleotides

and oligonucleotides that were instrumental in solving the genetic code. Ironically, the Ochoa-Heppel collaboration eventually yielded the initial polynucleotides used by Marshall Nirenberg, Heinrich Matthaei and their colleagues in experiments that defined the code, carried out during a highly competitive period with Ochoa's laboratory.

By the late 1950s, Heppel's laboratory had become a magnet for scientists interested in learning how to work with RNA and oligoribonucleotides. His expertise and store of specific purified enzymes and reagents, coupled with his generosity and hospitality, were legendary. He became a service for those trying to identify oligonucleotide products. This status was exemplified by his realization that Roy Markham (in collaboration with David Lipkin), and Earl Sutherland had unknowingly and independently isolated cyclic AMP; the Markham-Lipkin material was generated by heating ATP with barium hydroxide, while Sutherland, who had discovered its biological importance, had painstakingly isolated miniscule amounts from liver. Chance side-by-side co-chromatography of their preparations by Heppel revealed their identical properties, leading to a marked increase in the availability of cyclic AMP as well as the structure of this biologically important compound. Throughout this period, a large number of talented students, postdoctoral fellows and visiting professors spent time in Leon's laboratory (Henry Kaplan Marie Lipsett, Nancy Nossal, Gobind Khorana, Maxine Singer, Robert Lehman, Uri Littnauer, Audrey Stevens and many others), all contributing to the exciting and highly productive environment.

By the mid 1960s, Heppel's interests shifted to proteins localized in the periplasmic region of gram negative bacteria (located in the space between the cell membrane and cell wall) that were released by osmotic shock. In 1967, after 25 years at the NIH, Efraim Racker induced Leon to join the biochemistry department at Cornell University, where he continued and extended these studies to include specific amino acid binding proteins that participated in energy coupled transport into E. coli. His group applied cytochemical methods to establish the localization of a number of phosphatases to enlarged regions of the periplasmic space. By the mid 1970s, Leon began working on cultured animal cells. To gain more experience with animal cells, he spent time working in Henry Rozengurt's laboratory in London, England. During these visits, he discovered that low levels of ATP altered the permeability of transformed cells and later showed that it acted as a mitogen. Over the ensuing years, which included a period working in Claude Klee's laboratory at the NIH as a Fogerty Scholar, he showed that the mitogenic effects of ATP depended on the elevation of cAMP levels and activation of protein kinase A. The last research paper published by Leon, in 1997 at the age of 85, provided evidence for a role of the G protein $\beta\gamma$ subunits in the enhancement of cAMP accumulation and DNA synthesis by adenosine in human cells.

No description of Leon's legacy would be complete without reference to his unique humor which included long hand written letters (some 10–15 pages in length) summarizing the music played at the latest concert or art exhibit that he and his wife Adelaide attended. Included in these letters were quizzes in which he challenged you to name the restaurants or park depicted in paintings, the date the symphony was first performed, etc.

Leon was tremendously supportive of his associates. Many publications emanating from his laboratory were devoid of his name because he thought its absence would help his students and postdoctoral fellows get jobs. He noted that he stopped doing this when an editor accused him of being uninterested in their work. In a Journal of Biological Chemistry Reflection article summarizing his scientific career, Heppel mentioned nearly all of the people who held positions in his laboratory over the years and noted that the list was small because he preferred to work with a small group which permitted him to carry out experimental work himself. He also noted that he was especially pleased with the performance of women in his laboratory because he was aware that they had difficulties in obtaining positions at the time. In this article, he described the wonderful friendships he formed in research laboratories and acknowledged their role in his career. Those of us who had the good fortune of interacting with Leon during our careers are grateful for his guidance and inspiration. We shall miss him.

Jerard Hurwitz (j-hurwitz@ski.mskcc.org) is a Sloan-Kettering Institute professor and head of the William Randolph Hearst Laboratory of Radiation Biology at the Memorial Sloan-Kettering Cancer Center.

PHOTO CREDIT: OFFICE OF HISTORY, NATIONAL INSTITUTES OF HEALTH.

asbmb member spotlight

Stubbe and Walsh Garner Welch Award

STUBBE

WALSH

Joanne Stubbe, Novartis professor of chemistry and biology at Massachusetts Institute of Technology, and Christopher T. Walsh, Hamilton Kuhn professor at Harvard Medical School, are the recipients of the 2010 Welch Award in Chemistry.

"These two scientists, longtime friends who share a passion for knowledge, have made hugely important contributions to our understanding of the chemistry of biological functions in the enzymes that make life possible. Their work has led to new therapeutic treatments, including new antibiotics and new cancer treatments, among other advances that improve the quality of life," said Ernest H. Cockrell, chair of The Welch Foundation.

Stubbe has focused most of her career studying the mechanisms of enzymes involved in nucleotide metabolism, central to the biosynthesis of DNA and RNA. Her success in unraveling the specific steps in enzymatic reactions over the past four decades has had profound impacts on fields ranging from cancer drug development to synthesis of biodegradable plastics.

Walsh's primary focus is on understanding the mechanisms by which enzymes bring about chemical transformations in biological systems. His group currently is exploring the biosynthesis of natural product antibiotics and the chemical logic and enzymatic machinery of how they are made in order to identify new antibiotics, antitumor agents and immunosuppressants and to improve the efficiency of production.

Bertozzi Awarded Lemelson-MIT Prize

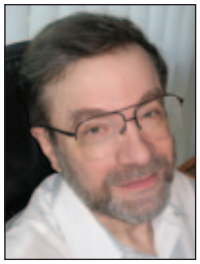
Carolyn Bertozzi, T. Z. and Irmgard Chu distinguished professor of chemistry and professor of molecular and cell biology at the University of California, Berkeley, has been awarded the 2010 Lemelson-Massachusetts Institute of Technology Prize. She accepted the prize and presented her research at MIT during the Lemelson-MIT Program's fourth annual EurekaFest this past June.

Bertozzi's research interests lie at the intersection of chemistry and biology, with a particular focus on understanding the relationship of cell surface glycosylation to normal cell function and to human disease. Bertozzi has designed experiments that have contributed to the way in which researchers can profile changes in cell-surface glycosylation associated with cancer, inflammation and bacterial infection. She is most noted for her pioneering work in the field of bioorthogonal chemistry on living systems.

In addition to her Berkeley appointment, Bertozzi is an investigator of the Howard Hughes Medical Institute, and director of the Molecular Foundry, a nanoscience institute at the Lawrence Berkeley National Laboratory.

PHOTO COURTESY OF CAROLYN BERTOZZI.

Varshavsky Wins Prize for Biomedical Science



Alexander Varshavsky, the Howard and Gwen Laurie Smits professor of cell biology at the California Institute of Technology, has won the 2010 Vilcek Prize for Biomedical Science for elucidating the process and biological significance of regulated protein degradation in living cells.

The Vilcek Prize has been awarded annually since 2006 to an established biomedical scientist whose work profoundly has advanced science over the course of his or her career. Varshavsky's research on ubiquitin led to the discovery of its fundamentally important biological functions in living cells, showing that regulated protein degradation underlies major physiological processes. His laboratory continues to study ubiquitin-dependent processes, with a focus on the N-end rule pathway of protein degradation which relates the in vivo half-life of a protein to the identity of its N-terminal residue.

According to the Vilcek Foundation, "As a pioneer and leader in the field of ubiquitin research who has ushered it into the age of molecular genetics, Dr. Varshavsky also has helped establish this field as one of the most important and 'ubiquitous' in biomedical science, a point of convergence for disparate disciplines."

Chu Receives Outstanding Investigator Award

Charleen T. Chu, associate professor of neuropathology in the pathology department at the University of Pittsburgh, is the 2010 winner of the American Society for Investigative Pathology Outstanding Investigator Award. The award recognizes mid-career investigators with demonstrated excellence in research in experimental pathology. Chu presented her award lecture titled "Parkinson's Disease: Converging Insights from Toxin and Genetic Models" at the Experimental Biology 2010 in Anaheim, Calif.

Chu studies the role of kinases in age-related neurodegenerative diseases with an emphasis on mitochondrial dysfunction and macroautophagy. Her work highlights the dual role of autophagy in neuronal injury. While autophagy reduces cell death by eliminating damaged mitochondria, it also elicits retraction and simplification of the neuritic arbor in multiple toxin and genetic Parkinson's disease models. Her laboratory's discovery of a novel phosphorylation site on the autophagy mediator LC3, which prevents neurite shortening, offers a potential mechanism by which neuroprotective kinases act to restore anabolic-catabolic balance.

Chu's other recent honors include induction to the American Society for Clinical Investigation and the 2010 Carnegie Science Award for Emerging Female Scientist, which recognizes a scientific leader whose cutting-edge work is inspiring change in math, science or technology.

Fenselau Receives Award in Bioanalytical Chemistry

Catherine C. Fenselau, professor of chemistry and biochemistry at the University of Maryland, received the Ralph N. Adams Award in Bioanalytical Chemistry from Pittcon and the Friends of Ralph N. Adams this past spring. The recently established award honors Ralph Adams, a visionary researcher and pioneer in the application of advanced analytical methods to study state-of-the-art biomedical problems.

Fenselau's research focuses on developing proteomic strategies for the analysis of changes in proteins in human cancer cells. She also explores mass-spectrometry-based methods for the rapid analysis of airborne microorganisms.

"The decision to give this award to me reflects the importance of mass spectrometry in biomedical research, its significant past contributions and its huge potential for critical future discoveries," said Fenselau. "Mass spectrometry currently is the most rapidly evolving analytical technology, a claim supported by the award of the Nobel Prize to two mass spectroscopists in 2002, and most of us believe that 'you ain't seen nothing yet.'"

Pittcon is an annual conference organized by the Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy, a Pennsylvania not-for-profit educational corporation comprised of the Spectroscopy Society of Pittsburgh and the Society for Analytical Chemists of Pittsburgh.

Six ASBMB Members Named HHMI Professors

This past spring, six American Society for Biochemistry and Molecular Biology members were among the 13 faculty members from around the nation to be named as Howard Hughes Medical Institute professors in the 2010 round of awards. Launched in 2002, the HHMI professors program recognizes accomplished research scientists who also are deeply committed to making science more engaging for undergraduates. The program awards four-year grants aimed at fostering innovations in undergraduate science education at the professors' home universities and providing other institutions with effective models for bridging research and teaching.

The ASBMB recipients are:

CATHERINE DRENNAN, professor of chemistry and biology at the Massachusetts Institute of Technology.

SARAH C. R. ELGIN, Viktor Hamburger professor of arts and sciences and professor in the department of biology at Washington University in St. Louis.

RICHARD M. LOSICK, Harvard College professor and Maria Moors Cabot professor of biology at Harvard University.

BALDOMERO M. OLIVERA, distinguished professor at the University of Utah.

SCOTT A. STROBEL, Henry Ford II professor of molecular biophysics and biochemistry and professor of chemistry at Yale University.

GRAHAM C. WALKER, American Cancer Society research professor of biology at the Massachusetts Institute of Technology.

Three ASBMB Members Awarded Kavli Prize

Three American Society for Biochemistry and Molecular Biology members were named recipients of 2010 Kavli Prizes. A total of eight scientists were selected to receive the 2010 award for expanding human understanding in the fields of astrophysics, nanoscience and neuroscience.

Members Thomas C. Südhof, a professor in molecular and cellular physiology at Stanford University School of Medicine, and James E. Rothman, chairman of the department of cell biology at Yale University, were joined by Richard Scheller in sharing the neuroscience award for work that revealed the precise molecular basis of the transfer of signals between nerve cells in the brain.

ASBMB member Nadrian Seeman, a professor of chemistry at New York University, received the nanoscience award, with Donald M. Eigler, for his work on structural DNA nanotechnology.

The Kavli Prizes were set up to recognize outstanding scientific research, honor highly creative scientists, promote public understanding of scientists and their work and to encourage international scientific cooperation.

Three ASBMB Members Earn Distinguished Scientist Awards

The Society for Experimental Biology and Medicine has honored three American Society for Biochemistry and Molecular Biology members with the newly established Distinguished Scientist Award. The award recognizes biomedical scientists whose seminal research accomplishments have established them as leaders in biomedicine and who have made significant contributions to SEBM.

Hector F. DeLuca, Harry Steenbock Research Professor at the University of Wisconsin, Henry C. Pitot, professor emeritus of oncology and of pathology and laboratory medicine at the University of Wisconsin, and Kenneth L. Barker of the State University of New York – Syracuse are among the eight past presidents of the SEBM who received the honor.

IN MEMORIAM:

Michael Anthony Cusanovich

Michael Anthony Cusanovich, Regent's professor of biochemistry and molecular biophysics emeritus, former vice president of research, head of the Arizona Research Laboratories, and active member of the University of Arizona community for more than 40 years, died on April 12.

Cusanovich received his Bachelor's degree from the University of the Pacific in Stockton, California and his doctorate in chemistry from the University of California, San Diego. After completing his postdoctoral research at Cornell University, he began his career as an assistant professor of chemistry at the University of Arizona in 1969. He had a distinguished career as an internationally renowned scientist focusing on energy transduction, especially in relation to photoactive proteins.

Cusanovich was a dedicated teacher, an advocate for the development of bioindustry, and a member of the Journal of Biological Chemistry editorial board. He retired in 2007 but continued to immerse himself in research and advocacy. He also was a fan of the outdoors, an avid golfer, horseback rider and skier.

ASBMB Presidential Primer: Suzanne Pfeffer

BY NICK ZAGORSKI

As someone who spent most of her career in the San Francisco Bay Area, Suzanne Pfeffer definitely has developed some of that Northern California vibe. When you first meet her, adjectives like content, easy-going and laid-back quickly spring to mind.

Speak with her for a little longer, though, and you realize that Pfeffer, a professor in the department of biochemistry at Stanford University School of Medicine, also carries herself with a quiet confidence, as well as strong determination, two qualities that will no doubt serve her well when she takes over as the American Society for Biochemistry and Molecular Biology's 82nd president this month.

Pfeffer, who studies the molecular basis of membrane trafficking and Golgi function, brings several other valuable attributes to the table. She has executive experience, having served as president of the American Society for Cell Biology in 2003. She also is familiar with the ASBMB process, having previously worked on both the ASBMB council and the Journal of Biological Chemistry editorial board; and, she is currently organizing the 2010 ASBMB small meeting on the biochemistry of membrane traffic.

Perhaps her most critical trait, however, is an unwavering belief in her new constituency. "We're a society to be reckoned with," she states firmly, "and should not have to take a back seat to anyone."

Given such a direct statement, it may be fitting that one of Pfeffer's primary goals as ASBMB president will be to try to improve science communication. That includes ensuring that ASBMB continues its excellent work in the public affairs arena, where it can reach the ears of the policy makers, while also expanding efforts in educating the public about the importance and value of basic research.

"When I travel on a train or plane I like to strike up a conversation with the person next to me, describe my work, and explain that their tax dollars paid for it," she says. "It's the kind of conversation all researchers should be doing when they can — the public doesn't realize that they are supporting biomedical research. When they learn about it, they agree on its importance. We should all be thanking the public for their support."

Pfeffer acknowledges that many scientists may be apprehensive, or uncertain, about how to be effective communicators, and already has hit the ground running in that regard. She's begun developing templates to help guide ASBMB members in discussing their work in specific circumstances. These templates will be available in ASBMB Today and on the society's website. Pfeffer also hopes to encourage more usage of new media, such as Wikipedia and YouTube, to get ASBMB's message across.

As new ASBMB President, Suzanne Pfeffer will be working closely with Journal of Biological Chemistry Editor Herbert Tabor.

It's the kind of conversation Pfeffer had as a freshman at the University of California, Berkeley. Entering college, she didn't know much about the molecular sciences, but she knew she wanted to know what made the human body work — or in the

More about Suzanne Pfeffer

Suzanne Pfeffer received her Bachelor's degree from the University of California, Berkeley, in 1978, during which time she did undergraduate research on bacterial RNA polymerase with Michael Chamberlin and published her first scientific article, in the JBC (1). She then moved on to the University of California, San Francisco, for her graduate studies, where she was encouraged to try something new scientifically, and so began working with Regis Kelly on the biochemistry of clathrin-coated vesicles — beginning her lifelong research love of membrane trafficking. After graduating in 1982, she did a postdoc at Stanford University with James Rothman on protein sorting and transport in the Golgi, subsequently joining the Stanford faculty in 1986.

Currently, she continues to work on the molecular basis of membrane trafficking, with an emphasis on the Rab GTPases, which are key coordinators of vesicle traffic between organelles.

When she's not hard at work in lab, Pfeffer enjoys tennis and scuba diving — the latter giving her an opportunity to meet her favorite animal, Metasepia pfefferi, also known as Pfeffer's Flamboyant Cuttlefish.

REFERENCE

1. Pfeffer, S. R., Stahl, S. J., and Chamberlin, M. J. (1977) Binding of Escherichia coli RNA Polymerase to T7 DNA. Displacement of Holoenzyme from Promoter Complexes by Heparin. *J. Biol. Chem.* **252**, 5403–5407.

case of diseases, what made it not work.

"But then at college, someone explained to me that what I was interested in was biochemistry, and that set up my path for my future career," she says.

At the same time, Pfeffer believes that established researchers need to open more lines of internal communication, namely with the graduate students and postdoctoral fellows that represent our next wave of scientific leaders.

"Most of our members are probably in academia, and therefore are involved in the business of training graduate students," she says. "But are we training them the right way?"

Science has changed dramatically over the past couple of decades, since Pfeffer first started conducting independent research. "Back then, researcher specialties were straightforward," she says. "It used be 'I worked on protein X, or pathway Y,' for example. But, with all the information available today, and the rapid rate at which new data becomes available, we can't do that anymore."

"We may have identified more than 10,000 proteins," Pfeffer continues. "But we don't have 10,000 labs to study these proteins in detail. Now, we need to identify the most important questions and work with whatever proteins, pathways or techniques are required to answer it."

So, Pfeffer believes it's important that professors adjust their mentoring to train students not just on facts or methodologies, but also how to ask the right questions and to identify and solve problems.

They also need to expose students to the full range of career options available. "The statistics show that many students, even in the very top programs, are not necessarily going to continue in academia," Pfeffer says. "And, from my own experiences at Stanford, I know that students are clamoring for more information about their future. So it's vital that our society look at how to better prepare students and postdocs to enter the greater society as a whole."

Pfeffer will explore the possibility of hosting some regional meetings specifically for students and postdocs to provide career-building assistance, and give the students a chance meet other students with similar, and different, interests. And, importantly, it might be a way to increase membership amongst the younger scientists, which is another major goal for Pfeffer.

"I have a lot of enthusiasm, and I like to see change happen," Pfeffer explains in discussing all her energy and ideas even as she is just settling in to her new post. If these first few days are any indication, ASBMB does indeed have a new president to be reckoned with.

Nick Zagorski (nzagorski@asbmb.org) is a science writer at ASBMB.

The Three Rs

Replication, Recombination and Repair in Genome Integrity, Cancer and Gene Therapy

BY JOANN B. SWEASY AND MARLENE BELFORT

The three Rs — replication, recombination and repair — hold the key to DNA proliferation, stability and integrity. Alterations in these processes lead to developmental disorders and cancer, whereas exploitation of the three Rs holds the potential of reversing defects that lead to genetic abnormalities. The four exciting sessions in this theme will focus on genomic instability, chromosome dynamics and gene therapy, processing of non-B form DNA by the cell and RNA as a mediator of genome plasticity.

Genomic Instability

The first session, titled "Aberrant DNA Repair, Genomic Instability and Cancer," will feature Richard D. Wood (University of Texas M. D. Anderson Cancer Center), who will describe work on several DNA polymerases that help human cells tolerate DNA damage. Results will be described using a mouse model deficient in DNA polymerase ζ. The enzyme is important in defending against chromosome instability, ultraviolet radiation sensitivity and mammary carcinogenesis. Recent information on the biochemical and cellular functions of two other DNA polymerases affecting genome stability, POLQ and POLN, also will be described.

Joann B. Sweasy (Yale University) will describe findings on the role of base excision repair as a tumor suppressor mechanism. Germ line variants in DNA polymerase β alter the function of the enzyme and lead to genomic instability and cellular transformation. Pol β is an enzyme that is important for filling in small gaps in DNA that result from the removal of DNA damage. Individuals who carry germ line variants in this gene may be at increased risk for cancer.

Bevin P. Engelward (Massachusetts Institute of Technology) will describe her work, which is focused on increasing our understanding of what causes genomic mutations, with an emphasis on how DNA repair protects the genome, and how our environment can put cells at risk for tumorigenic mutations. Of particular interest is crosstalk between base excision repair and homologous recombination, wherein one pathway can pressure the other. Engelward also will describe her development of novel technologies for detecting genetic changes, both in vitro and in vivo. These new tools have helped to shed new light on an old problem, yielding insights into the underlying mechanisms of exposure-induced genetic changes.

Sweasy

Belfort

Chromosome Dynamics and Gene Therapy

The second session, titled "Site-specific Recombination in Chromosome Dynamics and Gene Therapy," describes DNA transactions designed to repair genetic defects. Interestingly, in all cases, the agent that targets DNA to mediate recombination is derived from a naturally occurring mobile genetic element. First, Gregory D. Van Duyne (University of Pennsylvania) will describe the structure and function of a serine integrase. These integrases have great potential for use in a variety of transgenic and gene therapy applications. His group is working to develop a structural basis for understanding how these site-specific recombinases achieve what is effectively an irreversible integration reaction without the use of accessory proteins and auxiliary DNA sequences. Small angle X-ray and neutron scattering, combined with single crystal X-ray diffraction, have provided some important insights into this recombinase family.

In contrast, Alan Lambowitz (University of Texas at Austin) will describe group II introns as gene-targeting vehicles. Mobile group II introns, ribozymes that insert site-specifically into DNA, have been developed into gene targeting vectors ("targetrons") with the unique feature of readily programmable DNA target specificity. Targetrons are used widely for gene targeting in diverse bacteria, and recent work is focusing on adapting targetrons to function efficiently in eukaryotes.

Eukaryotic gene therapy also is being attempted by Nancy Maizels and colleagues (University of Washington School of Medicine), using homing endonucleases called meganucleases. Meganuclease-targeted gene correction is an especially powerful strategy for gene therapy, and, like the two aforementioned gene targeting agents, it uses

molecules and mechanisms optimized over billions of years of evolution to correct deleterious mutations in human cells.

Processing Non-B Form DNA

The third session is titled "Replication of Non-canonical DNA Sequences and Genomic Instability." Smita Patel (Robert Wood Johnson Medical School) will focus on the enzymatic mechanisms for coordinating leading and lagging strand DNA synthesis. The antiparallel nature of the double-stranded DNA and the 5'-3' directionality of the polymerase enzyme pose unique problems in copying the two strands in the same time span. Several mechanisms have been identified that allow the lagging polymerase to keep up with the leading polymerase. The replication enzymes stay physically associated, and, as a consequence, the displaced DNA strand rolls out into a priming loop. The synergistic actions of the replication enzymes allow the two strands of the DNA to be copied in the same time span.

Naturally occurring DNA repeat sequences can form noncanonical DNA structures such as H-DNA and Z-DNA, which are abundant in mammalian genomes. Karen M. Vasquez (University of Texas M. D. Anderson Cancer Center) will discuss her work showing that both H-DNA and Z-DNA structures are intrinsically mutagenic in mammalian cells. Her findings suggest that both H-DNA and Z-DNA, which have been reported to correlate with chromosomal breakpoints in human tumors, are sources of genetic instability and demonstrate that naturally occurring DNA sequences are mutagenic in mammalian cells and may contribute to evolution and disease.

Faye Rogers (Yale University) also will describe her work on naturally occurring H-DNA in human cells. To counteract the potentially devastating effects of altered helical structures on genomic integrity, an intricate balance between DNA repair and apoptosis is critical. Rogers has found that the TFIIH factor XPD is implicated in triggering apoptosis in response to excessive H-DNA induced damage. The maintenance of this mechanism may be of central importance for avoiding induction of mutations and progression to cancer.

RNA and Genome Plasticity

The fourth and last session switches to "Retroelements in Genome Plasticity and Cancer." The three talks in this session involve retroelements in organisms as diverse as bacteria, yeast and humans. Joan Curcio (Wadsworth Center, New York State Department of Health) will describe Ty1, a retrovirus-like transposon in *Saccharomyces cerevisiae.* Ty1 is associated with chromosome fragile sites and plays remarkably versatile roles in promoting chromosomal rearrangements and generating novel gene sequences. Chimeric cDNA molecules created by Ty1 reverse transcriptase function as molecular bridges, healing chromosome breaks and reordering the genome in the process. Her talk will examine how retrotransposition creates chromosomal sites that are prone to breakage and how DNA damage signaling pathways modulate the synthesis of cDNA molecules that straddle broken ends to form rearranged chromosomes.

Next, Marlene Belfort (Wadsworth Center, New York State Department of Health) will describe bacterial group II introns, which are mobile retroelements, and the presumptive molecular ancestors of spliceosomal introns and target-primed retrotransposons. She will explain how group II introns interact in cooperation with their bacterial host to transpose under conditions of cellular stress. In contrast, in a nuclear environment, group II introns inhibit host gene expression, possibly accounting for their evolution into spliceosomal introns.

Finally, Robert H. Silverman (Lerner Research Institute, Cleveland Clinic) will describe a newly discovered human retrovirus — xenotropic murine leukemia virus-related virus. XMRV was first detected in prostate cancer tissues from men with a deficiency in an innate immunity gene. XMRV infections focus interest on two major human diseases: prostate cancer and chronic fatigue syndrome.

Many different routes of genomic instability will be discussed in this thematic meeting, ranging from classical types of mutagenesis to more novel mobile genetic elements and the processing of non-B form DNA. The workshop will provide important insight into the molecular mechanisms of genomic instability. Harnessing these inherent cellular processes for gene therapy also is an exciting new development. Thus, technological innovation will be described with respect to genome manipulation, and new methodologies for mutation detection also will be discussed. We strongly encourage participation in the 3R's workshop, as groundbreaking discoveries in the field will be presented and discussed.

Joann B. Sweasy (joann.sweasy@yale.edu) is a professor in the department of genetics at Yale University, and Marlene Belfort (belfort@wadsworth.org) is a research scientist at Wadsworth Center, New York State Department of Health and a professor of biomedical sciences at the State University of New York at Albany.

SEE SESSION DETAILS ON PAGE 21

The Life of Proteins from Womb to Tomb

BY IVAN DIKIC AND RAMANUJAN HEGDE

Most biochemical reactions depend on proteins whose precise abundance, conformation and location are critical. Thus, every step in a protein's life, from its synthesis by ribosomes to culling by degradation pathways, is regulated tightly. Each of these four processes represents expansive fields on their own, and assembling a program to encompass everything proved challenging. The "Protein Synthesis and Degradation" theme aims to highlight some of the most recent frontiers in understanding how the life and death of proteins are regulated by the cell, as well as the importance of protein maturation and turnover pathways in the numerous human diseases related to protein misfolding, accumulation and aggregation.

The Ribosome

Proteins begin their life as they emerge from inside ribosomes during their synthesis. In recent years, ribosomes have become known as far more than the protein synthetic machinery. They increasingly are appreciated as platforms for a wide range of protein maturation reactions. This includes co-translational modifications, initial interactions with chaperones and central roles in protein targeting. These co-translational reactions must be coordinated spatially and temporally and require the selective recruitment of various factors to the ribosome.

The first session, titled "The Ribosome and Protein Translation" will investigate how this coordination is achieved. Shu-ou Shan (California Institute of Technology) will discuss biophysical analysis of how the signal recognition particle targeting pathway is regulated to ensure efficient and high fidelity delivery of nascent proteins to a cellular membrane. Nenad Ban (ETH Zurich) will describe how structural analysis of ribosome-associated factors is providing mechanistic insights to their function. Ramanujan S. Hegde (National Institutes of Health) will discuss new findings on understanding how a chaperone's recruitment to ribosomes facilitates correct targeting of certain membrane proteins.

Dikic

Hegde

Membrane Protein Biosynthesis

Protein folding and maturation has long been a challenging scientific topic. Within this area, complex membrane proteins are especially difficult to investigate because of their hydrophobicity and need to insert and fold in the context of a lipid bilayer. The session, titled "Membrane Protein Biosynthesis," will explore the insights into how complex membrane proteins are made and assembled properly.

Reid Gilmore (University of Massachusetts Medical School) will describe a novel application of in vivo methods to examine the kinetics of how successive transmem-

Protein Synthesis and Degradation

Session: The Ribosome and Protein Translation

Coordination of Translation and Protein Targeting, *Shu-ou Shan, California Institute of Technology*

Structure and Function of Ribosome-associated Factors, *Nenad Ban, ETH Zurich*

Ribosome-associating Chaperones in Membrane Protein Insertion, *Ramanujan S. Hegde, National Institutes of Health*

Session: Membrane Protein Biosynthesis

In Vivo Kinetics of Membrane Protein Integration, *Reid Gilmore, University of Massachusetts Medical School*

Cellular Mechanisms of Polytopic Protein Folding, *William Skach, Oregon Health and Science University*

Using High Content Microscopy Screening to Uncover Novel Insertion Pathways for Transmembrane Proteins, *Maya Schuldiner, Weizmann Institute of Science*

Session: Protein Folding and Quality Control

Mechanisms of Cytosolic Chaperone Function, *Elizabeth A. Craig, University of Wisconsin-Madison*

Mechanisms of ER-associated Protein Degradation, *Yihong Ye, National Institutes of Health*

Chaperone-mediated Protein Folding and Disease, *Arthur L. Horwich, Investigator, Howard Hughes Medical Institute, Yale University School of Medicine*

Session: Protein Aggregation and Autophagy

Ubiquitin and Autophagy Networks, *Ivan Dikic, Goethe University Medical School*

Autophagy in Physiology and Disease, *Beth Levine, University of Texas Southwestern Medical Center*

Mechanisms Underlying Protein Aggregation and Autophagy, *Anne Simonsen, Oslo University*

brane segments of a multispanning membrane protein are inserted during synthesis. William Skach (Oregon Health and Science University) will describe the use of biophysical in vitro methods to probe the interplay between membrane protein insertion and folding. Maya Schuldiner (Weizmann Institute of Science) will discuss how large-scale genome approaches combined with microscopy can uncover new components and pathways of membrane insertion.

Protein Folding

The session "Protein Folding and Quality Control" will focus on chaperones and their dual roles in facilitating substrate folding on the one hand and mediating quality control on the other. Elizabeth A. Craig (University of Wisconsin-Madison) will describe her efforts to understand the molecular basis of how chaperone diversity allows their wide-ranging functional properties. Yihong Ye (National Institutes of Health) will focus on quality control pathways involved in degrading misfolded proteins from the endoplasmic reticulum. And, finally, chaperone-mediated folding and its role in diseases of protein misfolding will be discussed by Arthur L. Horwich (Investigator, Howard Hughes Medical Institute, Yale University School of Medicine).

Autophagy

Degradation pathways that are both selective and nonselective are critical to the maintenance of protein homeostasis. Autophagy has emerged as being important in a wide range of degradation processes from specific proteins to whole organelles. The session "Protein Aggregation and Autophagy" will explore the role of autophagy in clearing terminally misfolded and aggregated proteins.

Ivan Dikic (Goethe University Medical School) will discuss his studies on the relationship of ubiquitin pathways to the regulation of selective autophagy processes. Beth Levine (University of Texas Southwestern Medical Center) will describe the physiologic functions of autophagy and its misregulation in disease. In addition, understanding how autophagy controls the metabolism of protein aggregates will be explained by Anne Simonsen (Oslo University).

When buttressed with 12 short talks selected from abstracts, this theme will provide a cross-sectional view of several of the most active areas in understanding the complex and regulated life of proteins. By combining talks that span a range of methods, experimental systems and topics, the sessions should stimulate new ideas and directions for future studies.

Ivan Dikic (dikic@biochem2.uni-frankfurt.de) is director of the Institute of Biochemistry II at Goethe University Medical School. Ramanujan Hegde (hegder@mail.nih.gov) is head of the protein biogenesis section of the cell biology and metabolism program at the National Institute of Child Health and Human Development, National Institutes of Health.

SESSIONS DETAILS FROM PAGE 19

DNA Replication, Recombination and Repair

Session: Aberrant DNA Repair, Genomic Instability and Cancer

The Role of Rev3L in Genome Maintenance, *Richard D. Wood, University of Texas M. D. Anderson Cancer Center*

Aberrant Base Excision Repair and Cancer, *Joann B. Sweasy, Yale University*

Delineating Drivers of Large-scale DNA Sequence Rearrangements in Vivo, *Bevin P. Engelward, Massachusetts Institute of Technology*

Session: Site-specific Recombination in Chromosome Dynamics and Gene Therapy

Structure and Function of Serine Integrases, *Gregory D. Van Duyne, University of Pennsylvania*

Mobile Group II Introns: Site-specific Retroelements with Programmable DNA Target Specificity in Bacteria and Eukaryotes, *Alan Lambowitz, University of Texas at Austin*

Gene Therapy Targeted by Meganucleases, *Nancy Maizels, University of Washington School of Medicine*

Session: Replication of Noncanonical DNA Sequences and Genomic Instability

Coordination of the Leading and Lagging Strand During DNA Replication, *Smita Patel, Robert Wood Johnson Medical School*

DNA Structure, Genetic Instability and Cancer, *Karen M. Vasquez, University of Texas M. D. Anderson Cancer Center*

XPD-dependent Induction of Apoptosis of Cells with DNA Containing Helical Repeats, *Faye Rogers, Yale University*

Session: Retroelements in Genome Plasticity and Cancer

Yeast Ty1 Retrotransposons and Genome Fragility, *Joan Curcio, Wadsworth Center, New York State Department of Health*

Group II Introns Collaborate with Their Host to Promote Genome Plasticity by Retrotransposition, *Marlene Belfort, Wadsworth Center, New York State Department of Health*

Xenotropic Murine Leukemia Virus-related Virus and Prostate Cancer, *Robert H. Silverman, Lerner Research Institute, Cleveland Clinic*

Structural and Mechanistic Enzymology

BY SQUIRE J. BOOKER AND L. MARIO AMZEL

The study of enzymes and the reactions that they catalyze is as vibrant today as it was forty years ago. Novel cofactors still are being discovered, and new paradigms still are emerging, as we delve even deeper into enzymatic reactions at the detailed molecular level using a variety of physical and structural methods in concert with computational methods. Moreover, enzymatic substrates are becoming more complex as the field moves from small molecules to reactions in which enzymes construct or modify macromolecules like other proteins, DNA, RNA, carbohydrates and fatty acids. At the 2011 American Society for Biochemistry and Molecular Biology annual meeting, four sessions in the "Structure, Mechanisms and Regulation in Enzyme Catalysis" theme will bring together various aspects of current work on structural and mechanistic enzymology. Given the diversity of the field, subjects were chosen to cover as many areas as possible while minimizing the overlap with those covered in other symposia.

Metalloenzymes

The session on "Metals and Redox Chemistry," chaired by Squire J. Booker, is expected to offer rich new insight into the remarkable abilities of metalloenzymes to catalyze complex and energy-demanding reactions. The theme of the session will highlight new mechanisms in which the combination of molecular oxygen and a metal cofactor is employed to create oxidants suitably potent to cleave unactivated C–H bonds.

Historically, the study of iron-dependent enzymes has predominated; however, exciting new findings are providing evidence for the use of copper in these transformations. The lecture by Carsten Krebs (The Pennsylvania State University), titled "Characterization of Two Reaction Intermediates in the Nonheme-Fe(II)-dependent Enzyme Isopenicillin *N*-synthase," will show how the use of rapid-kinetics methods combined with various spectroscopic techniques can unveil key intermediates in these reactions and allow for their structural characterization.

Amy C. Rosenzweig (Northwestern University) will give a lecture titled "Methane Oxidation by an Integral Membrane Metalloenzyme." This enzyme, featured in a recent Nature publication from Rosenzweig's lab (1), uses a dicopper center to hydroxylate the most inert carbon substrate, methane, which exhibits a homolytic bond-dissociation energy of approximately 104 kcal mol^{-1}!


Booker


Amzel

L. Mario Amzel (Johns Hopkins University School of Medicine) will continue with the copper theme, delivering a lecture detailing structural, mechanistic and computational characterization of peptidylglycine α-amidating enzyme. This protein is responsible for the maturation of a number of peptide hormones and neuropeptides and catalyzes two distinct reactions on separate domains: the copper-dependent hydroxylation of the peptide substrate and subsequent zinc-dependent fragmentation of the peptide to afford an amidate.

Sulfur Chemistry

The session on sulfur chemistry and biological redox, chaired by Carsten Krebs, features three diverse lectures highlighting the unique reactivity of the sulfur atom and its importance in biochemistry. Squire J. Booker (The Pennsylvania State University) will deliver a lecture, titled "Radical-dependent Mechanisms of Post-translational Modification," in which he will describe several novel modifications of proteins that involve the insertion of sulfur atoms into unactivated C–H bonds. These reactions are considered to be the anaerobic counterpart to some of the reactions discussed in the session "Metals and Redox Chemistry," involving activated forms of sulfur rather than dioxygen.

The lecture by Kate S. Carroll (University of Michigan), titled "Painting the Cysteine Chapel: New Tools to Probe Oxidation Biology," will detail new proteomic approaches for detecting modifications occurring on sulfur-containing amino acid residues, which has great impact in the ability to sense cellular oxidative stress.

Joseph Jez (Washington University. St. Louis) will give a lecture, titled "Sensing Sulfur Status in Plants: Biochemical Integration of Multiple Inputs," detailing mechanisms by which plants regulate their sulfur and thiol concentrations.

Processive Enzymes

Debra Dunaway-Mariano will chair a session on processive enzymes. This session does not include the classical nucleic acid polymerases that are discussed in other events of the meeting. Shiou-Chuan (Sheryl) Tsai (University of California, Irvine), under the title "Molecular Ori-

gami in Nature," will present structural and mechanistic data on natural polyketide synthases, as well as systems based on this chemistry that can be used to synthesize novel polyketides. Fungal polyketide synthases will be discussed by Yi Tang (University of California, Los Angeles) in a lecture titled "Polyketide Megasynthases from Filamentous Fungi." Luis E. N. Quadri (Brooklyn College, The City University of New York) will present his results on the synthesis and inhibition of bacterial virulence factors in a lecture entitled "Mycobacterial Polyketide Virulence Factors: Biosynthesis and Inhibition."

Phosphoryl Transfer Reactions

In a session titled "Kinases, Phosphatases and Phosphorus in Biological Reactions" and chaired by L. Mario Amzel, speakers will discuss diverse aspects of the chemistry of phosphoryl transfer reactions. Debra Dunaway-Mariano (University of New Mexico) will present results of her comprehensive work on phosphatases in a lecture entitled "Evolution of a Robust Catalytic Scaffold for Hydrolytic Cleavage of Phosphate Ester Metabolites."

Dustin J. Maly (University of Washington, Seattle), under the title "Bivalent Inhibitors of Protein Kinases," will present his results on the development of cell permeable small molecules that allow the activation or inactivation of specific signaling enzymes in living cells, in particular, enzymes that mediate intracellular phosphorylation (the protein kinases and phosphatases).

Detailed aspects of the mechanism of phosphoryl transfer reactions will be presented by J. Andrew McCammon (Investigator, Howard Hughes Medical Institute, University of California, San Diego) who has used molecular dynamics simulations as well as QM/MM computational methods to study kinases and other enzymes. His lecture is titled "Computational Studies of Protein Kinases."

The four symposia also will include presentations chosen from submitted abstracts and will be complemented by related poster sessions. These symposia will present a unique opportunity for investigators interested in the chemistry and the detailed chemical mechanisms underlying biological processes to be exposed to an exciting selection of some of the most important recent developments in this area.

Squire J. Booker (Squire@psu.edu) is an associate professor of chemistry and of biochemistry and molecular biology at The Pennsylvania State University. L. Mario Amzel (mamzel@jhmi.edu) is a professor and director of the department of biophysics and biophysical chemistry at the Johns Hopkins University School of Medicine.

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Structure, Mechanism and Regulation in Enzyme Catalysis

Session: Metals and Redox Chemistry

Characterization of Two Reaction Intermediates in the Nonheme-Fe(II)-dependent Enzyme Isopenicillin *N*-synthase, *Carsten Krebs, The Pennsylvania State University*

Methane Oxidation by an Integral Membrane Metalloenzyme, *Amy C. Rosenzweig, Northwestern University*

Structural and Mechanistic Studies on Peptidylglycine α-amidating Enzyme, *L. Mario Amzel, Johns Hopkins University School of Medicine*

Session: Sulfur Chemistry and Biological Redox

Radical-dependent Mechanisms of Post-translational Modification, *Squire J. Booker, The Pennsylvania State University*

Painting the Cysteine Chapel: New Tools to Probe Oxidation Biology, *Kate S. Carroll, University of Michigan*

Sensing Sulfur Status in Plants: Biochemical Integration of Multiple Inputs, *Joseph Jez, Washington University, St. Louis*

Session: Processive Enzymes

Molecular Origami in Nature, *Shiou-Chuan (Sheryl) Tsai, University of California, Irvine*

Polyketide Megasynthases from Filamentous Fungi, *Yi Tang, University of California, Los Angeles*

Mycobacterial Polyketide Virulence Factors: Biosynthesis and Inhibition, *Luis E. N. Quadri, Brooklyn College, The City University of New York*

Session: Kinases, Phosphatases, and Phosphorus in Biological Reactions

Evolution of a Robust Catalytic Scaffold for Hydrolytic Cleavage of Phosphate Ester Metabolites, *Debra Dunaway-Mariano, University of New Mexico*

Bivalent Inhibitors of Protein Kinases, *Dustin J. Maly, University of Washington, Seattle*

Computational Studies of Protein Kinases, *J. Andrew McCammon, Investigator, Howard Hughes Medical Institute, University of California, San Diego*

Chromatin and Transcription: A Symbiotic Relationship

BY KAROLIN LUGER AND QIANG ZHOU

Transcription and chromatin always have had an intimate, if somewhat unbalanced, relationship. During most of the past three decades, transcription meetings have featured only a somewhat decorative chromatin-related session. Most of the excitement has been in describing TBP, TAFs, transcription initiation apparatus and gene activation mechanisms that impinge on this apparatus. Gradually, the balance tipped when the central role of chromatin was pushed to the foreground through the discovery of transcription activators that serve as histone acetyltransferases. Since then, the roles of numerous posttranslational modifications of histones in transcriptional control have been elucidated. Most recently, things have been as they should be in a good relationship: The two subjects have been on an equal footing, with lots of communication and synergies between them. Their distinction has become blurred, and we have realized that eukaryotic transcription, in all its complexity, functions in the context of chromatin and is regulated by its multilayered structural organization. Likewise, chromatin structure is responsive to complicated manipulations by the cellular machinery that make the DNA more or less accessible for the transcriptional apparatus.

Structural Transitions

In the upcoming thematic session titled "Transcription/Chromatin," we have chosen topics that echo this symbiotic relationship. A session titled "Structural Transitions in Chromatin — An Exploration of Mechanisms" will highlight cutting-edge technologies devoted to studying the complexity of chromatin structure beyond the nucleosome.

Michelle D. Wang (Investigator, Howard Hughes Medical Institute, Cornell University) will discuss mechanical studies of nucleosome stability and structure and how DNA in nucleosomes may be accessed by motor proteins that are responsible for transcription-related chromatin remodeling. Michael G. Poirier (The Ohio State University) will present studies of post-translational modifications located within the DNA-histone interface, revealing that they function to controllably unlock different forms of nucleosome dynamics. And, James McNally (National Institutes of Health) will discuss progress in measuring transcription factor dynamics at specific promoters, and throughout the genome, using light microscopy in the living cell.

Alternative Structures

Luger

Zhou

A session titled "Alternative Chromatin Structures" will illuminate the fact that nucleosome and chromatin structure is affected by many factors that contribute to the transcription processes.

Steven Henikoff (Investigator, Howard Hughes Medical Institute, Fred Hutchinson Cancer Research Center) will present intriguing evidence that centromeric nucleosomes wrap DNA in a right-handed orientation, opposite that of left-handed canonical nucleosomes. Karolin Luger (Investigator, Howard Hughes Medical Institute, Colorado State University) will expand on our existing knowledge of nucleosome structures by illuminating the effects of post-translational modifications and of histone variants, as well as of chromatin assembly intermediates. Rui Ming Xu, (Institute of Biophysics, Chinese Academy of Sciences) will report structural and biochemical studies of several histone methyltransferases and methylhistone binding proteins, which have provided an in-depth understanding of histone methylation in regulation of higher order chromatin structure.

RNA Polymerase Pausing

Recent progress in the transcription field has also fundamentally changed our view of the primary regulatory step during gene activation. For a long time, the recruitment of the RNA polymerase (Pol) II transcription initiation apparatus to promoters was considered the major rate-limiting step for the expression of most eukaryotic genes. Recently, a paradigm shift has occurred with the demonstration that the expression of a very large number of metazoan genes, particularly those involved in developmental control, is controlled at the elongation stage. These genes contain paused Pol II at their promoter-proximal regions and are in a state of suspended transcription, which resumes rapidly upon stimulation. The widespread existence of paused Pol II in metazoan genomes suggests that elongation plays a prominent and general role in controlling gene expression.

To reflect this paradigm shift, a session will be devoted

to RNA polymerase pausing and elongation. David H. Price (University of Iowa) will present studies on how the positive transcription elongation factor P-TEFb, which causes the transition of paused Pol II into a productively elongating state, is controlled by reversible association with the 7SK snRNP and how gene specific regulation is achieved by coordinating the release of P-TEFb from 7SK snRNP and recruitment to specific targets. David S. Gilmour (The Pennsylvania State University) will examine the basis of promoter proximal pausing via biochemical and in vivo analysis of the association of a negative elongation factor, NELF, with the paused promoters. And, Julia Zeitlinger (Stowers Institute for Medical Research) will explore the mechanism of Pol II pausing in the *Drosophila* embryo using genome-wide techniques that map protein-DNA interaction, computational methods and genetics.

Transcriptional Regulation

Human diseases often are associated with aberrant gene expression. A session titled "Transcriptional Regulation in Growth, Differentiation and Diseases" will explore how alterations of a cell's transcriptional program can lead to aberrant phenotypes of multiple diseases. Anders Näär (Massachusetts General Hospital Cancer Center) will present studies on conserved gene regulatory circuits governing cholesterol/lipid homeostasis. The investigation of the SREBP family of transcription factors, which are "master regulators" of both cholesterogenic and lipogenic genes, will offer insights into disease mechanisms and potential therapeutic avenues. Jorge Iñiguez-Lluhí (University of Michigan Medical School) will demonstrate how a reversible modification called SUMOylation regulates the androgen receptor and how alterations in this program contribute to the pathophysiology of three androgen receptor diseases involving sexual differentiation, cancer and neurodegeneration. Finally, to close the loop between human diseases and elongation control, Qiang Zhou (University of California, Berkeley) will present evidence indicating that the HIV Tat protein recruits the host cellular elongation machinery to stimulate viral transcription and that this mechanism could be exploited to disrupt HIV latency for the subsequent elimination of the latent reservoir.

The chromatin/transcription field has never failed to produce novel, cutting-edge discoveries. The recent years have witnessed an acceleration of the pace of our discoveries. The upcoming American Society for Biochemistry and Molecular Biology session on this topic will once again provide an exciting opportunity for us to be in close contact with the major growth points of this ever-growing and fast-evolving field.

Karolin Luger (Karolin.Luger@ColoState.edu) is a Howard Hughes Medical Institute investigator and a university distinguished professor at Colorado State University. Qiang Zhou (qzhou@berkeley.edu) is a professor of biochemistry and molecular biology at the University of California, Berkeley.

Transcription/Chromatin

Session: Structural Transitions in Chromatin—An Exploration of Mechanisms

DNA Accessibility in Nucleosomes, *Michelle D. Wang, Investigator, Howard Hughes Medical Institute, Cornell University*

Unlocking Nucleosome Dynamics with Histone Post-translational Modifications, *Michael G. Poirier, The Ohio State University*

The In Vivo Dynamics of Transcription, *James McNally, National Institutes of Health*

Session: Alternative Chromatin Structures

Histone Variant Dynamics and Epigenetics, *Steven Henikoff, Investigator, Howard Hughes Medical Institute, Fred Hutchinson Cancer Research Center*

Histone Chaperones, Histone Modifications and Chromatin Dynamics, *Karolin Luger, Investigator, Howard Hughes Medical Institute, Colorado State University*

Structural Basis for Regulation of Histone Modifications, *Rui-Ming Xu, Institute of Biophysics, Chinese Academy of Sciences*

Session: RNA Polymerase Pausing and Elongation

Mechanisms Controlling Elongation by RNA Polymerase II, *David H. Price, University of Iowa*

Kinetic Control of Promoter Proximal Pausing, *David S. Gilmour, The Pennsylvania State University*

The Dynamics of Pol II Stalling during Drosophila Development, *Julia Zeitlinger, Stowers Institute for Medical Research*

Session: Transcriptional Regulation in Growth, Differentiation and Diseases

Conserved Gene Regulatory Mechanisms Controlling Cholesterol and Fat, *Anders M. Näär, Massachusetts General Hospital Cancer Center*

Impact of SUMOylation on Transcription Factor-based Diseases, *Jorge A. Iñiguez-Lluhí, University of Michigan Medical School*

Novel Mechanism and Host Cofactors for Regulation of HIV-1 Transcription, *Qiang Zhou, University of California, Berkeley*

NIGMS Introduces New PSI:Biology Initiative

BY PETER C. PREUSCH

PSI:Biology — generating novel structures leading to new knowledge of the secrets of life.

In a special session at the 2010 American Society for Biochemistry and Molecular Biology annual meeting, the National Institute of General Medical Sciences introduced its new Protein Structure Initiative:Biology phase. During this phase, highly organized networks of investigators can apply high-throughput structure determination to study a broad range of important biological and biomedical problems.

During the session, PSI Director Ward Smith (NIGMS) described the components of the PSI:Biology network and ongoing opportunities for investigators to apply to become part of the program. The network includes five main components: centers for high-throughput structure determination, centers for membrane protein structure determination, the PSI-Structural Biology Knowledgebase, the PSI-Material Repository and consortia for high-throughput structural biology partnerships.

The first four components will support the solution of structures, dissemination of information and the storage and sharing of clones and vectors generated by the PSI. The fifth component provides funding for research on important biological problems and aids collaboration with the structure determination centers. The first awards for these components will be made this summer.

Next, Helen Berman (Rutgers University) explained the features of the PSI-Nature Gateway Structural Biology Knowledgebase. The Knowledgebase contains information on targets selected by the PSI and the status of efforts to determine their structures (TargetDB), information on protocols applied to those targets (PepcDB), highlights of technology developments and other accomplishments of the PSI, links to tools for the annotation of protein structure and function and access to the latest models and capabilities to model protein structures (Model Portal). It also provides an opportunity for scientists who are not part of the PSI:Biology network to nominate targets for structure determination.

Joshua LaBaer (Arizona State University) then talked about the PSI-Material Repository, which is now maintained by DNASU. This resource collects, sequence verifies, stores and distributes clones and vectors developed by the PSI. Plasmids are available individually or in thematic collections (e.g., all members of a protein family or derived from a given species). Processes have been developed to accelerate material transfer agreements.

John Gerlt (University of Illinois) described his interaction with the current PSI large-scale centers as a model for the way PSI:Biology is expected to work. His team used bioinformatics analysis of genomes to identify targets of unknown function within large enzyme mega-families. Next, a large-scale center solved the structures of many of these targets. Gerlt's team then used a combination of in silico and in vitro methods to identify potential substrates for these enzymes.

And finally, Susan Taylor (University of California, San Diego) commented on how the PSI:Biology network could benefit many researchers working on diverse problems. Some of the areas mentioned in the funding announcements include families and complexes of proteins and metabolic pathways or cellular compartments or that may be important in specific disease states.

Thus, PSI:Biology provides resources to benefit researchers beyond simply determining structures.

Peter C. Preusch (preuschp@nigms.nih.gov) is chief of the biophysics branch in the division of cell biology and biophysics at the National Institute of General Medical Sciences.

For more information:

- Information about the PSI-Biology Program and these funding opportunities: http://bit.ly/a7DZEL.
- The PSI-Nature Gateway Structural Biology Knowledgebase: http://bit.ly/chbCys.
- To nominate targets for structure determination by the PSI centers: http://bit.ly/alyNJ6.
- The PSI-Material Repository: http://psimr.asu.edu.

Are in Vitro and in Silico Toxicity Testing Finally within REACH?

BY TERTIUS DE KLUYVER

An increasingly aware and educated public is demanding better determination and control of the toxicity of chemicals commonly found in manufacturing, agricultural and other uses. In response, the European Union introduced the REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) legislation in June 2007 (1). REACH applies to chemicals manufactured or imported into the EU in quantities equal to or greater than one metric ton.

About 86 percent of chemicals in current use in the EU, many of which were first produced prior to 1981, do not have REACH-compliant safety assessments (1). Assessment under REACH is tiered according to production or importation volume so that the degree of physicochemical and toxicological information required under REACH increases with each quantity band (2). As of December 2008, 65,000 companies have submitted more than 2.7 million preregistrations for about 144,000 substances (3). Eventually, up to one million chemicals and mixtures may be assessed (4).

The current approach to toxicological testing using animal-based methodologies provides regulators and industry with a defined testing regimen with internationally agreed testing guidelines. This regimen enables costs, timelines and outcomes to be predictable while limiting liabilities (5). However, in addition to the ethical dilemma of using large numbers of animals to adequately evaluate chemicals under REACH, current methodologies using long-term and maximum-dosing experiments on animals are imperfect and slow (1). The U.S. National Toxicology Program, in 1996, estimated that a thorough assessment of chemicals may take several years and cost $2 to $4 million (6). The current paradigm cannot generate the required data for toxicological risk assessments within a reasonable timeframe and at a reasonable cost. Therefore, a new approach is required "if science is going to maintain a significant role in environmental and public health policy" (6).

Significant efforts are underway internationally to develop new approaches to identify toxicants and determine which biological pathways they perturb — approaches that are based on in vitro and in silico technologies, many of which are specific for human biology. Experimental platforms include established and developing "omics" technologies, chemical and biochemical studies. In vitro platforms may employ "subcellular fractions, tissue slices or perfused organ preparations, through primary cultures and cell line to 3D organotypic cultures, which include reconstructed tissue models" (7).

REACH places significant burdens on industry and regulatory agencies. Industry must assume responsibility for the safety of substances throughout their life cycles as well as manage the uncertainties associated with the proposed shift in testing platforms (2). This will bring about greater exposure to liabilities and will increase regulatory discomfiture in many cases; for example, the reference dose for many chemicals may be increased based on these same studies (5).

The changes to toxicology testing methods and analysis ultimately will be defined by a concomitant increase in our understanding of underlying toxicological principals, the continued development of effective in vivo and in vitro test platforms and computational modeling capabilities and finally an acceptance of the new risk assessments by the community, regulatory authorities and industry.

Tertius de Kluyver (dekluyver@hood.edu) is an adjunct professor of biology and environmental science at Hood College.

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False Choices

BY PETER J. KENNELLY

In a recent Nature opinion piece titled "Financial Pain Should Focus Universities," (1) Diane Auer Jones reminds us that the clock is ticking. The transient bolus of extramural research and development funding generated by federal stimulus programs soon will be a memory. Jones sees a silver lining in this "dark cloud for the U.S. scientific enterprise," however. She outlines a clear and simple national strategy to insure continued innovation and success both in the laboratory and the classroom — divorce undergraduate education from research.

Under Jones' plan, competitive research would be concentrated in approximately 100 select institutions. A (competitive) research-null phenotype will be adopted by, or conferred upon, the nation's remaining 3,500 colleges and universities. Diminished demand for federal grants, she argues, will stabilize National Institutes of Health and National Science Foundation pay lines at higher levels, reducing the time spent chasing money and enhancing productivity. Faculty at "teaching-intensive" institutions, on the other hand, would be liberated from the administrative pressure to engage in the quixotic pursuit of scarce grant dollars. Students, she argues, would be the biggest winners as faculty devote their full time and energy to their educational mission.

Given that numerous opinion pieces are published every day, why respond to Jones? First, however shocking Jones' thesis may be to an informed reader, it possesses the type of appealingly straightforward logic that plays well in the sound bite world of politics and public opinion. Second, Jones' credentials include stints as a biology professor, NSF program officer, congressional staffer, and assistant secretary for postsecondary education in the Bush administration. Lastly, Jones' piece appeared in a prestigious and widely read journal. It also was subject to a follow-up piece in a "NewsBlog" for The Scientist with the less nuanced title, "Why Cutting Science Is Good" (2).

Jones raises some valid points, several of which have been the subject of discussion within the scientific community for many years. How do we raise pay lines if every increase in NIH funding elicits more applications? What is the best strategy for funding science and engineering such that both research and education are well served? In the end, however, her central thesis — that research and teaching fundamentally are incompatible — presents us with a false choice based upon several flawed assumptions.

Assumption 1: Participation in extramurally funded research causes educators to lose sight of their mission. Although Jones is correct inasmuch as the intensive demands of research and instruction confront faculty with a difficult balancing act, she dismisses the many positive contributions that active research programs make to an institution's undergraduate educational mission. Students get the benefit of learning from bona fide practioners of the art whose experiences and expertise remain current and vibrant. The experiential learning opportunities afforded undergraduate students not only enhance their knowledge and skills but also serve as powerful vehicles for informing their subsequent career choices. These benefits have been documented repeatedly in numerous studies on this topic. Moreover, "real world" validation of these scholarly studies can be readily found in the row upon row of job ads listing experience as a prime hiring criterion, even for entry-level positions.

Assumption 2: "If not managed carefully, the research programmes developed to improve the undergraduate experience for a select few students could lead to the devolution of the academic quality for the large majority." In other words, research is readily dispensable for the student body as a whole because it only impacts a handful of elite undergraduates. Although access to undergraduate research experiences may be limited in some institutions, in general, the prevailing trend has been to expand undergraduate research programs at colleges and universities. Indeed, my own university is about to hire its first director for undergraduate research, whereas the American Society for Biochemistry and Molecular Biology's 14th annual undergraduate poster session in Anaheim, Calif., drew a record 180 plus presentations. On the other hand, if Jones is correct, why not call for measures that would make such experiences available to greater numbers of students, rather than curtail them entirely?

Assumption 3: Innovation and creativity can be "managed." This is a recurring theme amongst advocates of big science, of running universities according to business models, etc. I do not pretend to posses the

“Rather than sitting back and accepting the ‘inevitable,’ as Jones suggests, I would argue that our attention and energies would be better spent engaging in public outreach and political lobbying, and — yes — sponsoring undergraduate research.”

ultimate answer to this longstanding debate. I would note, however, that for every example of a successful big science project, such as the Human Genome Project, the Manhattan Project and the Mercury/Gemini/Apollo moon program, there are manifold examples of the genius of the individual: both scientist and nonscientist. Each has his or her own place, and the unbroken record of success generated by the somewhat eclectic approach of the past several decades suggests that people — individuals, partners, groups and consortia — are the key to discovery, not some administrative philosophy or organizational regimentation. The danger of Jones’ proposed concentration is not just the damage it will do to undergraduate education. It likely will have deleterious effects on the research enterprise itself as a consequence of limiting the key element of discovery — human intellect and imagination.

Assumption 4: “There won’t be enough money in the U.S. Treasury over the next decade to even maintain the current federal R&D baseline.” Consistency is not a word oftentimes associated with the American system of government. Many of the members of Congress who vehemently decry the government’s growing indebtedness voted for many of the measures that led to the accumulation of these deficits a few years previously. Although the current atmosphere makes it more challenging to convince our elected representatives to invest in research and education, there remain many in Congress who understand the need to invest continually in the interrelated areas of education, health, technology and economic competitiveness. The economy continues to show encouraging signs of improvement, offering the hope of greater budgetary flexibility.

Although the budgetary realities can never be ignored, they should not become the primary driver of our national research and educational policies. Rather than sitting back and accepting the “inevitable,” as Jones suggests, I would argue that our attention and energies would be better spent engaging in public outreach and political lobbying, and — yes — sponsoring undergraduate research.

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Uphill, Both Ways, in the Snow

BY ANTHONY J. BAUCUM II

The current generation of postdoctoral fellows is often reminded what it used to be like "back in the day." Just as postdocs tell graduate students how it was when they were in their shoes, mentors and principal investigators like to remind postdocs how things were when *they* were postdocs. These discussions bring up several questions about the demographics and the current challenges for today's postdocs.

Postdoc Salaries — For Love of Science, not for Love of the Benjamins

The number of postdoctoral positions has expanded greatly over the past few decades — before 1972, 31 percent of people who graduated with science and engineering degrees did a postdoctoral fellowship, while 46 percent of 2002 — 2005 graduates did one (1). The number is especially high for postdoctoral fellowships in the life and physical sciences, with approximately 60 percent of graduates in these areas doing a fellowship. The number of postdocs in the biomedical sciences has grown from approximately 7,000 in 1972 to over 30,000 in 2002 (2).

Organizations such as the National Science Foundation, Sigma Xi and the National Postdoctoral Association constantly are compiling data on the postdoctoral population. In its 1995 survey, the NSF found postdocs had a median salary of $28,000. In 2005, a Sigma Xi survey found a median salary of $38,000 (3). Similarly, the most recent data from the NSF lists median salaries for academic postdocs at $40,000. Currently, the National Institutes of Health's minimum guideline for entry-level postdoctoral stipends is $37,740. To put this in perspective, we can evaluate purchasing power using the consumer price index. Table 1 shows what the estimated purchasing power of $37,740 in 2010 dollars would have been in 5-year decrements, back to 1975.

The current stipend level is too low. It is refreshing that the Obama administration has recognized this disparity, and the NPA and other organizations are pleased to support the current proposed 6 percent increase in NIH postdoctoral stipend levels. However, even with these changes, the postdoc is underpaid, one-third less than equivalent recent doctoral degree holders (1), compared to any work force with a similar level of education.

TABLE 1.
Purchasing power of $37,740 in 2010 dollars in 5-year decrements

Year	Estimated purchasing power
2005	$33,868
2000	$29,861
1995	$26,428
1990	$22,665
1985	$18,659
1980	$14,289
1975	$9,330

The Aged Postdoc — My Glucosamine Costs What?

In 2000, the National Academy of Sciences Committee on Science, Engineering and Public Policy p ublished its "Enhancing the Postdoctoral Experience for Scientists and Engineers" study, which said the median time spent in a postdoctoral position was approximately 3.5 years (4). The time spent in a postdoctoral fellowship had been steadily rising until 2005 (1). That trend may be turning around, but time to independent funding is still increasing. The average age at which a doctoral degree-holding researcher received his or her first NIH R01 funding increased from 34 in 1970 to over 42 in 2005 (5).

The increased time spent in a postdoctoral position and/or waiting for independent funding has led to an older population of postdocs, many of whom are starting families. While benefits such as health insurance for postdocs have improved at many institutions, there still is a lack of benefits such as retirement and paid paternity/maternity leave. The 2010 NSF "Science and Engineering Indicators" study showed that 90.1 percent or more of postdocs were receiving health benefits, but only 48.9 percent had retirement benefits (1). Furthermore, in the 2005 Sigma Xi study, only 42 percent of postdocs had disability insurance, only 36 percent had family leave and only 26 percent had childcare benefits. Part of the cause for this is the fact that a subset of postdocs are not considered employees, due to a tax code that does not allow postdocs who are paid through

Federal training grants or individual training fellowships to be classified as employees. Therefore, any benefits tied into having earned income, or being an employee, are unavailable to this group, including pre-tax retirement savings and childcare credits. Changes to the established mechanism literally would require an act of Congress.

A Changing International Work Force — Nihao, Namo namah, Guten Tag

The number of international postdocs has grown from 27 percent in 1972 to 55 percent in 2002 (2). Sigma Xi reports that in 2005, 54 percent of postdocs were non-U.S. citizens (3). This increase has affected the dynamics of the postdoctoral experience for both mentors and postdoctoral fellows, as international postdocs must not only adjust to a new country and culture but also learn about U.S. research protocol, procedures and ethics. As a side note, even though there are a large percentage of international postdocs, the number of international faculty members is much lower. A recent Association of Neuroscience Departments and Programs study found that non-U.S. citizens made up only 10 percent of neuroscience faculty (6).

Diversifying the Work Force — the Pipeline Not Only Leaks, It's Sluggish at the Top

There remains a serious need to increase the amount of diversity in the postdoctorate. The 2005 Sigma Xi survey found that only 4 percent of postdocs identified themselves as Black/African American and only 4 percent identified themselves as Hispanic/Latino (3). Women were fairly well represented overall, at 51 percent; however, in the physical sciences and engineering, only 23 percent were women. Unfortunately, the percentage of women in faculty positions (approximately 28 percent (7)) is not anywhere near their representation at the postdoctoral level, suggesting the need for better retention programs and incentives for women to pursue these positions.

The Snow Has Melted, but There Is Still That Hill

The postdoctorate and the postdoctoral experience are changing. The number of postdocs, the awareness of what a postdoc is and access to more training and mentoring opportunities have all increased. Postdocs are raising their voices, and the contributions of postdocs to the scientific enterprise are more highly recognized. Parents and grandparents talk about how they had to walk to school, uphill, both ways, in the snow. Institutions, governmental organizations and nonprofit organizations, such as the NPA, are recognizing the challenges that postdocs are facing and are responding to the changing environment. There is still a ways to go in improving the experience, but by recognizing where postdocs have come from, along with the current challenges and demographics, leaders in the U.S. scientific research enterprise can set a trajectory that enhances the postdoctoral experience for all.

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DID YOU KNOW?

Since its founding in 1906, the American Society for Biochemistry and Molecular Biology has had 82 presidents.

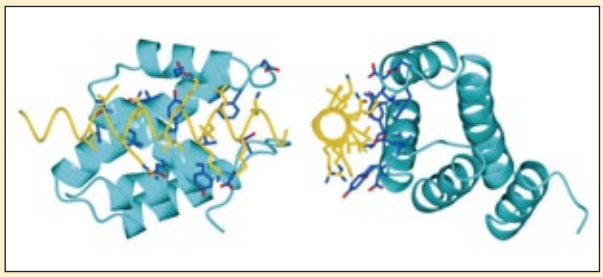
Russell H. Chittenden

- **Russell H. Chittenden**, who was the first president of ASBMB, also served as president of the American Physiological Society from 1895 to 1904.
- The first female ASBMB president was **Mildred Cohn**, who served in 1978. Since then, there have been nine additional female presidents, including our current president, Suzanne Pfeffer.
- Thirteen ASBMB presidents have been awarded Nobel Prizes: Edward A. Doisy, Carl F. Cori, Edward C. Kendall, Fritz A. Lipmann, Vincent du Vigneaud, Arthur Kornberg, Severo Ochoa, Konrad E. Bloch, Christian B. Anfinsen, Stanford Moore, Paul Berg, Edwin G. Krebs and Paul D. Boyer.
- Fourteen ASBMB presidents were born outside of the United States: Otto K. O. Folin (Sweden), Archibald B. Mcallum (Canada), Walter R. Bloor (Canada), Rudolph J. Anderson (Sweden), Hans T. Clarke (England), Carl F. Cori (Czech Republic), Hubert B. Vickery (Canada), J. Murray Luck (Canada), Severo Ochoa (Spain), Fritz Lipmann (Germany), Konrad E. Bloch (Poland), Elizabeth F. Neufeld (France), Martin F. Gellert (Czechoslovakia) and I. Robert Lehman (Lithuania).
- ASBMB presidents generally have served one-year terms (with the exception of a period from 1912 to 1948 where the terms were increased to two years). However, in 2000, the terms were officially changed to two years.

For more information about ASBMB presidents, go to the ASBMB history site at http://bit.ly/cGAebB.

Nab-bing onto Gfd1

During mRNA biogenesis, immature mRNA needs to be processed, packaged into ribonucleoprotein particles and transported out of the nucleus so translation can commence. This multistep trafficking involves the coordinated efforts of numerous nuclear and cytoplasmic proteins, such as Nab2, which binds to the mRNA poly-A tail and assists in the export and cytoplasmic disassembly of mRNPs. Nab2 interacts with a protein factor called Gfd1 at its N terminus, though not much is known about this interaction because Gfd1is nonessential, and deletion mutants do not alter mRNA export. However, in this study, the authors employed both crystallography and solution NMR to identify the molecular nature of the Nab2-Gfd1 interaction and exploit that information then to design specific mutations for use in genetic and cell biological assays. They found that a Gfd1 mutant defective in Nab2 binding could not rescue the temperature-sensitive growth defects and poly-A accumulation seen in yeast cells lacking the helicase Dbp5 (a key component of the mRNP disassembly machinery), whereas wild-type Gfd1 could. These findings suggest Gfd1acts to facilitate the release of Nab2 from mRNPs in the cytoplasm, providing some detail into a poorly understood aspect of the gene expression pathway.



Structure of the Nab2-N:Gfd1 interface, shown in two views rotated 90° about the vertical axis; Nab2-N is in blue, and Gfd1 is in yellow.

Structural Basis for the Function of the Sacchromyces cerevisiae Gfd1 Protein in mRNA Nuclear Export

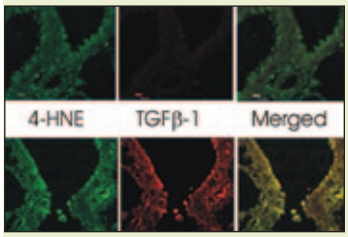
Chao Zheng, Milo B. Fasken, Neil J. Marshall, Christoph Brockmann, Max E. Rubinson, Susan R. Wente, Anita H. Corbett and Murray Stewart

J. Biol. Chem. published online May 12, 2010

jbc

Good Cholesterol, Good Lungs

High-density lipoprotein is predominantly composed of the apolipoproteins apoAI and apoAII. These apolipoproteins are responsible for collecting lipids from arteries and transporting them back to the liver for reutilization, which provides protection against cardiovascular diseases. While many studies examine the cardiovascular effects of HDL and its apolipoproteins, few have looked at whether these molecules maintain the health of other bodily systems and organs. In this study, the authors show that apoA1 maintains pulmonary function in mice. Along with inhibiting stressors such as proinflammatory HDL formation and the activity of paranoxonase 1 (PON1) and 3-nitrotyrosine (3NT) in the plasma, apoA1 was shown to limit pulmonary inflammation and oxidative stress markers, such as 3NT, 4-hydroxynonenal adducts (4-HNE), transforming growth factor-β (TGFβ), xanthineoxidase, myeloperoxidase and endothelial nitric oxide synthase in the lung milieu. Additionally, apoA1 was shown to enhance arterial relaxation responses, as well as decrease airway hyper-responsiveness and the presence of pulmonary collagen deposition. Thus, apolipoproteins appear to sustain the function of both the pulmonary and cardiovascular systems. Together, these data suggest that apoA1 limits pulmonary inflammation and maintains airway physiology, findings that may clarify observations linking abnormal cholesterol and/or apolipoprotein levels with pulmonary irregularities.



ApoA1-KO lung sections (bottom) show increased level and colocalization of pulmonary 4-hydroxynonenal adducts and transforming growth factor β-1.

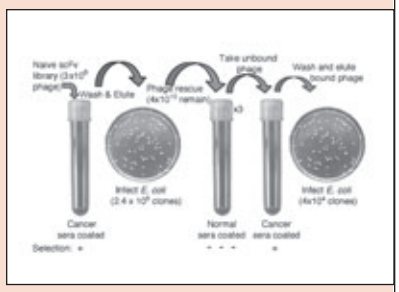
Genetic Deletion of Apolipoprotein A-I Increases Airway Hyperresponsiveness, Inflammation and Collagen Deposition in the Lung

Weiling Wang, Hao Xu, Yang Shi, Sandhya Nandedkar, Hao Zhang, Haiqing Gao, Thom Feroah, Dorothee Weihrauch, Marie L. Schulte, Deron W. Jones, Jason Jarzembowski, Mary Sorci-Thomas and Kirkwood A. Pritchard, Jr.

J. Lipid Res. published online May 24, 2010

Biomarker Pipeline for Ovarian Cancer

Ovarian cancer is a "silent killer" because symptoms generally do not present themselves until the disease has advanced. The discovery of novel early detection biomarkers may offer a way to reduce the morbidity and mortality caused by ovarian cancer. In this study, 108 antibodies from a single antibody variable fragment antibody (scFv) library were selected for their recognition and specificity to ovarian cancer proximal fluid or serum samples. Resulting scFvs were printed on antibody microarrays and incubated with pooled sera from cancer patients or controls, enabling the selection of antibodies that best discriminated markers of ovarian cancer in a successive manner. The top 19 scFvs were incubated on a nucleic acid programmable protein array to identify their protein targets. Targets for 15/19 scFvs were identified, some of which overlapped, increasing the probability that the target is a marker for ovarian cancer. Dot plots were used to validate that the scFvs were specific for their targets and that their targets were overexpressed in samples from ovarian cancer patients. Together, this work demonstrates a new pipeline to identify antibodies that bind proteins elevated in serum samples from cancer patients, which can be subsequently analyzed for their usefulness as an ovarian cancer biomarker.



As part of identifying new ovarian cancer biomarkers, single-chain variable fragment antibodies (scFv) were positively selected using cancer derived sera (left) and then negatively selected using normal sera (right).

Use of a Single Chain Antibody Library for Ovarian Cancer Biomarker Discovery

Arturo B. Ramirez, Christian M. Loch, Yuzheng Zhang, Yan Liu, Xiaohong Wang, Elizabeth A. Wayner, Jonathon E. Sargent, Sahar Sibani, Eugenie Hainsworth, Eliseo A Mendoza, Ralph Eugene, Joshua LaBaer, Nicole D. Urban, Martin W. McIntosh and Paul D. Lampe

Mol. Cell. Proteomics, published online May 13, 2010

Going Full Circle: *Taking a Leap from the Bench to a Career in Research Administration*

BY DAVID TAYLOR

David Taylor currently serves as the academic programs officer of The Children's Hospital of Philadelphia Research Institute. He also serves on the National Postdoctoral Association Board of Directors and functions as a career advisor on the Science Careers Forum. Taylor earned his doctorate from the University of Virginia, graduating in 2006 and did a postdoctoral fellowship at The Children's Hospital of Philadelphia. He then transitioned into a research administration fellowship at Children's Hospital, which led his current position with Children's Hospital.

I was about three years into graduate school when a persistent nagging feeling took up residence in my head. For a while, I just ignored it. I was, after all, neck-deep in gel shifts and Western blots, trying my hardest to eke out that last bit of data I needed for a first author publication. But without fail, whenever I had a bit of downtime or was drifting off to sleep, the panicked sensation would return.

It wasn't until about a year later, when I was home for Christmas on a well deserved break from the lab, that a simple question from my father led me to vocalize what I had been thinking for quite some time.

"So, what are you doing when you graduate?" he asked over dinner. It was nothing I hadn't heard before — from my mentor, my classmates, my friends — but something about that moment broke open the floodgates.

"I have no idea," I responded, a sinking feeling of shame and embarrassment settling into my stomach. Hearing those words come out of my mouth suddenly made it real, and I was frightened. All those years priming myself for a career in research and I didn't know what I wanted to do for a living. How could that be?

"Well, I wouldn't worry about it," my father said between bites of his meal. "You're only 26. Most people don't even know what they want to do when they're 50."

The History of a Love Affair

I first fell in love with the idea of research during my undergraduate days. As soon as I stepped on to my college campus during orientation, I pushed my way into a lab as the most basic of technicians. When space freed up, I started up my own project. In the backdrop of my college education, research stimulated an analytical part of my brain that had long been yearning for satisfaction. A travel award and a few recognitions later, I suddenly found myself in a graduate program at the University of Virginia.

Graduate school was even more my speed, albeit much more stressful. I loved my classes and learning across a wide number of scientific disciplines. Soon I found myself obsessing over pharmacologic pathways and G protein coupled receptors. I was fortunate enough to find my way into a wonderful thesis lab, with a great mentor and a solid project. Nothing could have been better…or so I thought.

When classes ended and I joined the lab full time, something suddenly felt like it was missing. Was it the solitary atmosphere of the lab setting, somehow bereft of the camaraderie inherent among struggling classmates? Or, was it the feeling that I was leaving behind the global view of science afforded by my classes, forced to focus on one tiny little iota of the big picture? Either way, I began to feel trapped. This growing discontent loomed in my head for a few years, continuing through my thesis defense and a postdoctoral fellowship. As those

thoughts took shape and form through a variety of experiences, I finally decided that it was time to make a move.

Taking Stock and Taking Steps

Taking that huge leap away from the bench is very intimidating. As scientists, we're pushed day after day to follow specific protocols, where deviation can mean the loss of a day or week or month's worth of work. It shouldn't be surprising then, that veering sharply from the standard academic research career track can feel wholly unnatural.

At the time, my thoughts were quite mixed. I wondered if my past mentors would brush me off, suddenly branding me as a big waste of their time. I was afraid of what my friends and my colleagues would think about me "giving up." I was afraid that my research skills were all I had, and that they wouldn't get me anywhere. I felt overqualified for everything but had experience for nothing. Fortunately, a renewed sense of purpose helped me to send these concerns to the sidelines. I did need a career, after all.

The number and quality of career resources available to me were amazing. I visited the campus postdoctoral affairs office. I looked to the Internet for advice and tips. I took stock of the skills I valued and the leadership I'd learned and drafted my first nonscientific resumé. I was lucky. While I made a few missteps and went through my share of frustrations during the job hunt, my path moved forward fairly quickly.

One day, I happened upon a program called the "research administration fellowship" at The Children's Hospital of Philadelphia. The listing said it would "provide the fellow with key experience rotating through a number of different areas within research administration," including scientific communications, technology transfer, clinical trials management, strategic planning and many others. If there was something I was familiar with from graduate school, it was rotations. I timidly tossed in my application and waited to see what would happen.

About one month later, I was hired into the fellowship program. Man, was I in for culture shock!

A Strange New World

The strangest thing about having my first "real job" was just that: It was a real job. No more walking into the lab whenever I felt like it, wearing jeans and a ratty t-shirt. No more stopping by unannounced to idly chat up department heads. No more downloading music on my iMac when I had downtime (and no one was watching). Now, I was in a world of dress shirts and ties, appointments and hierarchies and overly regulated PCs. Funny thing is, other than losing my iMac, I found the whole thing very appealing.

Over the next year and a half, I took to my rotations with great enthusiasm. I worked with the communications department to hone my writing skills for nonscientific audiences, learned about human subject protections with the clinical trials office, participated in the strategic planning process for the research institute and teamed up with the compliance office to develop a proposal for creating a novel assent tool for pediatric research subjects. As I navigated each administrative group at Children's Hospital, I found myself becoming an integral part of the community. I understood the research institute inside and out, from the perspective of the scientist and the administrator. And, as the fellowship finally came to a close, I was fortunate enough to successfully land a job at Children's Hospital that matched all of my newfound interests. Call it a strange twist of fate, but I joined the office of postdoctoral affairs as an academic programs officer, responsible for providing guidance and programmatic support for research trainees much like myself only a couple of years prior.

Full Circle

My roles in the office of postdoctoral affairs are many: I'm a guidance counselor, project manager, web editor, hiring manager, program coordinator, event planner, career advisor, committee organizer, strategic planner, mentor and ombudsman. I have my hand in many projects and work in a collaborative team atmosphere with a common goal and purpose. I support all of our research trainees as they traverse whatever career path they choose.

Most importantly, I wake up in the morning and, more often than not, I look forward to going to work.

If there's one tidbit of advice I can give to those seeking out their ideal career in science, it's this: Find yourself a career that you love. I try my best to convey this to all of the postdocs that contact the office looking for advice. Inevitably, some will lament about being completely lost.

"You have the opportunity to explore a ton of career options," I tell them. "Besides, you're ahead of the curve. Most people don't even know what they want to do when they're 50." XXXL

Phosphoinositide Signaling: Getting to the Root of the Matter

BY WENDY F. BOSS

Plants are totipotent, sessile organisms that must adapt to a changing environment in order to survive. Although plant phosphoinositide (PI) metabolism changes rapidly in response to environmental cues, PIs also appear to regulate fundamental metabolism.

The biosynthesis of phosphatidylinositol(4,5)bisphosphate (PtdInsP$_2$) is regulated tightly, suggesting that it may function as a signaling molecule. The ratio of PtdInsP$_2$ to PtdInsP is approximately 1:10, and there are no reports of PtdInsP$_3$.

Biochemical and genetic comparisons in plants and mammals support the hypothesis that plants use only select aspects of PI signaling. In contrast to mammals, which have five distinct families of PtdInsP$_2$-phospholipase Cs, plants only have one family, which is most similar to the mammalian zeta family of "sperm-specific" calcium regulated PLCs (1, 2). This is very different from phospholipase D signaling, in which plants have six different families of PLDs with distinct functions (3).

Although the additional types of PLCs are not essential for plant growth and development, PLC-mediated signaling and the polyphosphorylated inositol lipids affect fundamental processes such as differential cell growth, vascularization, cell polarity, asymmetric division during stem cell development, tip growth and basal metabolism.

Tip growing cells such as root hairs and pollen tubes have provided a platform for dissecting the selective functions of the type III PtdIns 4-kinase and PtdInsP 5-kinase isoforms in polar growth (4). Developmental studies of plant stem cells also recently revealed that PtdIns4P can activate POLTERGEIST, which is essential for the maintenance of asymmetric division during stem cell development (5). Proteins that regulate carbon portioning and the energy balance of the cell directly interact with PtdInsP kinases and inositol polyphosphate 5Ptases (6, 7).

It is not surprising then, that genetically altering InsP$_3$ signaling has provided a new approach for engineering drought tolerant plants. Dampening the InsP$_3$ signal by increasing the hydrolysis of InsP$_3$ decreases the rate of gravitropic response, enhancing drought tolerance (8).

These are just a few examples of the insights gained from studying plant PI metabolism. Comparative analyses of the functions of PIs and PI binding proteins in diverse systems should continue to reveal insights into the regulation of fundamental metabolism. Although plant PI signaling may seem somewhat limited in scope because of the inherent differences in the regulation of their PI pathway, plants provide an excellent eukaryotic platform to build and test novel synthetic signaling systems.

Tomatoes (Micro-toms) transformed with genes from Pyrococcus furiosus, an Archaeal hyperthermophile.
PHOTO CREDIT YANG JU IM.

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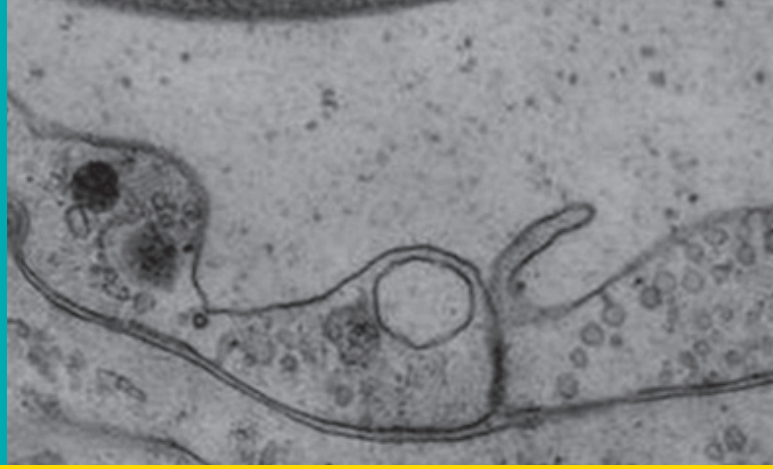

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WHAT
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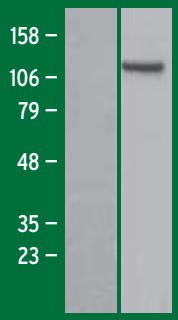

HEK293 were transfected with L) empty vector R) TrueORF for Myc/DDK-tagged hTERT(Cat# RC217436). The lysates were analyzed using anti-DDK antibody to show over-expression of hTERT. *DDK is the same as FLAG.

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