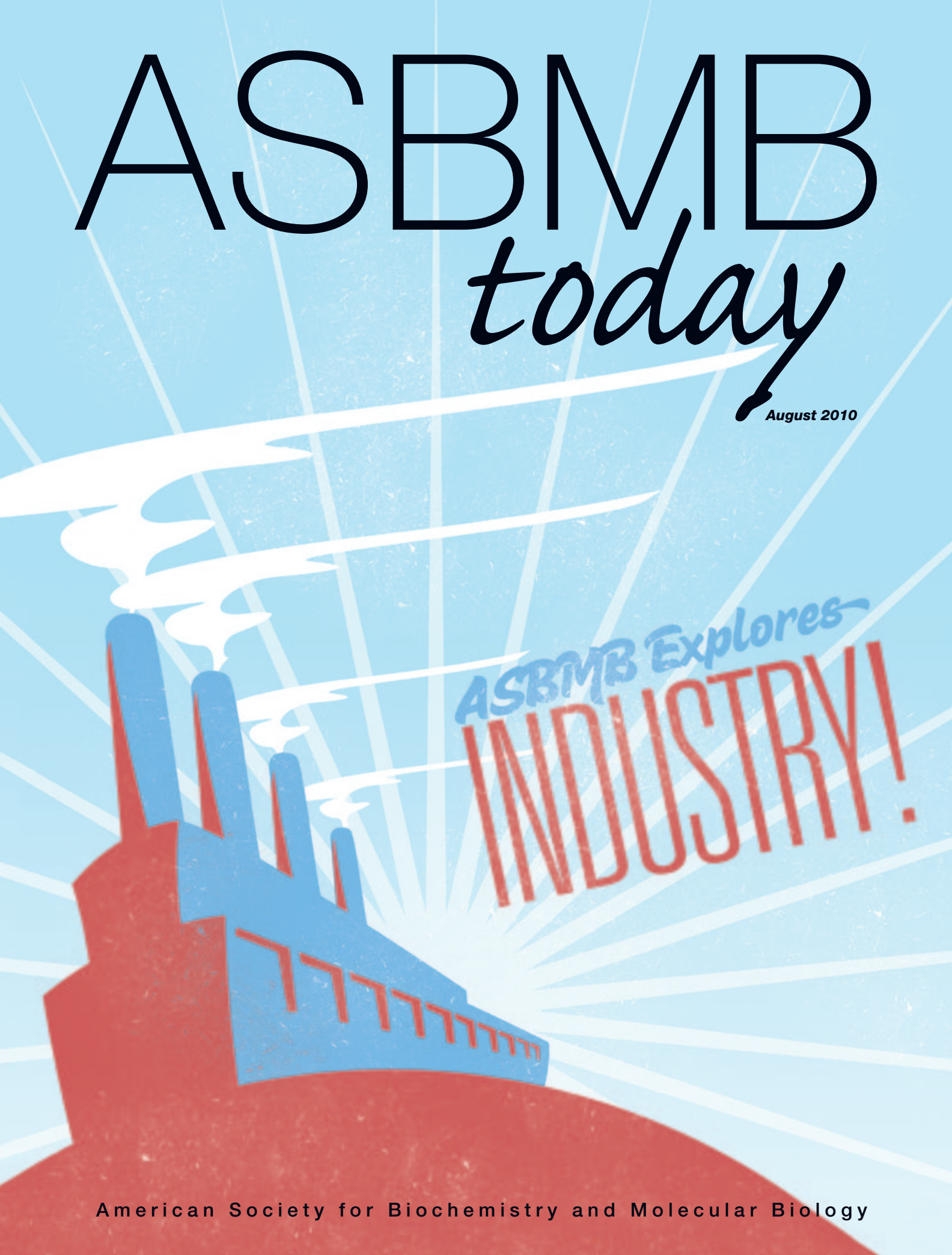
ASBMB today

August 2010



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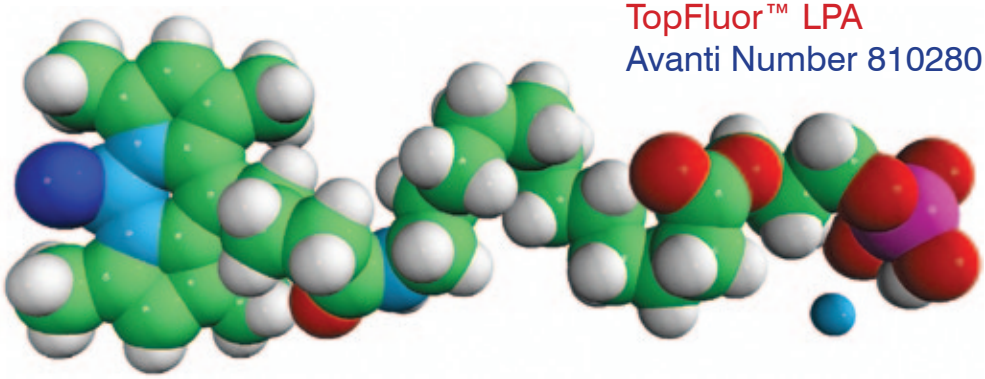

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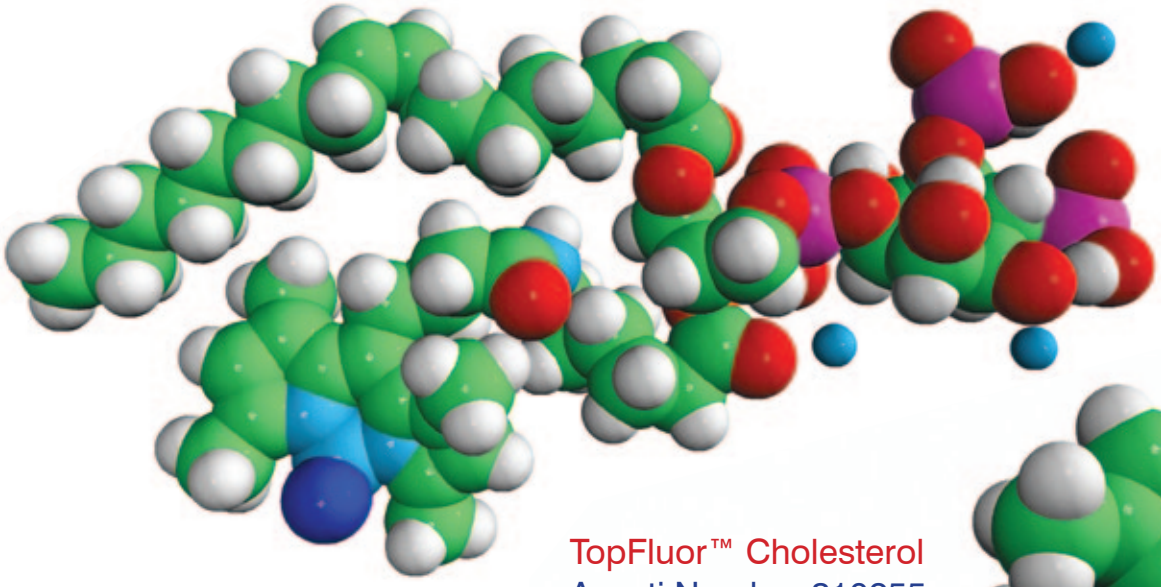

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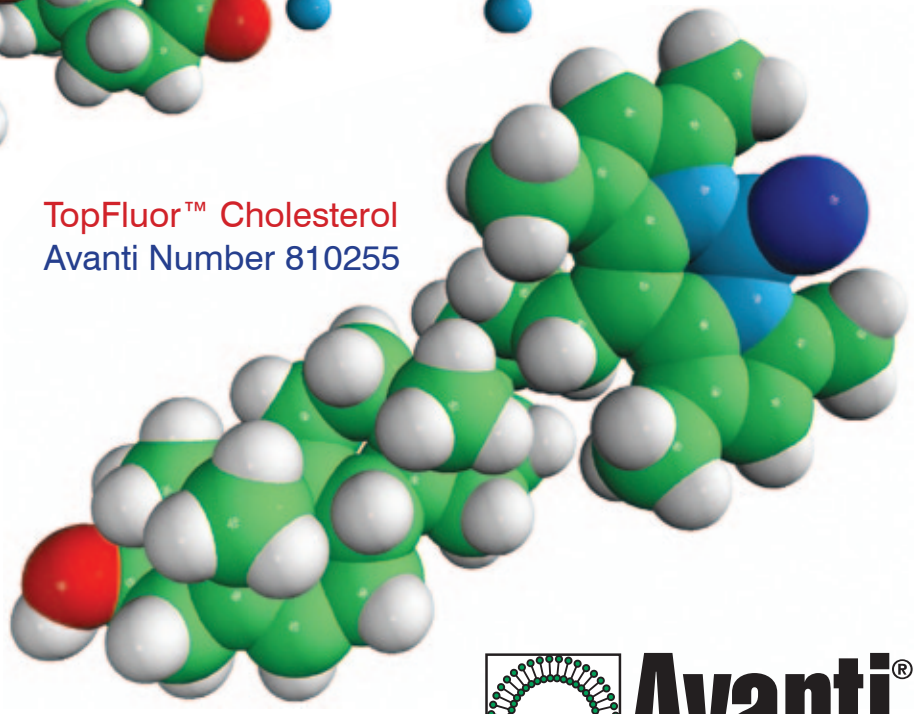

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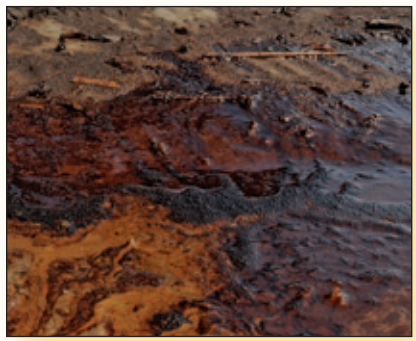

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Visit the ASBMB Today website for online-only content, including a look at the JBC thematic minireview series on hepatitis C and an article by Gregory Petsko about why he wants your Phase II failures.

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Erratum:

The references for letter to the editor titled "Basic versus Translational Research" on page 2 of the July issue of ASBMB Today should read:

1. Dam, T. K., and Brewer, C. F. (2010) Lectins as Pattern Recognition Molecules: The Effects of Epitope Density in Innate Immunity. *Glycobiology* **20**, 270-279.
2. Dam, T. K., and Brewer, C. F. (2010) Maintenance of Cell Surface Glycan Density by Lectin-Glycan Interactions: A Homeostatic and Innate Immune Regulatory Mechanism. *Glycobiology* (in press).

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2008 APEX AWARDS FOR PUBLICATION EXCELLENCE

president's message

Payback Time

BY SUZANNE PFEFFER

What if every National Institutes of Health grant recipient was required to donate one hour per year to communicate science to the general public? What if the requirement included the option of presenting a public lecture, hosting visitors to your lab or visiting a local school to talk with children? The NIH supported approximately 9,000 investigators last year. Imagine 10,000 hours of "science ambassador" activities across the U.S. over the coming year.

Some of my colleagues have responded with, "be careful what you wish for — some scientists may be terrible at this and may do more harm than good." For those who might not be great scientific ambassadors, maybe their lab members could do the talking for them. Other colleagues have said, "don't add more requirements to our lives." Fair enough.

But, the National Science Foundation already may have beaten us to the punch. NSF applicants must now "describe as an integral part of the narrative, the broader impacts resulting from the proposed activities, addressing one or more of the following: how the project will integrate research and education by advancing discovery and understanding while at the same time **promoting teaching, training, and learning;** ways in which the proposed activity will broaden the participation of underrepresented groups; how the project will enhance the infrastructure for research and/or education… **how the results of the project will be disseminated broadly to enhance scientific and technological understanding;** and potential benefits of the proposed activity to society at large."

To achieve broad dissemination, NSF guidelines suggest that scientists, "Partner with museums, nature centers, science centers, and similar institutions to develop exhibits in science, math, and engineering. Involve the public or industry, where possible, in research and education activities. Give science and engineering presentations to the broader community (e.g., at museums and libraries, on radio shows, and in other such venues.). Publish in diverse media (e.g., non-technical literature, and websites, CD-ROMs, press kits) to reach broad audiences. Present research and education results in formats useful to policy-makers, members of Congress, industry, and broad audiences. Participate in multi- and interdisciplinary conferences, workshops, and research activities. Integrate research with education activities in order to communicate in a broader context." As someone not currently funded by NSF, I was intrigued to learn this. NSF is calling on scientists to share their knowledge today. They are telling us what we already should be doing. This call is not just for NSF awardees.

Explaining science to the public is very important. First, we owe it to them. Taxpayers support a large proportion of biomedical research in the U.S. and in other countries around the world. At a time when public understanding of science could use a major boost, who better to explain the excitement and importance of scientific discoveries than highly

trained biomedical researchers?

The public is interested in and excited by scientific discovery. I recently gave a public lecture explaining how microarray analysis enables researchers to distinguish between different types of cancers and how this will help us devise therapies best suited for specific cancer subtypes. This is not my own research area, but it was a topic appreciated widely by my Palo Alto, Calif., audience. I invited my oncologist colleague, Gil Chu, to join me, to help answer the "cancer" questions. Tom Baldwin, a member of the American Society for Biochemistry and Molecular Biology's Public Affairs Advisory Committee, hosts a monthly public lecture series at the University of California, Riverside, that is extremely popular. Indeed, so-called, "Med School for a Day" programs have taken off on many campuses across the U.S.

Contributing to public science education will benefit us all in many ways. Technological innovation, support for science research and even good health can come from a science-savvy electorate. As biochemists, we are especially well suited to educate the public in vital medical areas. Consider the estimate that obesity cost the U.S. $147 billion in 2009. That represents almost five times the annual budget of the NIH. (Imagine if even half of those funds instead were available for biomedical research!) Biochemists are experts in metabolism. We should be on center stage, explaining how the sugar in "fat-free" foods is converted directly to fat in our bodies; how calories-in and calories-burned control our weight; how our bodies have an endless capacity to store fat. We can explain diabetes and why exercise makes a difference. We can explain how to read a label on food products and what the labels mean. And, of course, we can always explain what we work on in our labs and why it is important for life.

> "Imagine 10,000 hours of 'science ambassador' activities across the U.S. over the coming year."

Scientific literacy will be essential for the competitiveness of the U.S. economy going forward. If our students don't learn the math and science needed for future technological innovation, our economy (and research programs) will fall behind. On May 28, the U.S. House of Representatives passed reauthorization of the America Competes Act; it now awaits action by the Senate. The Act includes text to "encourage all elementary and middle schools to observe a Science, Technology, Engineering, and Mathematics Day twice in every school year, initiate a program to encourage federal employees with scientific, technological, engineering or mathematical skills to interact with school children on such Days; and promote involvement in such Days by appropriate private sector and institution of higher education employees."

Part of the Act, titled "Teachers for a Competitive Tomorrow," states that institutions receiving NSF awards under the Integrative Graduate Education and Research Traineeship program should "train graduate students in the communication of the substance and importance of their research to nonscientist audiences." How many of your programs are doing this today?

Our graduate students are hungry for opportunities to try teaching; here is a chance to put them in front of a classroom. They will need mentorship for this. And, as scientists, we will benefit from changing the perception that scientists are disconnected from, or somehow unlike, "regular" people. We can be important role models for children (and adults) who've never met a scientist, and we may even inspire a few to pursue careers in science. Public trust in scientists only will come when scientists engage the public and earn their trust. Volunteering now will add much to our credibility when we ask members of the U.S. Congress for their continued support of biomedical research. It's our turn to step up and make a difference. Will you give an hour this year? XXX

Re-examining Biosecurity

BY KYLE M. BROWN

On July 2, President Obama issued an executive order that will restructure biosecurity regulations at the nation's laboratories within the next two years.

Since 1996, the U.S. Congress has passed several pieces of legislation to regulate research with bacteria, viruses or chemicals that pose a severe threat to human, animal or plant health. More than 80 deadly and disease-causing pathogens and chemicals have been designated as "select agents and toxins" by either the U.S. Department of Health and Human Services or the U.S. Department of Agriculture. To conduct research on these agents, laboratories must register with the government, develop and submit biosafety and biosecurity plans and allow for inspections "without prior notification."

But, several reports have highlighted concerns about the select agent program. In 2008, the Commission on the Prevention of Weapons of Mass Destruction Proliferation and Terrorism issued report that recommended conducting a comprehensive review of programs that secure dangerous pathogens and tightening government oversight over laboratories. A report by the National Research Council recommended select agents be stratified into groups based on their level of risk. The NRC also recommended that researchers and government inspectors be provided with adequate training and scientific expertise to appropriately conduct research and inspections.

Created by a presidential executive order in 2009, the Working Group on Strengthening the Biosecurity of the United States agreed that the select agent list should be stratified and recommended that the "numerous, uncoordinated inspections" to which labs are subjected be coordinated among the various government agencies.

In September 2009, U.S. Sens. Susan M. Collins, R-Maine, and Joseph Lieberman, I-Conn., introduced legislation to address the concerns of the WMD Commission with a particular focus on heightening security at laboratories that work with select agents.

"Some of the world's most dangerous pathogens are not secure," said Collins during a Sept. 22 hearing of the Homeland Security and Government Affairs Committee.

The bill would create a Tier 1 category of select agents and toxins and put the Department of Homeland Security in charge of inspections of Tier 1 agent laboratories to ensure compliance with security standards.

But, not all senators were convinced by the bill's approach. During subsequent hearings on Oct. 28 and Nov. 4, U.S. Sens. Carl Levin, D-Mich., and George Voinovich, R-Ohio, questioned the increased role of the Department of Homeland Security and a system of overlapping regulations. Saying the bill was in conflict with the commission's recommendations, Levin cited letters from a number of scientific societies, including the Federation of American Societies for Experimental Biology, expressing their concerns about the effects of new regulations on research.

Against the vocal objections of Levin, the Senate committee passed Lieberman and Collins' bill. However, Lieberman acknowledged that it is unlikely to be considered by the full U.S. Senate.

Since the Senate bill's passage, the House Committee on Homeland Security passed a similar bill. Introduced by U.S. Reps. Bill Pascrell, D-N.J., and Peter T. King, R-N.Y., the House version diminishes the role of DHS, giving HHS and the USDA the authority to conduct inspections of laboratories while coordinating simultaneous lab inspections and creating common inspection procedures.

Not waiting for the outcome of a potentially lengthy and uncertain legislative process, on July 2, Obama issued an executive order to address many of the WMD Commission and Working Group recommendations.

The resulting executive order likely is to take some of the momentum away from biosecurity legislation in Congress. Following the Working Group's recommendations, it creates different categories of select agents. The executive order also directs HHS and the USDA to consider "reducing the number of agents and toxins on the select agent list" while working to coordinate inspections and oversight of select agent labs.

It will be some time before scientists know exactly how the executive order will affect their research. But, there is hope that tiering and shrinking the select agents list while coordinating regulations and inspections may help to reduce the burden that many labs face.

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

Innovative and Translational Research

BY ANNE M. DESCHAMPS

Two commonly heard buzzwords associated with research endeavors today are "innovation" and "translation." Although most people agree that conducting innovative and translational science is essential, few are clear on how to incorporate these concepts into their research. Thus, the Federation of American Societies for Experimental Biology sought to define "innovation" and "translation" in relation to research and to explore ways to incorporate them.

What does it mean to be innovative? How is innovation evaluated? Are some mechanisms of research support more successful than others? These were some of the questions addressed at FASEB's annual Science Policy Committee meeting this past June. The meeting brought together scientific leaders to discuss how institutions encourage and evaluate innovation. The Howard Hughes Medical Institute favors a "people over projects" approach, giving their investigators the freedom to pursue their own research interests and encouraging them to focus on high risk, high reward projects. The Defense Advanced Research Projects Agency is mission-focused, funding projects strictly aligned with agency goals. The National Institutes of Health's Transformative R01 program provides grants to investigators who have demonstrated potential as "explorers," whereas the NIH New Innovator Award focuses on impact and innovation rather than preliminary results. The Linkages Program at the Harvard Clinical and Translational Science Center has experimented with "collective intelligence" models through online collaborations to generate innovative answers to tough research questions.

But, do these institutions promote innovation? The Science and Technology in America's Reinvestment — Measuring the Effect of Research on Innovation, Competitiveness and Science initiative hopes to determine that. The program is a "federal and university partnership that is developing an empirical framework to measure the outcomes of science investments and demonstrate the benefits of scientific investments to the public."

Following the SPC meeting, members of FASEB's translational research steering committee convened to produce some of their own innovative ideas for promoting translational research. Like innovation, translation means different things to different people. It is often described as the bidirectional process in which information acquired through basic research is used to develop new medical treatments (T1) and the implementation of those medical treatments into clinical practice (T2). Increased emphasis on translational research stems from concerns that discoveries in basic science are not converted readily into medical breakthroughs. Although a number of initiatives have been developed to address this concern, such as NIH's Clinical and Translational Science Award program and the Cures Acceleration Network, few have focused specifically on the importance of engaging basic scientists.

FASEB's "Forum on the Critical Role of Basic Scientists in the Translational Research Enterprise" aims to encourage and facilitate the participation of basic scientists in translational research, particularly at the T1 stage, where their knowledge of basic biological processes is often important to understanding and treating human disease. However, moving discoveries from bench to bedside is challenging. For example, just as clinical researchers may not understand fundamental mechanisms of the diseases they study, basic scientists aren't always aware of how their work applies to clinical problems. In addition, regulatory complexities, particularly navigating human subjects' protection processes, could deter basic scientists from entering into translational research. There are also obstacles at the institutional level. In addition to the organizational and structural issues that make collaboration a challenge, many basic scientists are concerned that it will be harder to publish translational research, that they will not have the support of their departments and that their work will not be rewarded with tenure and promotion.

FASEB aims to explore these issues from basic scientists' perspectives in hopes of elevating their excitement and involvement. The steering committee currently is organizing a symposium to explore opportunities for basic scientists in translational research, the obstacles to their participation and how to overcome them.

Anne M. Deschamps (adeschamps@faseb.org) is a science policy fellow in the Office of Public Affairs at FASEB.

Retrospective: Bert Lester Vallee (1919–2010)

BY GORDON G. HAMMES AND S. JAMES ADELSTEIN

Bert Lester Vallee, the Paul Cabot professor of biochemical sciences emeritus at Harvard Medical School, passed away in his sleep on May 7, a few weeks short of his 91st birthday. A brilliant biochemist, Bert left a legacy of many significant discoveries and a large cadre of scientific collaborators. He will be remembered as a passionate scientist, dedicated to finding the answers to important questions. A remarkably generous and kind colleague, Bert could be a formidable opponent when discussing science. He had a wonderful sense of humor and would often start out his scientific talks with a joke. In private, he frequently exchanged jokes with friends — always looking for new material. He enjoyed good food and wine (particularly Alsatian) — a visit with Bert was a guarantee to gourmet dining.

Bert was born in Germany on June 1, 1919 and grew up in Luxembourg. He received his Bachelor of Science degree from the University of Bern in Switzerland. He came to the United States in 1938 as the first (and only) fellow of the International Student Service of the League of United Nations. He was fortunate to be taken under the wing of Richard Courant, founder of the New York University Courant Institute of Mathematical Sciences, and ultimately received his medical degree from the New York University College of Medicine in 1943. Although he was an able physician who actively helped his friends with their medical problems throughout his life, his true calling was biomedical research. During World War II, he was assigned to the joint Harvard Medical School-Massachusetts Institute of Technology blood-preservation project directed by the protein chemists Edwin Cohn and John Edsall. This experience shaped his future career in biochemistry and biophysics.

At MIT, Bert became interested in the metabolism of iron and other metals such as zinc and copper. He quickly recognized the potential of spectroscopy, particularly emission and arc spectroscopy, for the detection of metals in biological systems. At that time, assessing the role of metals in biological systems was a quagmire for two reasons: inadequate purity of biological materials and the lack of sensitive methods to analyze for the metals. He was awarded a National Research Council Fellowship in 1948 to pursue both of these challenges in the world-famous spectroscopy laboratory affiliated with the physics, chemistry and biology departments of MIT. In 1954, he established the Biophysics Research Laboratory at Harvard Medical School and Peter Bent Brigham Hospital. This laboratory became the locus of Bert's scientific prowess. At Harvard, Bert was named assistant professor of medicine in 1956; he rose swiftly through the ranks to become the Paul C. Cabot professor of biological chemistry in 1965.

Bert believed that scientific discovery relied heavily on technical advances. Throughout his career, he either developed his own technologies or was an early adapter of techniques developed by others. Consistent with this philosophy, he proceeded to build a flame spectrometer designed to detect and quantify sodium, potassium, magnesium and calcium in biological samples. This early instrument was prototypical of later instruments that are used for monitoring these elements in clinical samples and the detection of diseases associated with their dysregulation. Very quickly, Bert's laboratory became the world center for the analysis of trace metals in biological samples. These analyses depended on two factors: the ability to obtain an uncontaminated biological sample and the unique equipment available in his laboratory.

Trace metals were found in unexpected places, and, in some cases, the putative role of metals in biological mechanisms was ruled out after careful analysis.

Visiting Bert's laboratory in the Peter Bent Brigham Hospital was an adventure. To gain entry, it was necessary to wander through the basement of the hospital, among the steam pipes. Upon opening the door to his lab, a wondrous transformation occurred — a modern laboratory equipped with every conceivable instrument used in biophysics emerged, with people scurrying about, hard at work.

Bert Vallee is especially well known for his identification of zinc in various metalloproteins and enzymes. Because of his work on the role of metals in biological systems, many consider him to be the "father of metallobiochemistry." Among the many zinc proteins studied in his laboratory, carboxypeptidase merits special mention. His laboratory carried out very careful and extensive mechanistic studies of this enzyme that not only elucidated its reaction mechanism but also provided structural information. Again, multiple techniques were used in this work, including spectroscopy, stopped-flow kinetics and chemical modification. In particular, the roles of specific amino acid residues at the active site were assessed. When the X-ray structure ultimately emerged, Bert's results proved to be remarkably accurate.

"Bert believed that scientific discovery relied heavily on technical advances."

Alcohol dehydrogenase was another zinc-containing enzyme extensively studied by the Vallee laboratory. Bert was especially interested in the role of this enzyme in alcohol metabolism and the general problem of alcohol addiction. He showed that genetics are important for the disease of alcoholism, and his work has led to clinical trials of drugs for the treatment of the disease. In 1957, he discovered the unique protein metallothionein, a low-molecular weight cysteine-rich protein. The protein binds zinc atoms very tightly and has been implicated in the homeostasis of zinc metabolism. It also binds many other metals tightly, and recent results suggest that the redox properties of copper, when bound to metallothionein, may be of significance in neurodegenerative diseases.

As a consultant to Monsanto, he initiated one of the early collaborations between a university and industry. The research was directed toward isolating chemicals that led to new blood vessels in tumors. His laboratory characterized one of these chemicals, angiogenin, which proved to be a ribonuclease analog.

Bert's bibliography includes more than 650 publications, comprising research articles, books and reviews. He was recognized widely for his scientific accomplishments and was elected to the National Academy of Sciences and the American Academy of Arts and Sciences. Among his many awards were the Linderstrom-Lang Medal, the Willard Gibbs Medal from the American Chemical Society and the William C. Rose Award from the American Society for Biochemistry and Molecular Biology. He received honorary degrees and professorships throughout the world and served on the editorial boards of multiple journals.

Bert wanted to leave a living memorial for science, and, in 1995, he and his wife Natalie, known as "Kuggie" to her friends, established the Vallee Foundation to foster originality, creativity and leadership in science. A primary activity of the foundation is to fund honorary Vallee professorships for well-known scientists. The purpose of these short-term (typically four weeks) visiting professorships is to permit accomplished scientists to explore new areas and to establish close interactions with other successful senior investigators that might lead to new knowledge. Bert approached this foundation with his usual passion and zeal, and many researchers and laboratories already have benefited from his endeavors. At the time of his death, he was organizing a meeting of the Vallee Foundation for the summer of 2010. Although Bert was adamant about not wanting a memorial service, this meeting will be held as a living tribute to a remarkable man. He will be sorely missed by his friends and colleagues, but his scientific accomplishments and the Vallee Foundation remain as lasting remembrances.

Gordon G. Hammes (hamme001@mc.duke.edu) is the university distinguished service professor of biochemistry emeritus at Duke University, and S. James Adelstein (james_adelstein@hms.harvard.edu) is the Paul C. Cabot distinguished professor of medical biophysics at Harvard Medical School.

asbmb member spotlight

For our industry issue, ASBMB Today asked three of its members who work in industry — Weiping Jiang, Matthew Olson and Anthony S. Serianni — to answer questions about themselves and their research. To read more answers, go to the online version of this article at http://bit.ly/bzPxqf.

Weiping Jiang

Director, R&D Systems

How long have you been an ASBMB member?
I've been a member since 1992.

What do you study?
I study enzymes for the development of products, including proteins, antibodies and assay kits.

Why did you go into industry?
To generate new research tools to advance our understanding of health and disease.

How do you feel ASBMB could best help scientists in industry?
The society could foster more interactions among the scientists in industry as well as between scientists from both industry and academia.

Where do you see research in industry going in five to 10 years?
I think there will be a focus on increased sensitivity and specificity of detection tools.

Has the downturn in the economy affected your job or your company?
No.

Matthew Olson

Principle Research Scientist, Johnson and Johnson

How long have you been an ASBMB member?
I've been a member since 2002.

What do you study?
I'm part of a team engaged in the development of cell-free and cell-based assays, which take advantage of label-free detection technology to monitor the enzymatic and biophysical properties of enzymes and proteins with their appropriate substrates and ligands. My role is to provide complete kinetic characterization of enzymes and evaluate signal transduction systems using substrates/effectors that are as "in vivo-like" as possible. Then, I determine the ability of small molecule antagonists and agonists to modulate these macromolecular systems.

Why did you go into industry?
I received a job offer from Wyeth Pharmaceuticals during my second postdoctoral fellowship. My wife and I considered other options at the time, but we made the decision to go to Pearl River, N.Y., where I joined the infectious disease department.

How do you feel ASBMB could best help scientists in industry?
Partnership and synergy. There is a need for industry and academics to partner. Industry needs academic innovation. Academia needs industry to develop that innovation for drug discovery. Combined, they will create jobs for young scientists to carry the baton passed to them in both fields. ASBMB already is playing a major role in bridge building between academics and industry by using their current platforms: LIPIDMAPS, PSI, the ASBMB journals and the Experimental Biology meeting as a whole.

Where do you see research in industry going in five to 10 years?
Personalized medicine has been given much fanfare in recent years. This very well may be the future because there is a need for drug development taking genetic differences into account. Other areas gaining popularity in the coming years may be epigenetics and stem cells. These technologies are being evaluated for intervention of cancer and metabolic diseases. Another topic which may make resurgence is anti-infective drug discovery.

Has the downturn in the economy affected your job or your company?
The easy answer is, "What industry has not been affected?" All industries have been under pressure to increase efficacy. I think the more relevant issues affecting my job and the pharmaceutical industry as a whole are monitoring patent expirations, halting patent infringement and producing a robust pipeline. Although patent expirations are a given, rule updating could help. On the other hand, patent infringement is an undesirable reality with unpredictable consequences resulting in significant revenue losses translated into the research and development of an organization. R&D assets protected by patents are linked closely to current corporate profits. Often, unknown to the general public, is the fact that my

industry reinvests up to 40 percent of its profits into R&D for a robust pipeline. Therefore, any unpredicted loss in revenue due to infringement undoubtedly will translate into budget reorganization and affect the future pipeline. Without a pipeline, we can't exist.

Anthony S. Serianni

Professor, University of Notre Dame
President and CEO, Omicron Biochemicals Inc.

How long have you been an ASBMB member?

For more than 15 years.

What do you study?

I am a structural glycobiologist. I am interested in developing new NMR-based tools to investigate the structures of simple and complex carbohydrates in solution. We aim to apply these new tools to improve our understanding of the chemical and biochemical properties of saccharides.

Why did you go into industry?

I co-founded Omicron Biochemicals Inc. in 1982, a few months before I accepted a faculty position at the University of Notre Dame. The company was started because, during my graduate studies at Michigan State University, we had developed new chemical methods to introduce stable isotopes site-specifically into saccharides that allowed access to a much greater array of labeled sugars than was accessible previously. This improved capability led to a number of requests for labeled compounds from the research community. As I was intent on pursuing an academic research career, I solved the problem by starting a small company during my postdoctoral stay at Cornell University to satisfy the needs of the research community, thinking at the time that this company would last perhaps three to five years. The company still is in operation 28 years later.

How do you feel ASBMB could best help scientists in industry?

By supporting basic discovery in the life sciences through which new applied technologies will be born. ASBMB should be a home for, and an advocate of, the discovery of core scientific knowledge. It should embrace fundamental inquiry as the agent that spurs new practical solutions. Industrial scientists need access to new, radical ideas and findings on a continuing basis to develop new ways to solve contemporary problems. Industrial scientists frequently do not have the time or money to pursue basic research — they largely are product-driven and thus depend on the academic community in great measure to supply the fundamental knowledge from which practical solutions can be developed.

Where do you see research in industry going in five to 10 years?

I know better than to predict the future. But, we are experiencing a time of significant change in both academic and industrial research. There is not enough space here to explain why this is occurring, but one factor is that the public is becoming more aware of the fact that, after more than 60 years of relatively generous federal research funding in the U.S., there still are major deficiencies in our ability to solve old and persistent problems, especially in the health-related areas. This partly may explain the shift in academic scientific research to solving practical, real-world problems. It is hard to say how long this trend will continue. In due course, however, a proper balance between basic and applied research needs to be struck, otherwise the discovery of fundamental, disruptive technologies that change the course of research, and our world, could be compromised. We need liberal minds thinking about lofty problems and people solving current problems with current technologies. Applied science without its basic research partner to support, stimulate and nourish it, is a formula for mediocrity and stagnation in the long term.

Has the downturn in the economy affected your job or your company?

As my main job is as a professor at the University of Notre Dame, the downturn has had a minimal impact, apart from perhaps reducing my pay raises in recent years! Federal research funding for academic research also has become more challenging in recent years. At Omicron, we largely have been immune to past economic downturns, which largely were limited to the U.S. This is because our clients are worldwide, and we are not dependent on U.S. clients for a large percentage of our sales. In the recent downturn, however, being global in nature, the situation may be different, especially if the downturn persists. Over the past 12-18 months, the effect has been small. What happens over the coming 12-18 months will depend on how well the global economy recovers, and how well governments, foundations and the private sector are willing or able to invest in chemical and biological research.

ASBMB's Industrial Revolution

BY NICK ZAGORSKI

Although a majority of the American Society for Biochemistry and Molecular Biology community hails from the world of academia, the society also has a rich and diverse set of members in the industry sector. In this special Science Focus feature, we profile just a few of these "industrious" individuals to showcase the scope of research being carried out in this arena, from the traditional (drug development) to the slightly more exotic (flavor enhancement).

Bruce Morimoto

Vice President for Drug Development
Allon Therapeutics Inc., Vancouver, BC
www.allontherapeutics.com

Not long ago, Bruce Morimoto was presenting research at a conference in which the speaker ahead of him described his 400-employee biotech firm as a "small company." When it was Morimoto's turn to speak, the V.P. for drug development at 20-member Allon wryly noted, "Well, if they're small, we must be micro."

Not that Morimoto would want it any other way. "Working at a really small company is much like running a lab in academia," he says. "There's a real sense of ownership, and everyone on the team is empowered to do whatever it takes to get the job done; that kind of environment fits my personality well."

At Allon, which specializes in combating neurodegenerative diseases, Morimoto's job entails moving drugs from discovery to market, which means he oversees a little bit of everything, from basic chemistry to manufacturing.

Morimoto never envisioned having such responsibilities when he was an undergraduate at the University of California, Los Angeles; in fact, back then, he believed his only options for pursuing his fondness of science were to become a physician or engineer.

But, his chemistry lab teaching assistant introduced him to undergraduate research, and his eyes opened up to a whole new world of possibilities.

He continued on the academic path, first getting his doctorate at UCLA (finishing the undergraduate project he started), then moving on to a postdoctoral fellowship with Daniel Koshland at the University of California, Berkeley and finally a faculty position at Purdue University.

Life seemed settled, but a few years into his professorship, Morimoto headed to the San Francisco Bay Area for a two-day consulting trip with a biotech company. Once he was done, the company surprised him by offering him a position.

While moving closer to the ocean was appealing to the native Angeleno, the thought of switching to industry was nerve-wracking; however, when Morimoto was given the chance to bring along his whole research group so his students could finish out their projects, he was sold. "That gave me a nice transition period to wind down my basic research and avoid any potential culture shock."

Morimoto began industry life working in drug discovery research, but over the years, as he gained experience and moved around, he began shifting more to the applied research and product development side of things, leaving his lab coat behind.

Because of the size of the company, Allon does not handle the development process in-house; rather, it is one of many biotech companies that have embraced the "virtual drug development" model, outsourcing the various stages of development to contract labs across North America and Europe while managing the overall flow.

Currently, the major company effort involves their lead drug davunetide, which has demonstrated efficacy for some forms of cognitive impairment. Allon is beginning clinical trials for an orphan disease known as progressive supranuclear palsy, or PSP.

"A major neurodegenerative disease like Alzheimer's is just too big for a small company like Allon," Morimoto

explains, "but we can use PSP, which is much rarer, as a proxy, because it displays pathology of entangled Tau protein, which happens to be one of the two major pathologies of Alzheimer's."

"Therefore, once we get data and approval of our drug for PSP, it opens up the market for us to partner with a larger company and move the drug to more prevalent diseases."

Morimoto notes that in this regard, Allon serves as an excellent bridge between basic academic research and major industry. "We have the freedom to pursue scientific avenues that big pharma typically overlook," he says, "which we can then translate to a form that appeals to large companies."

As for any concerns that a large biotech firm may end up buying out Allon to remove the middle man? "Well, that possibility comes with any small company," says Morimoto, "but if you look at recent news, with Pfizer buying Wyeth for example, there's no stability guarantee in a big company either, so we're not going to get too worried about it."

John Purcell

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MONSANTO

Ask John Purcell what his favorite part of working for a major global company like Monsanto is, and you get a surprising answer. It's not the access to top-notch scientific resources like the company's discovery labs and sequencing capabilities, or the incredible pool of talented scientists at the company, though he notes those are great.

For Purcell, currently the vice president of global technology development in Monsanto's vegetable seeds division, his favorite moments are the ones literally in the field, walking with farmers to see how Monsanto's crops are performing.

"I've met with farmers and walked in plots ranging from small vegetable gardens to giant corn fields on every continent except Antarctica." says Purcell, who's loved the outdoors since his childhood days. "And I've learned that farmers everywhere share the same fundamental desires; they want to produce a high quality product and use their resources as efficiently as possible."

It's a desire Purcell has been trying to help materialize for more than 20 years at Monsanto, during which time he has been involved in almost every stage of the agricultural biotechnology process, from discovery and development to marketing and monitoring.

And, it's a desire shared by his employer; Purcell recalls his first visit to Monsanto's headquarters in St. Louis back in 1989 when he was looking for a position and toured the company's then-new life sciences research center.

"From a biologist's perspective, it certainly looked like nirvana," Purcell notes, "but, at the same time, it showed me that this company had made a major investment to change the way we think about agriculture, namely how we can use biological tools to solve problems typically managed by chemical means."

Purcell began his work to find such tools in Monsanto's insect control division, which built on his existing research strengths; as a graduate student at the University of Massachusetts Amherst, he had studied insect biochemistry in Jack Nordin's lab, and later he did a postdoc at the U.S. Department of Agriculture, where he studied nematode biology and potential control mechanisms.

Over the next decade, he helped in the development of many breakthroughs, perhaps most notably the engineering of Bt crops, which are fortified with Bacillus thuringiensis toxins, designed to kill specific insect pests while remaining safe for humans and other beneficial species. Purcell then proceeded with stints in both the corn and cotton divisions, before settling in last year to his position in the vegetable seeds division.

His current efforts follow the same overall mission statement of helping farmers achieve the most efficient yields, but advances in technology have enabled him to expand his scope. Monsanto's approaches to crop biotech-

nology are from an agronomics perspective, primarily focusing on helping farmers control problems like weeds, pests, nutrients and water (Purcell notes the latter will be an especially significant concern in the coming years), but now they have begun to explore quality in addition to yield.

"In the vegetable division, we've started to use advanced breeding techniques and our increased knowledge of molecular markers to try to improve the appealing characteristics of our products, such as taste," he says. He cites the recent advancement of developing a sweet onion with a milder flavor, for use in salads and sandwiches, which can be grown in season in the U.S. and stored and sold all winter long.

Purcell notes that it is important to broaden the research effort because global institutes like Monsanto face challenges that smaller companies don't. "One issue with being well known is that people expect a lot out of you, and you have to continually earn their trust."

Fortunately, in that regard, Monsanto has one more advantage: Although taste may be varied, food is a constant. "There always will be strong demand for our products, because people always will need to eat."

Jay Slack

Principal Investigator, Molecular Biotechnology
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Givaudan

In 1999, groundbreaking research from Charles Zuker's lab group identified the first two genes encoding taste receptors — T1R and T2R. Although the discovery of these long-speculated taste receptors was notable for its intellectual advancements, it also opened up a whole new commercial research sector.

Jay Slack found himself in the right place at the right time to reap the benefits.

Slack was finishing up his postdoctoral work on the genetics of the immune system with John Monaco at the University of Cincinnati, and was considering a career move. "The department where I was working had just hired three new faculty members, so I witnessed firsthand the scientific pain associated with trying to get tenure in academia," he says. "So, I decided to maybe carve out my niche somewhere in industry."

Having done his graduate training in pharmacology (focusing on calcium signaling in the heart), Slack initially explored pharmaceutical options, but, a chance conversation with the head of the transgenic animal facility revealed that a local company called Givaudan Flavors was looking to build on Zuker's findings and establish an in-house taste receptor research group.

"I knew very little about the business of flavors, but working for Givaudan appealed to me because the science was interesting, and it was an emerging field," he notes. "But what really sold it for me was that my daughter was taking antibiotics and absolutely hated their taste, so I thought instead of working for 20 years and maybe getting a drug to market, I could try to make existing drugs taste better and help patients immediately."

And, although Slack and Givaudan have not quite reached that goal yet, they are making solid progress; just a few months ago, his group identified an inhibitor that blocks the bitter aftertaste associated with artificial sweeteners, which they can now use as a template to find future compounds that can make bitter pills a little easier to swallow.

But that work is just one aspect of Givaudan's goals, which makes Slack's work all the more enjoyable. "Our group is active in all the classical areas of taste, from sweet to savory, as well as in taste chemesthetics, which includes sensations such as pungency or cooling." As an example, he notes that his group recently has developed a high potency analog of menthol that produces a cooling sensation that lasts for more than two hours, so you can have that fresh breath feeling from breakfast to lunch.

In addition, he has the freedom to pursue basic research pursuits. One area he's particularly interested in involves the genetic variability of taste perception, at both the individual and population levels. He hopes to understand the mechanisms underlying the variation, whether it occurs in the receptor genes or in downstream pathways, and whether this variation influences behavior.

"Scientists have continued to identify more and more taste receptors," he says, "and they've even begun finding them in non-taste cells, places like the gut, nasal cavity and even the brain. It's possible that these internal taste receptors are linked to hormonal signals and mediate hunger or satiety."

One thing that won't be satiated any time soon, how-

ever, is the opportunities in the taste industry. Although this formerly orphan area of research has exploded over the past decade, it still remains a relatively new field with many unexplored avenues. "Taste research involves numerous fields of study, including organic chemistry, analytical chemistry, natural products, pharmacology and enzymology," Slack says, "so, it definitely provides numerous options for young scientists."

Patricia Weber

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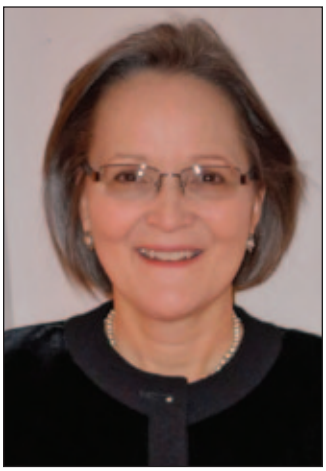

Re-entering the work force after taking an extended leave can be a challenging proposition. Such was the case with Patricia Weber, who took a break from a long and fruitful career in the industry sector in 2001 to spend more time with her family (though she remained active by doing scientific consulting and serving on the editorial boards of the Journal of Biological Chemistry and Faculty of 1000).

A few years later, with her younger son now ready for college, Weber felt an itch to resume her research pursuits. Considering her options, she decided to try something a little bold; teaming up with a former co-worker, Ray Salemme, she formed a new company called Imiplex, billed as offering nanosolutions for the 21st century.

"Nanotechnology is a relatively young field, especially protein-based nanotechnology, which is our focus," Weber notes. But, it's also a field that has tremendous growth potential in many disciplines (as noted in the June issue of ASBMB Today).

The idea behind Imiplex, which was started with the help of a pair of Phase 1 Small Business Innovation Research grants, is to design modular molecular protein nanostructures that can self-assemble into a variety of architectures. Weber and her team use highly stable proteins taken from thermophiles as the starting point, making them easier to manipulate and derivatize while retaining their native structures.

Once complete, Imiplex will sell both the individual modules of the platform and the technology required to assemble the supramolecular structures. Customers can purchase prefunctionalized modules or functionalize the components themselves, offering flexibility in how the technology is used.

Of course, Weber has her own visions and interests, and plans on making some specially designed products as well. "My personal interest is to help improve quality of life in developing countries, and thermostable nano-assemblies can be used outside of biological settings, so I see potential in areas like water purification."

This type of endeavor brings together all of Weber's previous biological expertise, built up over 25 years in academia and industry. It all began with her doctorate at the University of Arizona in 1979, followed by a postdoc with Nobel-winning crystallographer Thomas Steitz at Yale University. Afterwards, she joined Genex Corp. where she worked on one of the first teams involved in engineering industrial enzymes, and then took positions at DuPont and Schering-Plough, where she carried out structure-based drug design.

"I often point out to students that during most of my career, I remained at the bench," Weber says, "because I think that's an advantage of industry if you like the hands-on aspect of doing experiments."

Weber certainly will need to do a lot of hands-on work at Imiplex, a true start-up employing a handful of staff and collaborators. The company is currently in the proof-of-concept stage, trying to demonstrate that these modular platforms can self-assemble under a variety of conditions.

"The work has been progressing well," Weber notes, "so I'm hopeful that within the next few months, we will be ready for the next stage, when we can bring in venture funding to help us grow the company and increase production."

Weber always has been a positive person, and it's important to keep a positive attitude while nurturing a start-up; even with the combined knowledge and expertise Weber and Salemme bring to the operation, biotechnology is a tricky business that requires someone with a sense of adventure and fearlessness.

The right frame of mind helps too, which Weber definitely has. "My goals are to keep the company moving forward, create high technology jobs and eventually bring the benefits of nanotechnology to many people."

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Green Solutions to the Gulf Oil Spill

BY NANCY VAN PROOYEN

On April 20, an explosion in the Gulf of Mexico, off the coast of Louisiana, rocked the Deepwater Horizon oil rig. Colossal environmental damage caused by the oil spill has continued since this incident dominated headlines around the world. British Petroleum, the oil giant that operated the rig, has come under relentless public pressure and mounting criticism for its ineffectual handling of this ecological tragedy. Even now, hundreds of thousands of barrels of oil are spilling into the ocean each day and are carried inward by currents to delicate marshes and wetlands. The coastal wetlands already suffer from overpopulation, pollution and lingering effects from Hurricane Katrina. It will take years for us to realize the true impact of the spill on the surrounding ecosystems.

A worker cleans up oily waste on Elmer's Island, just west of Grand Isle, La., in May.

PHOTO CREDIT: U.S. COAST GUARD PETTY OFFICER 3RD CLASS PATRICK KELLEY.

Old Technology

Unfortunately, the United States coastline is no stranger to catastrophic oil spills. Although the BP spill is now the largest ever, the previous holder of this dubious distinction was the Exxon-Valdez spill of 1989. Currently, BP is implementing crude and outdated methods inherited from past spills for the offshore cleanup.

There are three conventional methods that are used widely to collect or clean up oil from water:

1. Water-oil separation: BP has employed hundreds of vessels, including some of the largest skimmers in the world, to skim the surface of the water and manually collect floating oil. Although this method works well in calm, isolated water, strong ocean currents largely render it ineffective. BP also uses centrifuges to separate oil from the gathered seawater. However, these centrifuges have varying efficiency in removing the oil, making this a rather costly procedure in terms of time, effort and money.

2. Controlled burns: In a more extreme attempt to remove the oil, BP is burning large areas of oil on the sea surface. This releases greenhouse gases such as sulfur dioxide, nitrous oxides and methane into the air. The thick black clouds are then carried into the lungs of workers and residents in the coastal communities. People with asthma or serious heart problems are particularly susceptible to the toxic burn-off. Tragically, large numbers of marine wildlife that live near the water surface often are corralled into the areas demarcated for combustion, and are, quite literally, burned alive.

3. Chemical dispersants: The third main method BP is using to clean up oil involves sprinkling large amounts of chemical dispersants by boat, aircraft and workers on the shore. Dispersants cause the oil to break up into smaller

droplets, which become miscible in water. However, these dispersants may result in more ecological harm than good. The chemicals contain nonbiodegradable toxins that can kill fish and migrate great distances. Dispersants also are blamed for the massive oil plumes several hundreds of feet underwater, harmful to all aquatic life, especially fish larvae and filter feeders. Moreover, because of the large volume of oil that has been spilled, the amount of dispersant required and the amount of oil dispersed simply suppresses the problem, rather than solving it.

Bioremediation

The most high-profile and promising new technology available to clean up the oil spill is bioremediation, which potentially could remove the oil in a harmless manner, from even the most intractable and messy environments, where it has sunk into beaches and mangrove swamps, and even in underwater oil plumes. Some naturally occurring microbes that process crude oil are known to exist in the ocean. However, the amount of oil gushing into the ocean as a result of the BP oil spill is far more than the natural habitat can handle. Thus, many companies have turned to bioremediation, which is any process that utilizes bacteria, fungi, green plants or enzymes to naturally remove contaminants.

Biostimulation

Potential bioremediation applications for an oil spill mainly fall into two categories: biostimulation and biofermentation. Biostimulation involves modifying the environment to stimulate the indigenous bacteria capable of bioremediation. Many biotech companies are pursuing novel ways of boosting the natural flora to help remove the excess oil. One product accidently discovered by National Aeronautics and Space Administration scientists is called "Petroleum Remediation Product," now distributed by the Pittsburgh-based Universal Remediation Inc. PRP is a powder that contains thousands of beeswax microspheres with hollow centers. The 0.25- to 0.65-µm spheres are impervious to water, but oil is absorbed in their centers as they float on the water surface. The capsules can absorb up to 20 times their weight in oil. The beeswax attracts naturally occurring microorganisms, which eat the wax and oil, safely biodegrading the petroleum and PRP. After the PRP and oil are consumed, the expanded microbe population dies off. Thus, the oil is removed, the bacterial bloom is controlled, and the natural environment is restored.

PRP products also can contain Pseudomonas bacteria that eat hydrocarbons found in crude oil. This combination of introducing oil-eating bacteria and providing a food source for native bacteria effectively can speed the rate of oil decomposition. PRP is extremely useful in ecologically-sensitive regions, such as wetlands, marshes, nesting areas and grasslands, where conventional methods are impossible.

Biofermentation

Biofermentation uses genetically engineered microbes that metabolize oil at a rapid rate, which can dramatically speed up the rate of oil cleanup. However, often when these designer bacteria are introduced into diverse and hostile environments, they are outcompeted by native bacteria. Evolugate, a bioremediation company in Gainesville, Fla., is working to increase the oil-consuming efficiency of naturally occurring bacteria through adaptive pressure. Scientists at Evolugate isolate natural oil-consuming bacteria found in the Gulf and place selective pressure on the microbes to improve their oil-eating abilities. Each time the bacteria divide, their genomes mutate. Providing oil as their only food source creates a strong selective pressure that enhances bacterial evolution. And, because the designer bacteria are derived from native flora, they have a better chance of surviving when reintroduced into the Gulf.

The superbacteria are dispersed in large quantities, using biofermentors to build up dense growths for immediate dispersal into the sea water. This way, the targeted delivery of relatively high concentrations of oil-eating bacteria near the biggest oil spills prevents them from being outcompeted for oxygen and nutrients by the local flora. These large biofermentors also can be mounted on boats for a ready supply of healthy oil-digesting bacteria.

As the monetary value of the oil collected by centrifugation is miniscule in comparison to the money being spent containing the spill, the main focus of the cleanup effort should now be to rapidly and efficiently scrub the oil from the sea surface, the underground oil plumes and the coastlines where the oil has washed ashore. To effectively clean up a disaster of this magnitude, we need to use a multitude of techniques, and green remedies that use bioremediation should be part of the solution.

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From Aha! to Entrepreneur

BY LESLIE W. CHINN

For Stephen Cary, the most important realization of his graduate school career came when it nearly was all over. Late one night, he was working on his dissertation when he had his "aha!" moment.

Cary's graduate work, conducted in Michael Marletta's lab at the University of California, Berkeley, had focused on molecules that modulate nitric oxide signaling. An example is hemoglobin, which binds oxygen and carbon monoxide, as well as NO, through its heme group. Several decades ago, a number of government institutes and companies had attempted to develop hemoglobin-based oxygen carriers, or HBOCs, as substitutes for blood and for other therapeutic purposes. These attempts had failed for a variety of reasons, including toxicities that were likely related to the HBOCs' interference with physiological NO signaling.

But Cary and his lab mates had been working on a novel oxygen-binding protein family — one that did not scavenge nitric oxide. This, Cary realized that night, was a technological breakthrough. "Our new protein family could be the answer for millions of patients that could benefit from novel therapeutic oxygen carriers," Cary recalls.

The Lone Entrepreneur

Cary gathered his thoughts and presented them to Marletta and two postdoctoral fellows in Marletta's lab — Elizabeth Boon and Jonathan Winger. The four ultimately would become the founders of Omniox, a company created to commercialize novel oxygen delivery technology based on their research at Berkeley. "Though we were four co-inventors, I was the lone entrepreneur," says Cary. So, he shifted his focus from science to the intricacies of starting a business.

With the support from UC Berkeley's Office of Technology Licensing and Stanford Research Institute International (whose PharmaSTART program helps academic researchers advance promising compounds past the discovery phase), Cary began to gain an understanding of, as he calls it, the "landscape of drug development." The most important step, he realized, is to define one's intellectual property, or IP. "In biotech, you live and die by the strengths of your IP agreement," said Cary.

Cary selected an attorney to handle the IP aspects of Omniox, and he also chose a corporate attorney to assist with the technical aspects of starting a business. Both attorneys accepted deferred payment, receiving their fees once Omniox had raised enough venture funding. It was important to Cary that both attorneys were the best in their fields, as this gave credibility and a sense of permanence to Cary's fledgling company.

The Valley of Death

Omniox was now in a transitional phase, during which, in general, the financial support is weakest. Up to that point, their studies had been funded by traditional research grants, but the science was not yet mature enough to convince venture capitalists to provide commercial funding. This tenuous period is often referred to as the "Valley of Death" for young companies.

However, Omniox was fortunate. The company received a two-year Rogers Family Foundation "Bridging the Gap" award for translational research, allowing research to continue during the year in which Cary was meeting with lawyers and recruiting scientists to Omniox's advisory board.

A number of other factors also worked in Omniox's favor. One, ironically, was the economic downturn: biotechnology companies, young and old, were struggling to survive, sometimes without success. Omniox was able to acquire used lab equipment at bargain basement prices — a million dollars' worth purchased for $25,000, Cary estimates. Another helpful factor was Omniox's location in the San Francisco Bay Area, where prominent law firms were more willing to take chances on biotech start-ups. What's more, Omniox was able to take advantage of a new institute at the University of California called QB3.

Stephen Cary and Jamie Romero of Omniox in the QB3 Garage.
CREDIT: ROBIN HINDERY, UCSF.

The Incubator

The California Institute for Quantitative Biosciences (QB3) is a consortium formed by three UC campuses: Berkeley, San Francisco and Santa Cruz. One of its goals is to "speed the movement of innovation from the laboratory into peoples' daily lives," according to the 2001 Governor's Budget Summary, in which the foundation of QB3 was established.

In the institute's early days, Associate Director Douglas Crawford and Director Regis Kelly sifted through case studies of UC faculty members, postdocs and graduate students who were interested in starting businesses. But, "the cost of a start-up is prohibitive," explains Crawford, and all they found was frustration. Crawford and Kelly wondered how they could leverage UC resources to help scientist-entrepreneurs, with the ultimate goal of increasing societal impact. Soon, the QB3 Incubator Network was born.

The Incubator Network rents small office and lab spaces – in some cases, as little as 120 square feet — to young companies, thereby minimizing the cash demands on start-ups. Most of the spaces, called "Garages" in recognition of the innovators such as Bill Hewlett, Dave Packard and Steve Jobs who founded companies out of their own garages, are at the UCSF Mission Bay campus; a smaller amount of space became available at UC Berkeley in May of this year.

QB3 also provides funding for work that is, as Crawford says, "too applied for the National Institutes of Health," but not developed enough for venture capitalists – for example, the validation work that follows up on promising compounds generated by high-throughput screening experiments. "The NIH will fund screening for therapeutic hits," notes Crawford, "but from there to clinical [trials] is a gap of $20-40 million" for further work on chemistry, toxicity and other research that might be considered less scientifically interesting. Through grants such as the Rogers award, QB3 assists companies like Omniox in their early years.

Companies housed in the QB3 Garages also have access to what Crawford calls the "intellectual vitality at the university." There are countless seminars on both science and entrepreneurship, and QB3 provides a valuable shared experience between nascent companies.

Casting a Wide Net

As one might expect, there's a huge demand for the resources available through QB3. Crawford estimates he receives between two and four inquiries a week from companies (the majority of which have some UC connection) who want to join the network. Currently, there still is space available in the QB3 Garages, but competition is fierce.

Initially, when the UCSF Garage first opened in 2006, QB3 performed rigorous reviews to evaluate the scientific and commercial merits of each start-up. Since then, they've come to the conclusion that there's a better way of doing it. "We really want to have a very wide net on the science," says Crawford. Instead of focusing on a specific scientific area or therapeutic need, they look for people who are passionate and have demonstrated the initiative to guide a start-up through the challenges of the so-called Valley of Death. "Biotechs are where the really innovative stuff happens," Crawford explains. They adapt, depending on how the science goes and what the market wants. The best start-ups aren't sidetracked by failure. Instead, they find success on another path, which is why Crawford thinks passionate people make exceptional entrepreneurs.

This strategy seems to be working: of the six companies first housed in the UCSF Garage, four secured venture funding and a fifth was acquired by Affymetrix. There currently are 25 companies in the Incubator Network, and Crawford expects to expand to 30 in the next year. As the economy recovers, other opportunities for biotech start-ups are bound to increase as well. Crawford's advice for budding entrepreneurs? Just do it. "It will be one of the most stimulating things you'll ever do," he says.

Cary might agree: his company is halfway through a two-year term in the UCSF garage. "QB3 has supported Omniox from its very early stages," he says. His company recently received half a million dollars through a Bridge Award from a Small Business Innovation Research Program financed by the National Cancer Institute. Omniox's funding finally is falling into place; at the same time, its science is moving forward constantly — proof that, as Cary says, "you don't have to be at a university to do good science."

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For more information:

- Small Business Innovation Research Program, National Cancer Institute: sbir.cancer.gov
- QB3 Incubator Network: qb3.org/innovation-toolkit
- Omniox Inc.: http://tinyurl.com/24ku6hd
- Article: "Accelerating the Commercialization of University Innovation:" http://tinyurl.com/ydvl6cd
- Center for Integration of Medicine and Innovative Technology: http://www.cimit.org

Partners in Crime

UCSF-Genentech partnership offers a brave new world of industry-academia interactions

BY NICK ZAGORSKI

This past January, the University of California, San Francisco and Genentech Inc. reached an agreement on a joint drug development program for neurodegenerative disorders. On the face of it, the deal, potential worth $13 million plus future royalties, doesn't seem too splashy. After all, business ventures between industry and academia are a common occurrence, and Genentech and UCSF have had a master agreement for scientific exchange in place since 2005.

However, this modest proposal may be a turning point in how industry and academia conduct their business.

"What makes this deal unusual is that it is a true partnership where scientists at UCSF and Genentech are in continual communication and make joint project decisions," notes American Society for Biochemistry and Molecular Biology member James Wells, professor and chairman of the department of pharmaceutical chemistry at UCSF and director of their Small Molecule Discovery Center, as well as the recipient of the 2010 ASBMB-Merck Award.

Wells explains that pharmaceutical companies typically have followed one of two classic paths when working with universities. The first involves a company recognizing an asset and licensing it from a university; the school benefits from licensing fees, but, at the same time, the company drives the product forward and communication between the parties, outside of some occasional consulting, is minimal. The second path occurs when a university or lab has a particular skill or technology which a company finds useful, so, they pay a straight fee for the service.

In this new UCSF-Genentech agreement, scientists from both sides will work directly with each other on project teams; and, while the research will focus primarily on drug development, there also will be a strong push to answer intellectual questions and to publish papers in top journals.

So, in addition to some standard benefits — UCSF receives funding and potential royalties while Genentech gets access to expertise and technology that they don't have to develop — staff members on both sides become enriched.

"Since the work is done under confidentiality, which puts some restraints on publication, we didn't involve graduate students or postdocs because they rely on getting papers out," says Michelle Arkin, adjunct assistant professor at UCSF and associate director of biology for the SMDC. "But, staff scientists on our side and junior scientists at Genentech are still learning and training, and this is a great educational experience if they want to work on the other side in the future."

"It's a tremendous step forward; it really resembles a deal that two biotech companies would make," Wells adds. "And, to think, just 12 years ago, none of this probably could have happened."

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Indeed, 1998 sometimes seems like an eternity to Wells, who, at that time, had just left Genentech's protein engineering department to head his own biotech company, Sunesis, while also serving as an adjunct faculty member at UCSF. And, although Wells was involved in both industry and university pies, back then, the two existed along clearly demarcated lines.

But, some interesting trends occurred on both sides over the next few years that would blur that clear distinction.

On the pharmaceutical end, it was becoming apparent that their longstanding business model was not working effectively. As a result, there were many layoffs, which not only increased a demand for external help, but also seemed to hinder the company's innovative nature.

"With slowing business, they could no longer afford to be adventurous in drug screening, and now have become pretty mechanical, limiting their drug development efforts mainly to highly validated mechanisms and targets," Wells says.

Adds Arkin, "In speaking with friends in the business, most pharmaceutical research today seems to center around 50 targets; I think researchers at UCSF alone are working on more than that."

This strong target validation effort at UCSF represents the second trend that brought industry and academia closer; namely, that academics started to realize the value of small molecules or probes for basic research.

This understanding nucleated from a National Institutes of Health initiative in 2005, as part of their roadmap

to speed up drug development, by seeding molecular screening centers in a handful of academic institutes across the country. Soon afterwards, other top universities like Harvard, the Massachusetts Institute of Technology and UCSF saw the value of screening and set up their own centers — often with former industry people in charge.

"We've been seeing a general shift where academics are becoming more and more translational," notes Morgan Sheng, the vice-president of Genentech's neuroscience division and actively involved in the UCSF partnership, "through a combination of economic changes, NIH initiatives and the accumulation of all the basic discoveries that have been made."

"Academia definitely is getting savvier in drug screening and target validation," agrees Wells, citing the SMDC as an example; not only do they have robust screening capabilities, but they also have strong biology and chemistry groups (headed by Arkin and Adam Renslo, respectively) that follow up on the screening — analyzing structures and mechanisms to get a more thorough idea of how these compounds work.

And, that caught the eye of Genentech.

• • •

The courtship began some two years ago when Wells gave a talk at Genentech. Afterwards, he spoke with numerous Genentech scientists and talked about some projects the SMDC was interested in, not thinking much of it.

Then, a few weeks later, Wells received a call from Genentech. "They said that our interests in neuroscience struck a chord with them, and they wanted to have some people come in and discuss a possible collaboration."

"Generally, you don't get into bed with someone you don't know," Sheng says. "But in this case, we knew Jim quite well; he worked at Genentech and still knows people there and has a fondness for the company. In addition, he's local, making the partnership easier to foster."

"Now, it's not all backslapping," Sheng continues. "Wells also is a great scientist with strong industry experience and a proven record in finding small molecule drugs. Together, everything converged at just the right historical, geographical and situational nexus to make a bold plan possible."

It also was helpful that the protagonists involved didn't have a language barrier; besides Wells' extensive industry background, Sheng only came to Genentech two years ago, following a long tenure at Harvard Medical School and MIT.

UCSF researchers Michelle Arkin and Jim Wells will provide their expertise on small molecule screening and medicinal chemistry in a new partnership with Genentech.

"The mobility between academia and industry has been steadily increasing, which is why I think we'll see more of this interplay in the future," Sheng says. "If you're a former academic at a management position in industry you're prone to collaborate with academics, since you're familiar with them."

"And, that's a positive development, because the two groups need each other," Sheng continues. "Even though companies spend billions on R&D, that only contributes to a small percentage of total scientific discoveries. Working closely with academia is vital to help drive science forward."

Assuming, of course, that this endeavor doesn't fail, which always looms as a possibility. "It's kind of like the early days of flying machines," Arkin says. "Eventually, one design is going to revolutionize the field, but, before that, many others failed to get off the ground."

However, things are proceeding well for this partnership, and Wells notes that both sides expressed great excitement at the last project meeting over the progress that had been made, so, perhaps UCSF and Genentech could be the Orville and Wilbur Wright of scientific collaboration.

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

This article describes one of the themes that is part of the ASBMB annual meeting, which will be held April 9-13, 2011, in Washington, D.C.

Signaling from the Plasma Membrane to the Nucleus

BY CHARLES E. SAMUEL AND KAREN L. O'MALLEY

Complex signaling networks govern the function of all cells, allowing them to respond to diverse environmental stimuli and carry out specific cellular tasks. Understanding the molecular mechanisms underlying the vast array of signaling pathways continues to be one of the most intensely studied areas of cell biology. The 2011 annual meeting theme, "Signal Transduction from the Plasma Membrane to the Nucleus," will explore exciting progress in four areas that span disciplines from microbiology and immunology to neurobiology and physiology.

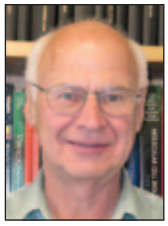
Janus Kinase-STAT Transcription Factors

On Sunday, April 10, the first session of the theme, titled "STATus of JAKs and STATs in JAK/STAT Signaling," will examine three aspects of the Janus kinase-STAT transcription factor signaling paradigm. Originally identified as downstream mediators of interferon signaling, four JAKs and seven STATS are utilized in overlapping combinations in signaling by the large family of cytokine receptors.

Sandra Pellegrini (Institut Pasteur) will describe signaling responses elicited by binding of α and β interferons to their cognate receptor. Curt M. Horvath (Northwestern University) will discuss mechanisms by which negative-stranded RNA viruses target STAT proteins and disrupt their signaling activities. STAT factors also play important roles in cell growth and differentiation. John J. O'Shea (National Institutes of Health) will provide insights into T cell differentiation using genome-wide analysis of epigenetic changes and STAT transcription factor binding. As a prelude to this theme, on Saturday, April 9, George Stark, a co-discoverer of the JAK-STAT signaling pathway, will give the Herbert Tabor/Journal of Biological Chemistry Lectureship.

Intracellular Signaling

Although dogma holds that cells respond to extracellular signals via activation of cell surface proteins such as growth factor receptor tyrosine kinases (RTKs) and G protein-coupled receptors, emerging evidence suggests that many of these same channels and receptors function from intracellular locations as well. On April 11, some of these possibilities will be explored during the second signal transduction session, titled "Signaling from New and 'Arrestin' Sites."


Samuel


O'Malley

Rosalind A. Segal (Harvard Medical School and Dana-Farber Cancer Institute) will describe how RTKs such as Trk receptors are internalized along with bound ligands to form "signaling endosomes." These can serve as retrograde carriers that traffic back to the nucleus, affecting transcription and neuronal survival. Marc G. Caron (Duke University Medical Center) will then discuss signaling pathways that are activated by β arrestin proteins binding to dopamine receptors and how β arrestin signals differ from those mediated by G proteins. Finally, Karen L. O'Malley (Washington University Medical School) will present data showing that some G protein-coupled receptors primarily are expressed on intracellular membranes, including the nucleus, where they can influence unique cellular responses.

Innate Immunity

The third session of the signaling theme, on April 12, is titled "Sensors and Adaptors in Innate Immunity." Two of the classes of pattern recognition receptors that initiate signaling cascades in response to pathogen infection are Toll-like receptors (TLRs) and NOD (nucleotide-binding oligomerization domain)-like receptors (NLRs). The TLRs and NLRs act through adaptor proteins to trigger the innate immune response and inflammation.

Luke A. J. O'Neill (Trinity College) will describe recent advances in understanding signaling by TLRs, and Jenny P.-Y. Ting (University of North Carolina, Chapel Hill) will focus on the NLRs as regulators of innate immunity and inflammation. Finally, the protein kinase PKR is an RNA-regulated enzyme involved in the action and induction of interferon.

Charles E. Samuel (University of California, Santa Barbara) will discuss the mechanism by which PKR functions as an RNA sensor in innate antiviral immunity.

Circadian Rhythms

Almost all organisms possess an internal biological clock that coordinates physiology and behavior with the outside world. The fourth session, on Wednesday, April 13, titled "Synchronizing the Synchronizers," will explore how circadian rhythms are generated, how they are linked intimately with sleep and how they are maintained by complex autoregulatory signals.

Michael Hastings (MRC Laboratory of Molecular Biology) will discuss how circadian pacemaker cells are synchronized. Michael N. Nitabach (Yale University School of Medicine) will use Drosophila as a model system to explore the neural circuitry underlying circadian rhythms. And, finally, Ying-Hui Fu (University of California, San Francisco) will describe exciting new studies that molecularly dissect human sleep variants.

To stimulate new ideas and present cutting-edge research, each symposium will include three short talks selected from submitted abstracts. Young investigators (faculty, postdoctoral fellows and graduate students) are encouraged to submit an abstract for possible inclusion in one of the selected symposia.

Given the rapid pace at which each of these areas is advancing, the 2011 signal transduction theme promises to be very exciting and informative.

Charles E. Samuel (samuel@lifesci.ucsb.edu) is the C.A. Storke II professor of molecular, cellular and developmental biology as well as a professor of biomedical sciences and engineering at the University of California, Santa Barbara. Karen L. O'Malley (omalleyk@pcg.wustl.edu) is a professor of anatomy and neurobiology at the Washington University Medical School.

Signal Transduction from the Plasma Membrane to the Nucleus

Session: STATus of JAKs and STATs in JAK/STAT Signaling

Parameters Governing Binding and Signaling Responses of Interferons α and β, *Sandra Pellegrini, Institut Pasteur*

Regulation of JAK-STAT Signaling by RNA Viruses, *Curt M. Horvath, Northwestern University*

Insights into T Cell Differentiation using Genome-wide Analysis of Epigenetic Changes and Transcription Factor Binding, *John J. O'Shea, National Institutes of Health*

Session: Signaling from New and "Arrestin" Sites

Retrograde Response Genes and Neuronal Survival, *Rosalind A. Segal, Harvard Medical School and Dana-Farber Cancer Institute*

β Arrestin-dependent Signaling of Dopamine D2 Receptor in the CNS: Opportunities for Functionally Selective Therapeutic Approaches? *Marc G. Caron, Duke University Medical Center*

Signaling from the Inside: Functions of Intracellular Metabotropic Glutamate Receptor, mGluR5, *Karen L. O'Malley, Washington University Medical School*

Session: Sensors and Adapters in Innate Immunity

Signaling by Toll-like Receptors and Nalp3 in Inflammation and Innate Immunity, *Luke A. J. O'Neill, Trinity College*

The Nucleotide-binding Domain-, Leucine-rich Repeat-containing Protein (NLR) Family of Intracellular Sensors, *Jenny P.-Y. Ting, University of North Carolina, Chapel Hill*

Protein Kinase PKR as an RNA Sensor in Innate Immunity, *Charles E. Samuel, University of California, Santa Barbara*

Session: Synchronizing the Synchronizers

The Secrets of Synchronizing Circadian Pacemaker Cells, *Michael Hastings, MRC Laboratory of Molecular Biology*

Genetic Dissection of Neural Circuit Physiology, *Michael N. Nitabach, Yale University School of Medicine*

Molecular Genetics of Human Sleep Variants, *Ying-Hui Fu, University of California, San Francisco*

This article describes one of the themes that is part of the ASBMB annual meeting, which will be held April 9-13, 2011, in Washington, D.C.

Communications of the Metabolic State

BY BARBARA E. CORKEY AND MARC PRENTKI

Metabolic regulation represents the front line in the control of intermediary metabolism as well as transcriptional and protein synthetic adaptation to changes in the cellular environment. The increased sensitivity of analytical tools and recent advances in molecular genetics and imaging have fostered greater understanding of interconnections between metabolic networks and the diverse molecular mechanisms involved in cellular functions. As a result, "classical" intermediary metabolism has been found to be involved directly in signaling functions as diverse as apoptosis, cell growth and transcriptional control, which impact not only the single cell, but all basic physiological processes.

The 2011 American Society for Biochemistry and Molecular Biology annual meeting "Metabolism and Disease" theme consists of four symposia that focus attention on novel roles of mitochondria in diseases, metabolic communication among various organs, mechanisms of metabolic signal transduction within the cell and the rekindled awareness of the important role of metabolism in cancer.

Mitochondrial Dysfunction

The first symposium, titled "Mitochondrial Function and Disease," will look at diseases directly related to mitochondrial dysfunction. Carlos Moraes (University of Miami) will discuss his experience with patients affected by mitochondrial oxidative phosphorylation disorders. He also will consider the various options that may improve respiration and ATP production in these patients' cells.

Next, Siegfried Hekimi (McGill University) will present research that challenges our current thinking about the role of increased mitochondrial ROS production in aging.

And, finally, Orian Shirihai (Boston University) will discuss mitochondrial fission, fusion and networking and consider the heterogeneity of mitochondria in terms of structure and function and association with a number of diseases, including ischemia-reperfusion and nutrient-induced pancreatic β-cell dysfunction in diabetes.

Information Transmission

The second symposium, titled "Metabolic Communication," will focus on mechanisms by which metabolic information is transmitted from one organ to another via the extracellular thiol redox state, clock proteins and free fatty acids. Dean P. Jones (Emory University) will discuss the connection between the redox potential of plasma cysteine/cystine and the risk factors for cardiovascular disease, namely age, smoking, type 2 diabetes, obesity and alcohol abuse. Data show that the proinflammatory effects of the oxidized plasma redox state are due to a mitochondrial signaling pathway that is mediated through redox control of downstream effector proteins.


Corkey


Prentki

Molly S. Bray (University of Alabama at Birmingham) will then explain how biological rhythms profoundly influence energy homeostasis and also how carbohydrate or fat consumption at a given time of the day may influence health.

Lastly, Richard Bergman (University of Southern California) will talk about how free fatty acids, and the pattern of free fatty acid release, regulates glucose homeostasis. He also will examine the possible consequences of free fatty acid release on the sympathetic nervous system in the obese or insulin-resistant state.

Signal Transduction

The third symposium, titled "Metabolic Signal Transduction," will concentrate on mechanisms by which metabolic changes within the cell are translated into signals that modulate functions, from secretion to metabolism to transcriptional regulation. Marc Prentki (University of Montreal) will discuss the biochemical basis of β-cell signaling in response to glucose, amino acids and fatty acids, as well as β-cell nutrient detoxification and the emerging role of glycerolipid/fatty acid cycling in these processes.

Next, Barbara E. Corkey (Boston University School of Medicine) will compare different fuel-induced signals in fat and β-cells with a focus on how the same signals subserve different cell-specific but complementary functions.

Johan Auwerx (École Polytechnique Fédérale de Lausanne) will then describe how protein acetylation-deacetylation reactions affect wide-ranging physiological

processes, with a particular focus on the NAD dependent deacetylase SIRT-1. He will develop the concept that boosting cellular levels of NAD^+ may ameliorate factors associated with the metabolic syndrome.

Cancer

The fourth and final symposium, "Metabolism and Cancer," will look at how altered metabolism can promote oncogenic pathways and tumor cell survival. Craig B. Thompson (University of Pennsylvania) will review his work on the role of glycolytic and Krebs cycle enzymes in controlling the production of metabolites with oncogenic or tumor suppression capabilities.

Next, Tak W. Mak (University of Toronto) will discuss how metabolic stress can influence various apoptotic pathways and cancer cell survival.

And, finally, Karen H. Vousden (Beatson Institute for Cancer Research in Glasgow) will discuss insights into the signaling and metabolic pathways involved in tumor cell invasion and the role played by p53 in metastasis.

Workshop

We also have scheduled a workshop, titled "New Tools to Study Mitochondrial Function" and chaired by Orian Shirihai (Boston University). Speakers at this event will demonstrate new ways to monitor bioenergetics, mitochondrial function and ROS and mitochondrial dynamics (fusion, fission and morphology) in vivo.

Barbara E. Corkey (bcorkey@bu.edu) is director of the Obesity Research Center and a professor of medicine and biochemistry at the Boston University School of Medicine. Marc Prentki (marc.prentki@umontreal.ca) is a professor of nutrition and biochemistry and Canada research chair in diabetes and metabolism at the University of Montreal.

Metabolism and Disease

Session: Mitochondrial Function and Disease

Beneficial Effects of Increased Mitochondrial Biogenesis in Aging, *Carlos Moraes, University of Miami Miller School of Medicine*

Revisiting the Role of Mitochondrial ROS in Aging and Age-dependent Diseases Transfer Proteins, *Siegfried Hekimi, McGill University*

Metabolic Regulation of Mitochondrial Dynamics, *Orian Shirihai, Boston University*

Session: Metabolic Communication

Redox Analysis and Metabolic State, *Dean P. Jones, Emory University*

The Role of Cell-specific Clocks in Metabolism and Disease, *Molly S. Bray, University of Alabama at Birmingham*

Abdominal Obesity, Fatty Acids and Insulin Resistance, *Richard Bergman, University of Southern California Keck School of Medicine*

Session: Metabolic Signal Transduction

Lipid Cycling as a Signal in β-cells, *Marc Prentki, University of Montreal*

Signaling by ROS in β-Cells and Fat Cells, *Barbara E. Corkey, Boston University School of Medicine*

NAD and Cofactors in the Control of Metabolism, *Johan Auwerx, École Polytechnique Fédérale de Lausanne*

Session: Metabolism and Cancer

Metabolic Mutations that Cause Cancer, *Craig B. Thompson, University of Pennsylvania*

Regulation of Tumor Cell Survival under Metabolic Stress, *Tak W. Mak, University of Toronto*

Role of p53 in Metabolism and Invasion, *Karen H. Vousden, Beatson Institute for Cancer Research*

Workshop: New Tools to Study Mitochondrial Function

Chair: *Orian Shirihai, Boston University*

This article describes one of the themes that is part of the ASBMB annual meeting, which will be held April 9-13, 2011, in Washington, D.C.

Lipids Take Center Stage

BY VYTAS A. BANKAITIS AND TERESA M. DUNN

Distinct chemical families of lipids endow divergent biophysical properties to the membranes in which they reside. Thus, lipid distribution between various intracellular organelles must be properly regulated to insure appropriate membrane function. Many different classes of lipids also are known to serve as metabolic precursors to various second messengers or as signaling molecules in their own right. Because lipid signaling pathways interface with highly interdigitated networks of biological processes, diverse territories of intracellular lipid metabolism and trafficking need to be tightly coordinated. The 2011 American Society for Biochemistry and Molecular Biology annual meeting "Lipid and Membrane Metabolism" theme focuses on new progress regarding how the metabolism, trafficking, organization and biological functions of major lipid classes are coordinated. The theme consists of the following four sessions.

Phosphoinositides

Phosphoinositides are essential signaling lipids that modulate a diverse set of cellular processes. Phosphoinositide metabolism is subject to exquisite spatial and temporal regulation both at the level of synthesis (by lipid kinases) and degradation (by phospholipases and phosphatases). Yet, many aspects of phosphoinositide function remain unclear.

In the "Current Topics in Phosphoinositide Biology and Signaling" session, Christopher S. Burd (University of Pennsylvania School of Medicine) will discuss his new findings on the roles of phosphatidylinositol-4-phosphate (PtdIns-4-P) in Golgi retrograde trafficking pathways. Julie Brill (The Hospital for Sick Children) will describe her work on physiological functions of PtdIns-4-P production in multicellular organisms using Drosophila as an experimental model.

And, Vytas A. Bankaitis (University of North Carolina School of Medicine) will round out the session by discussing the mechanisms by which PtdIns-transfer proteins act as coincidence detectors for the coupling of disparate pathways from lipid metabolism to production of functionally privileged phosphoinositide signaling pools.

Sphingolipids

Sphingolipids facilitate the formation of membrane microdomains and act as signaling molecules that regulate a myriad of cellular processes. The "Sphingolipid Metabolism and Biological Regulation" session will feature newly described sphingolipid regulatory mechanisms.


Bankaitis


Dunn

Julie D. Saba (Children's Hospital Oakland Research Institute) will discuss her recent work on the role of sphingosine-1-phosphate lyase in DNA repair as an example of the underinvestigated problem of lipid signaling in the nucleus. The committed enzyme of sphingolipid synthesis, SPT, is also expected to be highly regulated, but the mechanisms are elusive. Jonathan S. Weissman (University of California, San Francisco) will present new insights into sphingolipid homeostasis, the role of the ORM/ORMDL family of proteins as regulators of that process and how this regulatory circuit provides new paradigms for etiologies of asthma. Finally, Teresa M. Dunn (Uniformed Services University of the Health Sciences) will describe novel stimulatory subunits of SPT that modulate acyl-CoA substrate selectivity and may hold the key to a molecular basis for the HSAN1 inherited peripheral neuropathy.

Phospholipases D

Phospholipases D (PLD) hydrolyze phosphatidylcholine (PtdCho) to phosphatidic acid (PtdOH) and choline. The potent signaling functions attributed to PtdOH, when coupled with the regulation of PLD activity by phosphoinositides, small GTPases and protein kinases, identifies these enzymes as potentially central integrators of phospholipid metabolism and signaling. Yet, the biological activities of these enzymes have been frustratingly difficult to discern — particularly in mammalian cells.

Research into this problem will be on display in the "Phospholipase D and Phosphatidic Acid Signaling" session. H. Alex Brown (Vanderbilt University School of Medicine) will describe the characterization of recently developed small molecule inhibitors of mammalian PLDs, the cellular effects associated with acute PLD inactivation and new mass spectrometry-based techniques for molecular tracking of PtdOH.

The presentations by Aaron Neiman (Stony Brook University) and Christopher J. R. Loewen (University of British Columbia) will focus on signaling roles for PtdOH. Neiman will discuss the regulation of PLD1 and the roles of PtdOH in developmentally regulated re-orientation of membrane trafficking and vesicle fusion during sporulation in yeast. Loewen will describe evidence that PtdOH plays a previously unappreciated role as a membrane pH sensor.

Neutral Lipids

The recent linkage of excessive storage of triacylglycerols (TAGs) to obesity and type 2 diabetes has spurred studies that elevate lipid droplets (LDs), major TAG storage depots, to the status of an intracellular organelle.

In the "Biology of Neutral Lipid Metabolism and Trafficking" session, Sepp D. Kohlwein (University of Graz) will discuss recent evidence of an unexpected link between fatty acid and triacylglycerol metabolism and the transcriptional regulation of phospholipid synthesis.

Aberrant cholesterol transport and storage underlie many diseases, and these processes have been studied intensively for many years. Nonetheless, fundamental aspects of intracellular sterol transport and distribution remain poorly understood. Frederick R. Maxfield (Weill Cornell Medical College) will present current progress on intracellular sterol trafficking and distribution. And finally, Neale Ridgway (Dalhousie University) will discuss how the enigmatic oxysterol binding proteins coordinate sterol trafficking and metabolism.

Teresa M. Dunn (tdunn@usuhs.mil) is a professor and chair of the department of biochemistry and molecular biology at the Uniformed Services University of the Health Sciences. Vytas A. Bankaitis (vytas@med.unc.edu) is a professor and chair of cell and developmental biology at the University of North Carolina School of Medicine.

Lipid and Membrane Metabolism

Session: Current Topics in Phosphoinositide Biology and Signaling

PtdIns-4-kinase Regulation of Protein Sorting in the Golgi Apparatus, *Christopher S. Burd, University of Pennsylvania School of Medicine*

Phosphatidylinositol-4-phosphate Signaling in Drosophila, *Julie Brill, The Hospital for Sick Children*

Coordination of Lipid Metabolism with Phosphoinositide Signaling by Phosphatidylinositol Transfer Proteins of the Sec14 Superfamily, *Vytas A. Bankaitis, University of North Carolina School of Medicine*

Session: Sphingolipid Metabolism and Biological Regulation

Sphingosine Phosphate Lyase and the DNA Damage Response, *Julie D. Saba, Children's Hospital Oakland Research Institute*

The Asthma-associated ORM/ORMDL Family Proteins Mediate Sphingolipid Homeostasis, *Jonathan S. Weissman, Howard Hughes Medical Institute Investigator, University of California, San Francisco*

Biology and Enzymology of Sphingolipid Synthesis, *Teresa M. Dunn, Uniformed Services University of the Health Sciences*

Session: Phospholipase D and Phosphatidic Acid Signaling

Chemical Biology Approaches to Defining Phosphatidic Acid Signaling Pathways, *H. Alex Brown, Vanderbilt University School of Medicine*

The Role of Phospholipase D in Vesicle Fusion, *Aaron Neiman, Stony Brook University*

Lipid Signaling Regulated by pH: Phosphatidic Acid as a pH Biosensor, *Christopher J. R. Loewen, University of British Columbia*

Session: Biology of Neutral Lipid Metabolism and Trafficking

The Ins and Outs of Fat Metabolism: New Insights from Yeast, *Sepp D. Kohlwein, University of Graz*

Intracellular Cholesterol Transport, *Frederick R. Maxfield, Weill Cornell Medical College*

Intra-organelle Sterol Transfer Activity of Oxysterol Binding Proteins, *Neale Ridgway, Dalhousie University*

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"Nucleosome Occupancy and Transcriptional Regulation"

Dr. Robert E. Kingston

Massachusetts General Hospital/ Harvard Medical School

www.asbmb.org/TranscriptionalRegulation2010

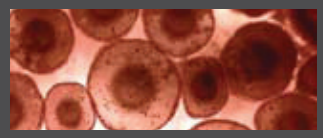
October 14 – October 17, 2010

Biochemistry and Cell Biology of ESCRTs in Health and Disease

Snowbird Resort, Snowbird, UT

Dr. Jennifer Lippincott-Schwartz,

National Institute of Child Health and Human Development, NIH



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Salk Institute for Biological Studies

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Dr. Scott Emr

Director, Weill Institute for Cell and Molecular Biology

Cornell University

www.asbmb.org/MembraneTraffic

Outsourcing to Emerging Global Markets

BY NICK ZAGORSKI

Outsourcing, which just a decade ago played a very small role in the biotechnology and pharmaceutical industry, steadily is becoming an integral part of the operation of such companies. And, among the numerous outsourcing destinations, contract research organizations in emerging global markets like China, India and Brazil rapidly are becoming the primary targets.

It's an ascent that Richard Soll knows intimately. In 2001, Soll, then head of chemistry at a small company named 3D Pharmaceuticals, was unsuccessfully looking for an industrial partner to help build a combinatorial screening library. Then, with a bit of luck, he stumbled on a nascent CRO in China called WuXi (pronounced woo-she) PharmaTec that was willing to develop his library on a fee basis. Soll became Wuxi's first customer.

Ten years later, that same company, now known as WuXi AppTec, brings in more than $250 million in yearly earnings while providing a full array of contract services to more than 500 clients worldwide, ranging from tiny startup companies to biotech behemoths, as well as private research institutes, nonprofits and even universities.

And Soll, who remained close to WuXi AppTec over the years, now oversees this process, having joined the company in 2008 to head their integrated services division. As someone who has been on the forefront of this growin relationship between pharmaceutical companies and CROs, ASBMB Today decided to ask Soll about the past, present and future of research and development outsourcing.

ASBMB: Is the practice of outsourcing aspects of drug development to CROs a relatively recent development in the business?

SOLL: Well, companies have been outsourcing for a while, but primarily in areas referred to as "noncore services." For core research areas like discovery biology, though, outsourcing services on a "cash and carry" basis was indeed fairly nonexistent 10 years ago; most large companies had the infrastructure to handle everything themselves. And, if you were a smaller company, that meant finding someone to assist you; the few places interested in working with you wanted a collaborative agreement, which included a large amount of money upfront.

ASBMB: What spurred the seemingly sudden change this past decade?

SOLL: As in many cases, economics proved to be a deciding factor; the theme for any industry is how to get the most bang for your buck. It's become a priority for the pharmaceutical industry, because they're facing some serious challenges, notably the stagnant drug development process that ends up approving only 20-25 new drugs a year.

So, the industry is trying to retool itself, following an era of mergers and acquisitions, to bring down costs and get more drugs to market. And, in the short term, outsourcing the early stages of drug development, including screening and validation, to foreign CROs can be a cost-effective option; some of the logic includes, "If I can put more drugs into the pipeline for the same cost, and the failure rate doesn't change, then I get more drugs out."

ASBMB: You also noted that universities are significant clients of CROs, including WuXi AppTec; it seems surprising that they would follow this path.

SOLL: Many people overlook the fact that universities are major innovation and economic engines as well centers of learning; think of all the businesses that are spun out of university discoveries. So, just like any biotech in these times, universities have to be creative with their dollars too, and that means looking at how to maximize the effectiveness of their graduate student and postdoc workforce and maximize the potential returns from university spinoffs.

ASBMB: Why China?

SOLL: Given my own history, I'm likely a little biased, but China, specifically among the emerging markets,

has the right combination of both a huge number of scientists in the workforce and a high quality of science that has been on a rapid rise these past few years. You just have to pick up any scientific journal, and you can see the growing number of articles published from Chinese labs. And, even in many Chinese CROs, you find staff that is eager, bright and driven. So, I personally think, in terms of scientific output, you are going to see China pull away from these other emerging countries over the next decade.

ASBMB: What are the main concerns in setting up a deal with a CRO? And, specifically in the case of China, are there cultural or political issues to worry about?

SOLL: The biggest risk for any outsourcing venture is that you pay, and you don't get the deliverables. So, that's why it's imperative that arrangements with CROs shouldn't be purely based on economics; consider quality and other variables as well.

In terms of China and the government, one big concern is the regulatory environment for drug development in China, which is different than in the U.S. and needs to be handled accordingly. The issue of intellectual property is a relatively new concept in China, so IP strategy is an important consideration.

ASBMB: Now that it's an established practice, how do you see outsourcing progressing over the next decade?

SOLL: Going forward, outsourcing will continue be a significant part of almost any R&D organization. Now, where the outsourcing pendulum will ultimately settle in the long term is an intriguing question, but it definitely is getting closer to the positive end right now.

However, I think outsourcing just reflects a bigger issue, namely the globalization of science. And, what you're seeing is more and more of these big companies setting up R&D institutes in emerging markets. It's not a new trend, but it really has accelerated over the past five years; right now, almost every major pharmaceutical firm has a research center in China, India or both.

ASBMB: What advantage would that offer as opposed to simply contracting?

SOLL: When the executives in the pharmaceutical industry look at the growth of these emerging markets, they see not only a new scientific workforce, but also potential new clients. By establishing a foothold in these markets, they can take on new initiatives by companies to identify regional therapeutics in addition to making it easier to sell their existing products.

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

Professional Master's Education

BY SHEILA TOBIAS

"Exciting experiments in master's education over the last decade, such as the Master of Biosciences program at the Keck Graduate Institute of Applied Life Sciences and the Professional Science Master's initiative seeded by the Alfred P. Sloan Foundation, have shown that graduate education in these fields can prepare professionals with both scientific knowledge and workplace skills (1)."

So concludes a 2008 National Academies review of non-thesis master's degrees in science and mathematics. The Academies believe the degrees "prepare a new kind of scientist with multidisciplinary skills and experiences."

Indeed, after 13 years of program expansion (from 15 programs in five universities launched in 1997 to nearly 200 in 97 universities in 2010), a sizeable cohort of PSM/MBS graduates now are moving steadily into new, and in some cases not so new, job categories that were never properly filled before. The positions carry with them significant value, authority and remuneration throughout the nation's tech-based workforce. It is no wonder that professional master's students are competitive. They don't need further on-the-job training beyond their bachelor's degree in science (or mathematics) and the two-years of "science-plus" coursework (culminating in a supervised business or government internship) required for the professional master's.

Once on the job, they move comfortably into research management, regulatory affairs, clinical trials management and quality control in government agencies and the private sector; they also find jobs in forensics, intellectual property, tech transfer, food safety and consulting. Employers in financial services prize them as well for their familiarity with marketing, risk assessment and being able to evaluate new product development. They often are lured to tech start-ups because of the breadth of their education.

Until the National Science Foundation (in 2009) launched a parallel science master's program, extending the professional science master's to engineering, professional master's degrees were directed largely toward biotech, with a sizeable subset of programs in bio-, medical and laboratory informatics. Enrollees either start their PSM/MBS immediately after getting their bachelor's degree or after spending a few years trying to parlay a bachelor's degree into a profession. A growing number are working professionals with science bachelor's degrees, whose employers underwrite their professional master's. (For this population, the internship is waived, and some of the work is done via remote video and online.)

At least as innovative as the programs' "plus" courses in business fundamentals, communication, regulatory affairs, ethics and/or intellectual property, is the participation by local and regional employers. Indeed, employers usually are the first group convened when a university has just begun to think about professionalizing a science (or mathematics) master's. While admissions, program design and assessment remain in the hands of faculty and deans, employers are an essential part of program planning and participate in designing internships and selecting case studies.

What are the prospects for continued expansion in the biosciences? There are enough potential students: Nearly 80,000 bachelor's degree holders are produced each year in the biological sciences (excluding agriculture), but, fewer than 9,000 receive master's degrees and only 6,700 get doctoral degrees (2). There's definitely room for growth. For the past 20 years, the number of undergraduate biology degrees awarded has risen by 40 percent, whereas master's degrees only have risen 23 percent. This may be, in part, because over the same period many biology departments have removed the thesis master's altogether from their official offerings.

But, even more significant will be the career trajectories of science master's graduates. Many already are being asked by hiring managers where they're employed to "find someone for us just like yourself" for their next hire. In five years time, PSM/MBS graduates will be hiring managers themselves. The programs are expanding, programmatically, into new fields bearing on stem cells, renewal energy and climate change, and geographically into statewide and systemwide configurations.

Sheila Tobias (sheilat@sheilatobias.com) is co-author of "Rethinking Science as a Career" and a field organizer for PSM.

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Overcoming Isolation in Science

BY SQUIRE J. BOOKER

For many underrepresented minorities, pursuing a career in science, technology, engineering or mathematics is often accompanied by isolation from their own culture or demographic group. Minority students frequently find themselves as one of a very few of their kind in a classroom, and, as their classes increase in scientific and mathematical complexity, they routinely become the lone survivor. These trends continue in graduate school and beyond, where minorities may be the sole representative of their demographic group in a lab, building, department or during week-long scientific gatherings in isolated venues.

The infrequent contact between underrepresented minority scientists in similar or complementary disciplines prevents the development of relationships that might prove beneficial while navigating the terrain of a scientific career. This is unfortunate, because there are various experiences and challenges that generally are unique to minority scientists. Avenues that allow minorities to share their experiences and discuss best practices for surmounting challenges may prove fruitful in fostering success, particularly among young individuals who are just starting their scientific careers.

To this end, the American Society for Biochemistry and Molecular Biology Minority Affairs Committee has established a minority scientist network called the "Partnership for Diversity." Anyone interested in diversity issues can join on the MAC website (http://bit.ly/1o7oT6). Network members receive updates on funding initiatives and summer research programs, information about scientific outreach, news about special functions — particularly those associated with diversity issues — at the ASBMB annual meeting and notices on obtaining or becoming a scientific mentor.

The network fostered a wonderful turnout at the 2010 annual meeting minority scientist networking reception, and, we hope that the registry will be used to identify future minority speakers for ASBMB and other scientific society meetings.

Another initiative of particular note is the recently created ASBMB MAC research spotlight page (http://bit.ly/b6RBv1) which highlights the careers of minority scientists. The profiles also allow the scientists to share some of the challenges they faced in their scientific development and their strategies for surmounting them.

To date, four minority scientists have been highlighted: John Alderete, professor of microbiology and associate director of outreach and development at the School of Molecular Biosciences at Washington State University-Pullman; Marion B. Sewer, associate professor in the Skaggs School of Pharmacy & Pharmaceutical Sciences at the University of California, San Diego; Leticia Marquez-Magana, professor of biology and founding member of the Health Equity Institute at San Francisco State University; and Aguilera Renato, professor of biology and director of the biology graduate program at University of Texas, El Paso.

Each spotlight offers candid and inspirational insight for budding minority scientists and will most likely resonate with those who have been around for a while. The similarities between the stories are fascinating, especially because each scientist hails from a different beginning. One common theme is that setbacks are to be expected; the key, however, is to not allow setbacks to engender self-doubt and to not confuse unpreparedness with lack of intelligence. This may have particular relevance to budding minority scientists who may lack the exposure to many of the sophisticated scientific concepts and laboratory experiences that their majority scientist peers have. One reflection by Sewer that had particular resonance was the reminder that scientists constantly are evaluated on a number of different levels by a great number of people, and that we shouldn't take comments and criticisms personally.

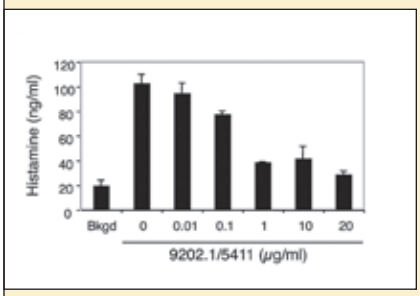
The ASBMB MAC hopes that these initiatives, and many others in the works, will serve as a launching pad for a fruitful exchange of experiences, ideas and best practices, particularly with the net flux of information toward young people, which will foster success and lead to an increase in the number of minority scientists at all levels.

Squire J. Booker (Squire@psu.edu) is an associate professor of chemistry and of biochemistry and molecular biology at The Pennsylvania State University.

Welcome to the newest MAC committee member, Marion B. Sewer, associate professor in the Skaggs School of Pharmacy & Pharmaceutical Sciences at the University of California, San Diego.

Better Bispecific Antibodies

Bispecific antibodies, which simultaneously recognize two different antigens, hold great therapeutic potential, but their broad application has been hindered by difficulties in developing stable antibody platforms, favorable pharmacokinetic properties and feasible large-scale manufacturing protocols. In this study, researchers from Genentech Inc. have taken a step in overcoming these problems, improving upon a previously used small-scale strategy, known as "knobs-into-holes," that employed sterically complementary mutations in the antibody heavy chain C_H3 domain to promote heavy chain heterodimerization with a single common light chain to prevent heavy chain/light chain mispairing. The researchers adapted this technology into a two-part strategy that consists first of small-scale generation of bispecific antibodies lacking a common light chain and hinge disulfides to facilitate proof-of-concept studies, followed by the identification of a common light chain-bispecific antibody for large-scale production with high purity and yield. They used their strategy to successfully generate a bispecific antibody that inhibits the activation of the high affinity IgE receptor FcεRI by cross-linking it with the inhibitory receptor FcγRIIb; this antibody displayed similar pharmacokinetic properties to regular human IgG antibodies, showing its promise as a therapeutic agent for asthma and other allergic diseases.



The bispecific antibody 9202.1/5411 lowers histamine release from RBL cells transfected with human FcεRI and human FcγRIIb and activated through human FcεRI.

Development of a Two-part Strategy to Identify a Therapeutic Human Bispecific Antibody That Inhibits IgE Receptor Signaling

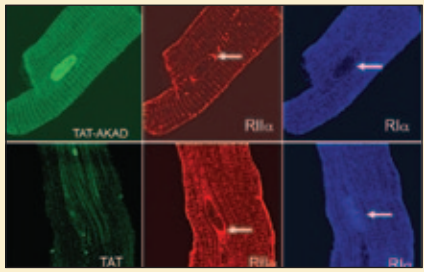
Janet Jackman, et al.

J. Biol. Chem. (2010) **285**, 20850 – 20859

jbc

PKA Localization Is Pivotal in the Heart

Proper localization of protein kinase A (PKA) via A-kinase-anchoring proteins (AKAPs) is important for cAMP responsiveness in many cellular systems, including cardiac signaling. In this joint study by the University of California, San Diego, the University of Calgary and Provid Pharmaceuticals, researchers examined the importance of AKAP-mediated targeting of PKA on cardiac function with a specially designed cell-permeable peptide, based on the PKA binding region of AKAP10, called TAT-AKAD (trans-activator of transcription-conjugated A-kinase-anchoring disruptor). After validating PKA interaction, they tested the effects of this peptide in isolated cardiac myocytes and perfused mouse hearts. In myocytes, TAT-AKAD decreased the phosphorylation of phospholamban and troponin I following β-adrenergic stimulation, indicating PKA knockdown; TAT-AKAD treatment also reduced myocyte shortening and the rates of contraction and relaxation. Injecting TAT-AKAD into the coronary circulation of isolated perfused hearts rapidly and reversibly decreased heart rate and left ventricular pressure, and these effects still were seen in hearts pretreated with the β-adrenergic agonist isoproterenol. Together, these results show that disrupted PKA localization produces negative effects on heart rate, contraction and relaxation, confirming that AKAP-targeting of PKA is a vital process for heart function.



The PKA-AKAP disruptor TAT-AKAD reduces the staining of both PKA-RI and PKA-RII in the nuclear and perinuclear space, respectively (arrows), in cardiac myocytes, suggesting a loss of AKAP-mediated PKA localization.

Disruption of Protein Kinase A Localization Using a Trans-activator of Transcription (TAT)-conjugated A-kinase-anchoring Peptide Reduces Cardiac Function

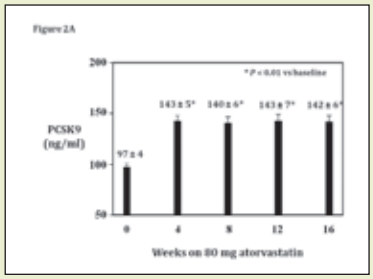
Hemal H. Patel, et al.

J. Biol. Chem, published online June 26, 2010

jbc

A Disruption Is Statin'

Maintaining normal cholesterol levels is critical for warding off heart disease. Proprotein convertase subtilisin kexin type 9 (PCSK9) is a major player in cholesterol regulation — mutations in this gene can lead to familial hypercholesterolemia, a genetic disorder characterized by abnormally high cholesterol levels and cardiovascular disease. Increased PCSK9 activity increases cholesterol levels by binding to low-density lipoprotein receptors (LDLR), which induces receptor degradation and the accumulation of low-density lipoproteins (LDL) in the bloodstream. Thus, high PCSK9 levels normally are associated with high cholesterol levels. However, a 16-week joint study by the University of Florida and Eli Lilly and Company used human volunteers to show that atorvastatin, a widely prescribed cholesterol-reducing drug, increases serum PCSK9 levels while lowering total cholesterol, triglycerides and LDL levels. This indicates that the relationship between PCSK9 and LDL serum levels are disrupted during atorvastatin treatment. Interestingly, the baseline or change in PCSK9 levels over the course of treatment did not strongly predict the change or end-point LDL levels. Combined with previous results, this study suggests that doubling the normal atorvastatin dosage does not further reduce LDL levels in a dose-dependent manner. The authors suggest that the atorvastatin-induced increase in PCSK9 levels may be inhibiting a dose-dependent decrease in serum LDL levels, giving insight into why increasing dosage fails to achieve a proportional decrease in LDL serum levels.



The most widely prescribed cholesterol-reducing statin, atorvastatin, causes a rapid and sustained increase in PCSK9 serum levels in humans.

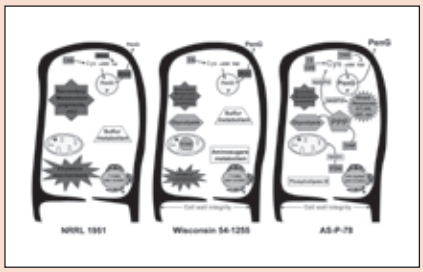
High Dose Atorvastatin Causes a Rapid, Sustained Increase in Human Serum PCSK9 and Disrupts Its Correlation with LDL Cholesterol

Greg Welder, et al.

J. Lipid Res., published online June 5, 2010

Penicillin: Gone Industrial

Although Alexander Fleming discovered the antibiotic effect of penicillin in 1928, his fungal isolate, Penicillium notatum, did not produce enough of the antibiotic for mass production. In 1944, the combination of new fermentation methods and the isolation of Penicillium chrysogenum, which produced 100-times more penicillin, enabled mass production and distribution of the antibiotic. Since then, P. chrysogenum strains have undergone several rounds of classical and mutation-induced selections, generating isolates that can produce up to 50,000mg/mL of penicillin. In this joint study from the Universidad de León and INBIOTEC, Spain, the authors perform a detailed comparative analysis of the proteomes from three P. chrysogenum isolates that exhibit low, medium and high penicillin output — a result of selection during the process of industrial strain improvement. The researchers identified several metabolic changes that appear to increase penicillin production, such as increased cytosine biosynthesis-related proteins and pentose phosphate-related enzymes, as well as decreased carbon-utilization-related enzymes and a putative penicillin-degradation protein. This work gives a global insight into metabolic changes that occur in fungal isolates selected for antibiotic overproduction, providing information that may improve the production of other bioactive secondary metabolites.



A proteomic comparison of three Penicillium chrysogenum isolates revealed networks and pathways that are modified during strain improvement programs.

Proteome Analysis of the Penicillin Producer Penicillium chrysogenum: Characterization of Protein Changes during the Industrial Strain Improvement

Mohammad-Saeid Jami, et al.

Mol. Cell. Prot. (2010) **9**, 1182 – 1198

How to Prepare for a Job in Industry

TERTIUS DE KLUYVER

When applying for a job in industry, "it's a given that you are an expert," says Jonathan Jacobs, a staff scientist and recent hire at MedImmune Inc. "It's the other things that are important in the decision on a hire." As an expert in bioinformatics and molecular genetics, Jacobs was headhunted by MedImmune for his combination of skills and knowledge. Even so, his selection for the job included several interviews and took a number of months. "Some [people] on the hiring committee were unsure of my prospects in industry," recalls Jacobs. "Apparently I had already spent too much time in academia." He was only partway through his second postdoctoral position.

Jacobs' experience reflects a divide that exists between academia and industry based on a perception of the type and quality of science each produces and the type of scientist each must then attract. One important difference between academic and industry-based research is that projects are shared between collaborators within a company. "You can't monopolize a project," says Jacobs. "Staff scientists aren't dependent on first authorships for their standing among peers and further funding, but they must be able to meet project milestones and move projects forward. This is where collaborations come in."

Although working toward project milestones may sound boring and not very creative, Jacobs is very enthusiastic about the industry work culture. "You work on a number of projects — I'm currently involved in five — and you get to work with different people who bring their own specialist viewpoint to bear on the problem. It's very dynamic."

Getting Your Foot in the Door

According to Jacobs, an early entry into the private industry job market is important. He advises starting a job search for an entry level staff scientist position when you are tidying up your doctorate rather than at the end of your first postdoctoral fellowship. Many larger pharmaceutical and biotech companies also are now developing their own postdoctoral programs. For example, MedImmune is about to rollout a postdoctoral program for next year. "We may have up to 16 positions available," says Jan Popp, director of project management and business operations at MedImmune.

Once you've identified some companies to apply for, "there are definite strategies applicants can undertake to snare an interview," says Popp. "Do not apply for every position the company advertises – stick to those that require your specialist knowledge. Write a resume, not a CV, write it to the job description, and keep it short – three or four pages – including references. Describe, in point form, how you are able to meet the requirements of the position. Use key words, as hiring managers will use these for the initial screening, and always use active language. Where possible, incorporate management experience, whether project, financial, people, time, etc., and be certain to highlight skills involving oral and written communication, collaboration and teamwork. Don't write about your hobbies or personal goals."

"Also, recruiters look for industry experience," says Popp. "Internships in industry during your undergraduate studies or having industry scientists involved in your projects or thesis can highlight connections and experience with industry."

Another piece of advice: if the company you're applying to is publicly-traded, call its investor relations office and ask for a copy of its prospectus — the document provides an incredible wealth of information.

The Interview

"The first phone conversation is a screen that may result in an invitation to a formal interview," says Popp. "You must be prepared for it. In the past, I have decided not to proceed with an applicant based on this first conversation. You must be clear and concise and able to think on your feet. Practice talking about yourself, but not in the sense of a biography. You need to be able to describe your skills and knowledge and how you apply them. Practice this with friends over lunch or whenever time is available. Get them to ask you questions about what you do and how you do it. This is something you should be relaxed with; it shouldn't be presented as if by rote."

The successful phone screen usually is followed by several one-on-one interviews with a panel. "Don't feel weird just because you are better dressed than members of the interview panel," says Popp. "If you don't know what to wear, then look at what

people in the public eye are wearing. News presenters and politicians are generally good role models in this respect."

You also will be asked to give a seminar on your research work to a broader company audience. Jacobs gave a seminar in each of his interviews. "Have a polished and practiced seminar ready," advised Popp. "And make sure you tell a story rather than just present a bunch of data. Also, do mock interviews. Practice."

"As well as being able to express yourself, you also must show that you have good listening skills," says Popp. "These things are important because they relate to your ability to collaborate, to work effectively with colleagues. And, lastly, have questions prepared that you can ask the panel. Being able to ask about the company and the job, rather than just the work conditions, gives you an opportunity to demonstrate some knowledge of the company and interest in the work it does."

Networking

To increase your chances of an interview, Jacobs emphasized the importance of networking. "Prepare a professional-looking business card and introduce yourself to other delegates at conferences, workshops and industry exhibitions. Be proactive."

When Jacobs was headhunted for his current position, a recruiter contacted him after reading his resume on LinkedIn. "My qualifications and experience matched what was required for a position at MedImmune," explained Jacobs. "It's a good strategy to post your experience and qualifications online using sites such as LinkedIn. Recruiters check these sites constantly. I had set up my LinkedIn page while a postdoc. Once it's set up, it simply works in the background for you." When asked what he placed on the LinkedIn page, he replied that it was basically his CV, minus his publications list, but with an emphasis on his technical experience and knowledge.

Institutional Resources

Starting a career in private industry can seem somewhat overwhelming without some structured guidance, but many universities and research institutions offer career and training resources.

"We alert our fellows as early as possible, at orientation, to the career training and counseling options available to them at the National Institutes of Health," says Lori Conlan, director of postdoctoral services at the NIH Office of Intramural Training and Education. "We develop new training packages and rotate our program from year to year. The workshops cover a variety of career related questions and are videocast and archived at www.training.nih.gov for the public to view. Many other academic institutions also will have career training and counseling programs, so look at your home institution as well.

"Our annual highlight is the NIH Career Symposium that offers a series of panel discussions on a variety of careers in science," says Conlan. "More than 1,000 people attended this year's symposium on the Bethesda campus in April. Also, every two months we bring a representative from a different company onto the campus to talk about recruitment opportunities with that company. These sessions are split between a 45-minute information session and a 45-minute networking session. This is a more intimate setting than at a career fair and gives postdocs an opportunity to ask specific questions about the company and careers there."

With only about 8 percent of today's postdoctoral scientists attaining tenure track academic positions, and with federal agencies now relying more on contract labor, private industry represents the future for many young scientists-in-training. Early career scientists seeking industry positions need to market themselves appropriately and highlight any professional competencies they posses that are desired by industry.

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

For more information:

- NIH career workshop podcasts: http://bit.ly/auwPti
- NIH career events: http://bit.ly/9XApWs

Skeletal Muscle Lipid Metabolism

BY DEBORAH M. MUOIO

In metabolic diseases such obesity and diabetes, skeletal muscle fails to respond appropriately to insulin, resulting in impaired glucose disposal after a meal. The onset of this "insulin-resistant" condition is associated intimately with generalized increases in adiposity as well as ectopic lipid deposition within skeletal muscle (1). However, a now famous exception to this rule emerged from studies in muscles of highly trained athletes, which have more lipid droplets but remain exquisitely insulin-sensitive (2). These paradoxical findings have fascinated and puzzled scientists for many years, and the fundamental questions of if and how intramuscular lipid droplets contribute to insulin resistance remain unanswered.

A major quest has been to identify specific lipid molecules that universally discriminate insulin responsive versus resistant states. To this end, our laboratory has employed a targeted metabolomics approach to survey several two-state models of insulin sensitivity. Results of these analyses piqued our interest in a class of molecules known as acylcarnitines. These metabolites are byproducts of substrate degradation, formed from their respective acyl-CoA intermediates by a family of carnitine acyltransferases that reside principally in mitochondria. Insulin-resistant states were accompanied by muscle accumulation of lipid-derived acylcarnitines (byproducts of incomplete β-oxidation) and a corresponding diminution in free carnitine levels (3-5). Conversely, exercise training enhanced mitochondrial oxidative capacity but lowered acylcarnitine accumulation in obese mice (3). Our interpretation of these results was informed by metabolic assessments using several complementary methods (3, 4). The outcomes supported a negative association between incomplete fat oxidation and glucose tolerance (3-5) and led us to ask whether excessive mitochondrial lipid catabolism contributes to insulin resistance (6).

This question was addressed using mice that were engineered to have reduced-fat oxidation via deletion of malonyl-CoA decarboxylase; an enzyme that relieves the inhibitory action of malonyl-CoA on the initial step in β-oxidation. The mcd-null mice had reduced intramuscular acylcarnitine levels, increased glucose oxidation and preserved glucose tolerance when fed a high fat diet, despite high IMTG levels (4). The findings implied that intramuscular lipids in obese/inactive mice are less insulin-desensitizing when fat transport into mitochondria is restricted. Likewise, we found that a surplus of local triacylglycerol in obese compared with lean Zucker rats promotes β-oxidation and dissuades glucose use during muscle contraction (7). A similar glycogen sparing effect of IMTG has been observed in endurance athletes. Also intriguing are recent reports suggesting that intracellular lipid droplets play a specific and essential role in activating transcription factors that promote β-oxidation (8, 9). In aggregate, these studies support the possibility that intramuscular lipid droplets encourage a shift in metabolic currency, both by providing a plentiful source of fatty-acid substrate and by metabolic reprogramming at the genomic level. Further studies are necessary to determine whether persistent mitochondrial catabolism of IMTG-derived fatty acids contributes to systemic glucose intolerance in the context of overnutrition and to better understand how synthesis and turnover of this specific lipid pool is regulated in physically active muscles.

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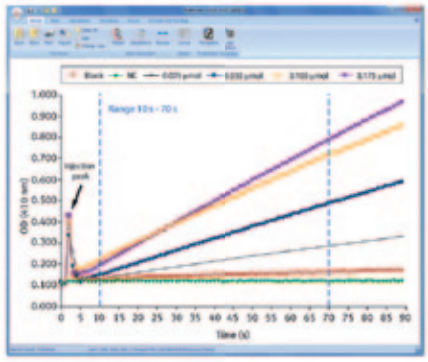

Overlay plot of esterase catalysed pNPA reactions at different concentrations.

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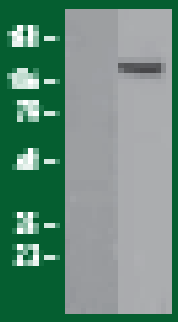

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