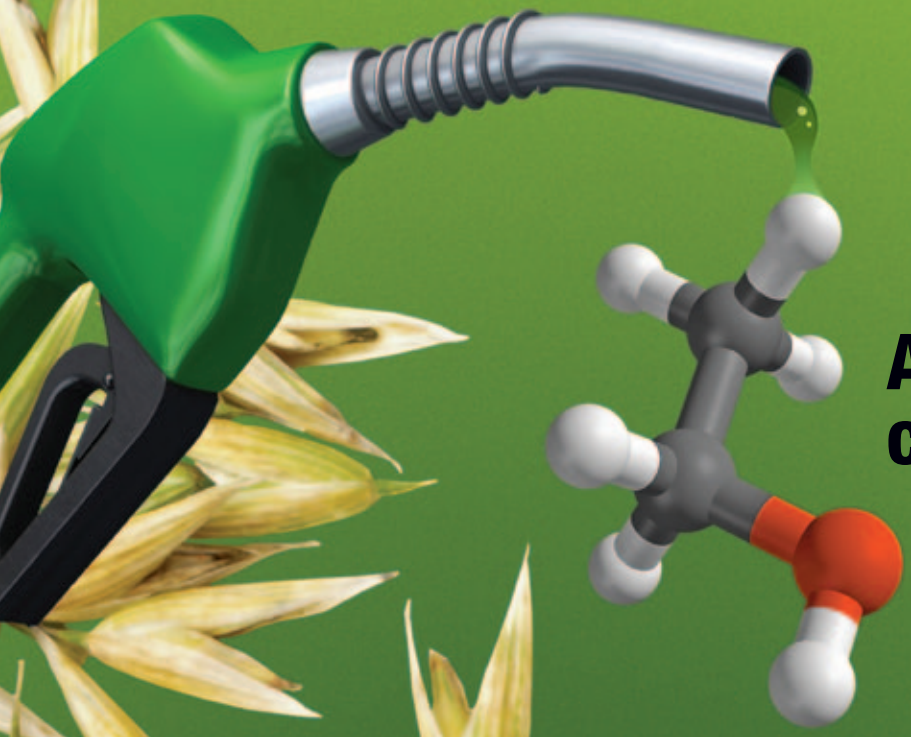
ASBMB today

July 2011



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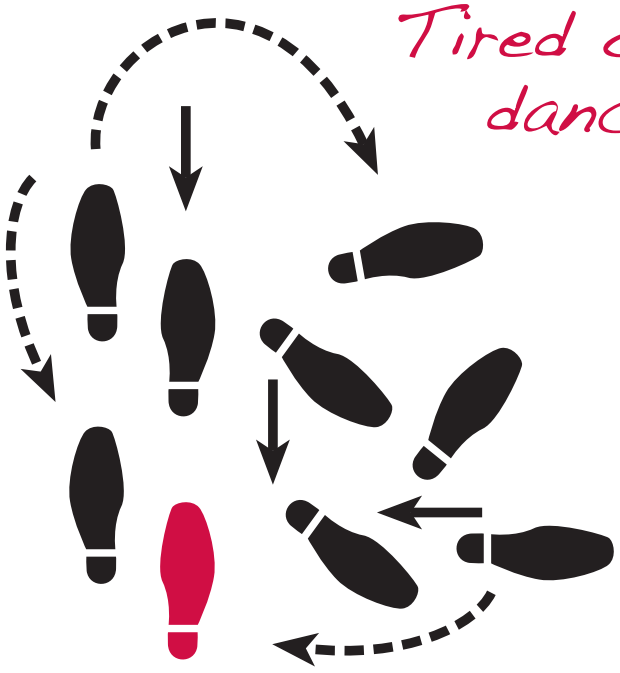

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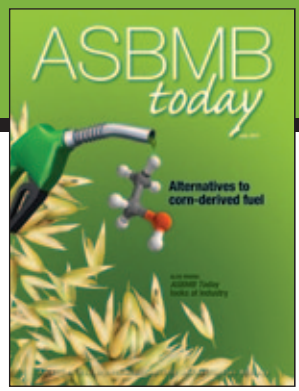

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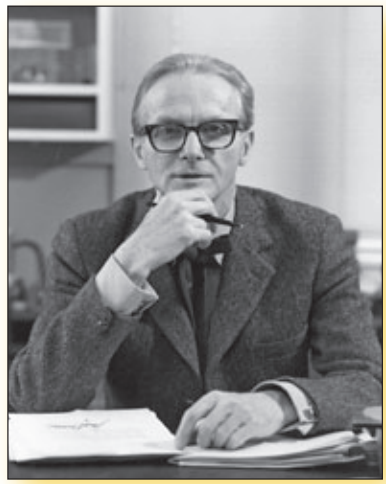

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2008 APEX AWARDS FOR PUBLICATION EXCELLENCE

president's message

The challenge of reviewing grant applications

BY SUZANNE PFEFFER

Given the status of the U.S. budget deficit, it is unlikely that the National Institutes of Health and the National Science Foundation can expect to see significant increases in funding any time soon. Indeed, the NIH has just enacted across-the-board budget cuts, and the percentage of grants that will be able to be funded is approaching a dangerously low level. This makes the process of application evaluation incredibly important — and given the fact that the NIH alone received 77,000 applications last year, the task of evaluation may never have been more challenging.

For students and postdoctoral fellows not familiar with the workings of the NIH, grant applications are evaluated by review panels (or study sections) composed of scientists from across the country. A scientific review officer oversees the panels and ensures that meetings follow specific guidelines. The SRO assembles the panel of expert scientists, seeking to ensure representation of men, women, under-represented minorities and institutions from all around the U.S. A member of the panel is appointed to chair the proceedings.

Although research is funded by one of the many institutes or centers at the NIH (e.g., the National Institute of General Medical Sciences or the National Cancer Institute), review oversight is provided by the Center for Scientific Review, whose sole task is to oversee application review. Thus, a panel may review applications that have the potential to be funded by different institutes. In rare cases, an institute may assemble its own review panels. The job of the panel is to rank applications in relation to the other applications evaluated in that general area of research. That information is then provided to the relevant institute, and funding decisions are made by the institute, not by the CSR, depending on the institute's budget and priorities. Individual review panels may be approach-based; for example, they may evaluate only applications in structural biology. Alternatively, they may be much broader in scope, with a single panel evaluating topics as diverse as chaperones, protein folding, membrane trafficking and mitochondrial function.

Review panels score an application after three reviewers read it (before the meeting), present their critiques to the group (during the meeting), and discuss its strengths and weaknesses. The reviewers suggest scores, and the entire panel votes based on their understanding of reviewer presentations and their assessment of how that science ranks in significance relative to other applications under discussion. The reviewers don't always agree, and it is the responsibility of the panel's chairman either to help achieve consensus or to identify the points of contention for the group. Panels usually meet three times a year and consider about 85 applications per meeting.

During the past several years, the NIH has sought to identify the highest impact applications, focusing all discussion on the significance of the science proposed. This is important: There is more science that can be done than dollars available, and it is essential that the NIH spend funds on the most important and impactful science. What many new applicants have trouble understanding is the

fact that review panels simply rank the applications that are received. Thus, if a famous scientist in a given area submits an application at the same time as a new faculty member, they will be compared and ranked accordingly. You can submit an excellent application and still rank lower based simply on who else submitted an application at the same time. Lucky for new investigators, their applications have a special demarcation, and institute staff members reach farther down the ranked list to ensure increased success for new applicants.

One of the most valuable aspects of a review panel discussion relates to relative significance. The chairman plays an incredibly important role: Because the entire panel votes, it is the chairman's responsibility to ensure that everyone understands the application and contributes to the discussion of its overall significance for the field. Members of the panel need to be encouraged to ask questions relating to significance, and the discussion can involve difficult questions, such as: Why is this chaperone study of greater impact to the field than another proposal to study mitochondrial fusion? How many other labs are also asking the same question using the same approaches?

The CSR faces many challenges, including recruiting the very best reviewers available. Some scientists claim to be too busy to serve; some prefer not to lose time to travel. Yet every panel must include experts with the requisite knowledge to evaluate the science under discussion. To manage this challenge, the CSR sometimes turns to telephone or internet-based reviews. There is no question that if a proposal utilizes an unusual technique it is important for an expert to be able to provide expertise regarding one or two applications. However, when reviewers phone in their comments, they don't usually listen in to the entire meeting's proceedings and are thus less able to contribute to the broader discussions that are so important when diverse science has to be ranked successfully. Similarly, internet-based review can be valuable when a small set of applications is under consideration. Three referees usually can reach a consensus or even carry out a heated debate in a bloglike forum. However, it is much more difficult for a larger group to discuss the relative significance of diverse areas of science using this format. The CSR is to be applauded for trying new technologies to save all of us travel time and money. Nevertheless, this applicant hopes that in-person reviews will continue to be supported, as the pursuit of high significance requires a level of discussion that is hard to achieve on a blog. In the past few years, the CSR has begun alternating meetings between the east and west coasts, a positive development that can save time and money for panel members and for the NIH.

Some American Society for Biochemistry and Molecular Biology members have written to me to share their frustration with the shorter format of critiques now provided by review panels. In previous years, when a higher percentage of submitted applications could be funded, these critiques provided important clues to aid applicants in crafting revised applications. Now, the NIH permits submission of only one revised application. This new rule was instituted so that there would not be backlogs of revised applications receiving priority over new and exciting submissions. While well intended, the new rule has frustrated many scientists, because at the moment, even outstanding proposals are not receiving a score that the institutes can fund. Perhaps the rule can be modified so that applicants who obtain a priority score in the 20th percentile or better would be able to submit one additional revised version ("A2"). An additional frustration stems from the fact that review panel rosters can change from one meeting to the next. Thus, a proposal revised in response to one set of comments may fail on resubmission due to a completely new set contributed by a different group of reviewers. Tight budgets also drive reviewers to find reasons not to fund something rather than to try to find reasons in favor of funding. This can lead to very good proposals being nitpicked to death over trivial issues of experimental detail. It is the responsibility of the panel chairman to stop this trend, but once a discussion has any negative tone, it is very difficult to turn it around.

While one can learn a great deal about the grant process by serving on a panel, I usually discourage junior faculty from serving until after they have obtained tenure. More senior scientists can provide a broad perspective in terms of what constitutes the most innovative science and what will offer the most significant advances, hopefully without nitpicking the details provided by a researcher with a strong record of previous accomplishment. These individuals also may have more time to commit to grant reading and critique writing, which is significant. How can we encourage more top scientists to serve on panels? ASBMB has provided the CSR with a long list of members who are willing to serve. ASBMB Past-president Gregory Petsko has called for a jury pool system where all grant recipients must be willing to serve if called upon; I support this approach wholeheartedly. I also encourage you

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The not-so-invisible hand

SBIR expansion delayed by contentious legislative language.

BY GEOFFREY HUNT

The Small Business Innovation Research program, a congressionally mandated, funding agency-administered program aimed at promoting and developing small business opportunities from basic research, is overwhelmingly regarded as an unequivocal success by researchers, politicians and independent observers. Yet congressional reauthorization of the program is being held up as legislators grapple with proposed changes to the program that would appear to decrease, rather than improve, its efficacy.

The SBIR program was launched in 1982 as part of the Small Business Act to speed technological innovation while also providing incentives for cooperation between government agencies and small businesses. The program instructs 11 federal agencies to allocate at least 2.5 percent of their overall research budgets for SBIR grants; in fiscal 2010, SBIR projects received more than $2 billion in government funding. Under the program, agencies generate their own grant solicitations and are allowed great flexibility in determining what types of projects receive SBIR funds. Though the program is aimed at using small businesses to help facilitate research and development that will aid federal agencies, the underlying assumption is that grant recipients ultimately will be able to commercialize their inventions, thereby stimulating economic growth. According to a 2009 National Research Council report, nearly 50 percent of approved projects end up being commercialized.

Efforts to support small business are a rare source of bipartisan agreement. With such favorable political winds blowing, reauthorization of the SBIR program in 2008, given its past successes, should have been a slam dunk. Yet three years later, Congress still has not passed a full reauthorization, instead relying on a series of temporary extensions to keep the program going. Reauthorization has been a priority for Senator Mary Landrieu, D-La., chairwoman of the Senate Committee on Small Business and Entrepreneurship and sponsor of the reauthorization bill, who lamented wasting "so much good technology and important investments" after the most recent reauthorization attempt was defeated in May. Ironically, it is Landrieu, proposing to increase the minimum set aside for SBIR funding to 3 percent of agency research budgets, who has in effect prevented the reauthorization from being consummated.

Agencies currently are free to allocate more than the mandated 2.5 percent of their budgets toward SBIR grants, so any increase above that value comes off as arbitrary and baseless. Moreover, funding for SBIR grants has grown during the past decade even as the number of applications has fallen, suggesting that economic market forces have determined that the current level is appropriate. For individual investigators already facing record-low application success rates and declining agency budgets, the redirection of funds to one area of research, even one as well received as the SBIR program, at the expense of others would represent a devastating blow. For example, the National Institues of Health would be forced to reapportion up to $180 million away from other grant types, including investigator-initiated grants such as R01s. Given that it is often the discoveries uncovered by individual investigators that are developed into the projects funded by the SBIR program, this situation would ultimately result in the roots of the scientific discovery tree being cut off at the expense of preserving the leaves.

Academic groups, scientific societies (including the American Society for Biochemistry and Molecular Biology) and government officials such as White House Office of Science and Technology Policy Director John Holdren have been vociferous in raising their concerns about this proposal in hopes that its removal from the legislation will allow the program as a whole to move forward. With all of the success enjoyed by the SBIR program, hopefully Congress finally will learn when to leave well enough alone.

Geoffrey Hunt (ghunt@asbmb.org) is the ASBMB science policy fellow.

Retrospective: William Nunn Lipscomb, Jr. (1919 – 2011)

BY NICOLE KRESGE

William Nunn Lipscomb, Jr., an emeritus professor at Harvard University who won the Nobel Prize in chemistry in 1976 for work on chemical bonding, passed away in April at age 91.

Lipscomb was born on December 9, 1919, in Cleveland, Ohio. He attended the University of Kentucky on a clarinet scholarship and graduated with a bachelor's degree in chemistry in 1941. He then enrolled in graduate school at the California Institute of Technology, intending to study physics, but he switched to physical chemistry after a year to work with Linus Pauling.

PHOTO: JAMES S. LIPSCOMB

As part of the wartime effort, Lipscomb worked for the National Defense Research Council during the day and on his doctoral research at night. He graduated in 1946 and became an assistant professor at the University of Minnesota, where he remained until 1959, when he moved to Harvard University to become a professor of chemistry. Lipscomb remained at Harvard for the rest of his career, becoming the Abbott and James Lawrence professor of chemistry in 1971 and the Abbott and James Lawrence professor of chemistry emeritus in 1990.

Lipscomb's research centered on three areas: nuclear magnetic resonance and chemical shifts, boron chemistry and the nature of the chemical bond, and large biochemical molecules.

He used NMR to investigate carboranes (clusters of boron and hydrogen shaped like polyhedra) and the sites of electrophilic attack on these compounds. This work led to his publication of a comprehensive theory of chemical shifts, and he provided the first accurate values for the constants that describe the behavior of several types of molecules in magnetic or electric fields.

Lipscomb deduced the molecular structures of numerous boranes (compounds made of boron and hydrogen) and their derivatives using X-ray crystallography. Since the stability of boranes could not be explained by traditional concepts of electron bonding, he developed new techniques that showed how a pair of electrons could be shared by three atoms. He later applied these techniques to carboranes. The work formed the basis for the extended Hückel theory, the first widely applicable use of molecular orbital theory to study chemical bonding, and also earned him the 1976 Nobel Prize in chemistry.

Lipscomb's later research focused on the atomic structure of proteins and how enzymes work. He used X-ray diffraction to solve the three-dimensional structures of carboxypeptidase A, aspartate carbamoyltransferase, leucine aminopeptidase, HaeIII methyltransferase convalently complexed to DNA, human interferon beta, chorismate mutase and fructose-1,6-bisphosphatase.

Lipscomb was affectionately called "Colonel" by his friends because of his Kentucky heritage. He was a skilled clarinetist who often played in chamber music groups, a tennis enthusiast and a practical joker. At mealtimes, he would steal butter off other people's butter knives and was known to remove the fruit from walnuts and glue the shells back together before offering them to guests. He also participated in the Ig Nobel Prize ceremonies held at Harvard and even agreed to be the prize in the event's Win-a-Date-with-a-Nobel Laureate contest.

Feel free to add your reflections on William Nunn Lipscomb, Jr. online at http://bit.ly/ATodayLipscomb.

Nicole Kresge (nkresge@asbmb.org) is the editor of ASBMB Today.

ASBMB announces its 2011 election results

Society selects new president, treasurer and council and committee members.

PRESIDENT-ELECT

Jeremy M. Berg has directed the National Institute of General Medical Sciences at the National Institutes of Health since November 2003. He left that position in June to become the associate vice chancellor for health policy and planning at the University of Pittsburgh as well as assume the role of professor in the University of Pittsburgh School of Medicine's department of computational and systems biology. "I am delighted to be elected to this important position at ASBMB," said Berg. "I am looking forward to working with the other members to promote science that has so much to contribute to American society." Berg's research focuses on the structural and functional roles that metal ions, especially zinc, play in proteins. He has made major contributions to understanding how zinc-containing proteins bind to DNA or RNA and regulate gene activity.

TREASURER-ELECT

Toni M. Antalis is a professor in the department of physiology at the University of Maryland School of Medicine. She studies the biology and function of membrane serine proteases and serpins.

COUNCIL MEMBER

David Sabatini is a member of the Whitehead Institute for Biomedical Research, a senior associate member at The Broad Institute, a member of the Koch Institute for Integrative Cancer Research and an associate professor of biology at the Massachusetts Institute of Technology. He is also an investigator for the Howard Hughes Medical Institute. Sabatini studies the regulation of growth and metabolism in mammals.

COUNCIL MEMBER

Wesley I. Sundquist is a professor and co-chair of biochemistry in the Bioscience Graduate Studies Molecular Biology Program at the University of Utah. His research focuses on the molecular and structural biology of retroviruses with particular emphasis on HIV.

NOMINATING COMMITTEE MEMBER

Judith P. Klinman is a professor in the department of chemistry at the University of California, Berkeley, and a member of the California Institute for Quantitative Biosciences. She studies the relationship of enzyme structure and dynamics with catalysis.

NOMINATING COMMITTEE MEMBER

Ian Wilson is the Hansen professor of structural biology at The Scripps Research Institute. He studies the structural basis of immune recognition.

PUBLIC AFFAIRS ADVISORY COMMITTEE MEMBER

John M. Kyriakis is an investigator and professor of medicine at the Molecular Cardiology Research Institute at Tufts Medical Center. He studies signal transduction in inflammation and cancer.

PUBLIC AFFAIRS ADVISORY COMMITTEE MEMBER

Leslie Parise is chair of the department of biochemistry and biophysics at the University of North Carolina at Chapel Hill School of Medicine and has a joint appointment with the department of pharmacology. The goal of her research is to gain a better understanding of how cell signals and adhesion receptors merge to control events in cardiovascular disease and cancer.

PUBLIC AFFAIRS ADVISORY COMMITTEE MEMBER

Robert Palazzo is provost and a professor of biology at Rensselaer Polytechnic Institute. His research interests include cell biology and biochemistry of centrosomes, mitosis and early development, cell-cycle regulation, fertilization and reproduction, regulation of cell motility, cell structure and function, cell evolution, protein biochemistry, and drug discovery.

PUBLICATIONS COMMITTEE MEMBER

Judith Storch is a professor in the department of nutritional sciences at Rutgers University's School of Environmental and Biological Sciences. Her research is focused on lipid traffic in cells with particular emphasis on long-chain fatty acids, monoacylglycerols and cholesterol.

PUBLICATIONS COMMITTEE MEMBER

Jeffrey L. Benovic is a professor and the chair of the department of biochemistry and molecular biology at Thomas Jefferson University. He studies the regulation of G-protein signaling.

Outgoing council and committee members

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

Dafna Bar-Sagi
Council member

Traci M. T. Hall
Meetings Committee member

Tony Hunter
Nominating Committee member

Thomas D. Landefeld
Minority Affairs Committee member

Carla Mattos
Education and Professional Development Committee member

Ishara A. Mills-Henry
Minority Affairs Committee member

Matthew W. Olson
Meetings Committee member

Gregory Petsko
Past-president

Mark M. Rasenick
Public Affairs Advisory Committee Member

Dagmar Ringe
Nominating Committee member

John D. Scott
Membership Committee member

Ali Shilatifard
Meetings Committee member

Thomas E. Smith
Council member

Ann Stock
Council member

James T. Stull
Finance Committee member

Michael Summers
Minority Affairs Committee member

The challenge of reviewing grant applications

continued from page 3

to contact SROs in your research area and suggest names of senior experts who would add depth and knowledge to current panels. Encourage your colleagues to serve, because there has never been a more important time for us to help out. By working together with the SROs at the CSR, we can enhance the review process. Thanks also to our members Bruce Alberts, Etty Benveniste, Heidi Hamm, David Korn and Keith Yamamoto, who advise the CSR, and to all ASBMB members who volunteer to review applications for the NIH and the NSF at this critical time in research funding.

ASBMB President Suzanne Pfeffer (pfeffer@stanford.edu) is a biochemistry professor at the Stanford University School of Medicine.

asbmb member update


LEBOY


BONIFACINO


SHILOH


DE LANGE


KANG

Leboy selected as AWIS fellow

The Association for Women in Science announced the selection of Phoebe Leboy as a 2010 AWIS Fellow at its 40th Anniversary and Fellows Reception held in conjunction with the annual meeting of the American Association for the Advancement of Science this past spring.

In her presentation, AWIS President Joan Herbers noted: "We are honoring Phoebe Leboy for her excellent and long-term efforts in furthering the mission of AWIS through her work as a faculty member at the University of Pennsylvania and her selfless service as a member of the board and president of AWIS."

Leboy is a professor of biochemistry emerita at the University of Pennsylvania. Her laboratory studies changes in gene expression associated with the formation and maintenance of skeletal tissue.

Bonifacino elected PABMB vice chairman

Juan S. Bonifacino recently was elected vice chairman of the Panamerican Association for Biochemistry and Molecular Biology. PABMB aims to foster and support the growth and advancement of biochemistry and molecular biology within the Americas.

Bonifacino received his doctorate in biochemistry from the University of Buenos Aires and moved to the National Institutes of Health to do a postdoctoral fellowship. He later became chief of the Cell Biology and Metabolism Branch.

Bonifacino's research looks at the molecular mechanisms that determine protein localization and fate in the secretory and endocytic pathways and diseases that result from dysfunction of these mechanisms. In particular, he has conducted research on signals and adaptor proteins that mediate protein sorting in the endosomal-lysosomal system.

Shiloh receives Clowes Memorial Award and Israel Prize

Yosef Shiloh, a David and Inez Myers professor in cancer research at Tel Aviv University's Sackler Faculty of Medicine, was selected to receive the 2011 Israel Prize, Israel's most distinguished national honor. The prize is awarded by the Israeli Ministry of Education to Israeli citizens who have demonstrated excellence in their chosen profession.

Earlier this year Shiloh was the first Israeli to receive the 51st annual G.H.A. Clowes Award from the American Association for Cancer Research. He was honored for his studies on the cellular DNA damage response and the rare genomic instability syndrome ataxia-telangiectasia.

Shiloh has been investigating ataxia-telangiectasia and the defect in the DNA damage response that leads to this disease for more than 30 years. He revolutionized the field when his lab identified the ataxia-telangiectasia gene in 1995 and successfully cloned it, calling it ataxia-telangiectasia mutated. The identification of the ATM gene opened many new avenues of inquiry and allowed research to race forward. Since then, the Shiloh laboratory has expanded its studies to the mode of action of the ATM gene product — the ATM protein kinase — and the extensive signaling network that it activates in response to DNA damage.

PHOTO CREDIT: AMERICAN FRIENDS OF TEL AVIV UNIVERSITY.

De Lange and Kang receive Vilcek Prizes in Biomedical Science

The Vilcek Foundation recently announced the 2011 winners of its annual prizes honoring the contributions of foreign-born scientists and artists.

The sixth annual Vilcek Prize for Biomedical Science, given in recognition of a sustained record of innovation and achievement, was awarded to Dutch-born Titia de Lange, the Leon Hess professor and head of the laboratory of cell biology and genetics at Rockefeller University. De Lange received the award for her research on mechanisms that help maintain genome stability. Her work has led to a greater understanding of how telomeres protect chromosome ends and what happens when telomere function is lost during the early stages of tumorigenesis.

The Vilcek Foundation also presented Yibin Kang with its 2011 Vilcek Prize for Creative Promise in Biomedical Science. The prize recognizes foreign-born scientists and artists not more than 38 years old who have made outstanding contributions in the early stages of their professional careers. Currently an associate professor of molecular biology at Princeton University, Kang's research contributes to the general understanding of the molecular basis of

WILLIAMS WILCHEK WARREN BLAU HANAWALT PRIVES

cancer metastasis. His work focuses on the identification of genes and pathways that control metastasis and their role in the propensity of cancer cells to metastasize to different organs.

Williams honored with Presidential Award

President Obama has named Michelle Williams, University of Washington professor of epidemiology and global health in the School of Public Health, as one of the nation's outstanding mentors in science, math and engineering.

Williams, an expert in maternal and infant health, was among 11 individuals and four organizations selected as recipients of the prestigious Presidential Awards for Excellence in Science, Mathematics and Engineering Mentoring. The awards are given by the White House each year to individuals or organizations to recognize the crucial role that mentoring plays in the academic and personal development of students studying science or engineering, particularly those who belong to groups that are underrepresented in those fields.

Williams is director of the UW's Multidisciplinary International Research Training Program and director of the Reproductive Pediatric and Prenatal Epidemiology Training Program at the UW. She also is co-director of the Center for Prenatal Studies at Swedish Medical Center in Seattle and an affiliate investigator at the Fred Hutchinson Cancer Research Center in Seattle.

PHOTO CREDIT: MARY LEVIN

Wilchek awarded Israel Chemical Society medal

Meir Wilchek, a professor at the Weizmann Institute of Science, was awarded the Israel Chemical Society Medal. He shares the award, which is the society's highest honor, with Eli Hurvitz, an industrialist who transformed Teva into Israel's largest company and a world leader in producing generic drugs.

Wilchek is best known for developing the modern concept of affinity between biological molecules. In 1968 he and his colleagues created a method for affinity chromatography, which revolutionized the isolation of biochemical materials and opened the door to new opportunities in biology, biotechnology, chemistry, nanotechnology, physics and many other fields. This method has contributed to many developments in the life sciences and medicine.

Warren honored by March of Dimes

Stephen T. Warren, the William Patterson Timmie professor of human genetics and Charles Howard Candler chairman of the department of human genetics as well as professor of biochemistry and pediatrics at Emory University School of Medicine, will receive the March of Dimes/Colonel Harland Sanders Award for Lifetime Achievement in the field of genetic sciences.

Established in 1986, the March of Dimes/Colonel Harland Sanders Award is given annually to an individual whose lifetime body of research and education has made a significant contribution to the genetic sciences.

Warren is a world-renowned researcher who identified the long-sought genetic abnormality responsible for fragile X syndrome. This disorder is an inherited genetic condition that involves changes in the X chromosome and specifically the FMR1 gene. It is the leading cause of inherited intellectual disability.

PHOTO CREDIT: EMORY UNIVERSITY

Three ASBMB members honored for cancer research

The American Association for Cancer Research has recognized three American Society for Biochemistry and Molecular Biology members whose work has significantly contributed to progress in the fight against cancer.

HELEN M. BLAU was awarded the Seventh Annual AACR-Irving Weinstein Foundation Distinguished Lectureship. Blau is the Donald E. and Delia B. Baxter professor and director of the Baxter Laboratory for Stem Cell Biology in the microbiology and immunology department at the Stanford Institute for Stem Cell Biology and Regenerative Medicine at the Stanford University School of Medicine.

PHILIP C. HANAWALT, the Morris Herzstein professor of biology at Stanford University and a pioneer in the field of DNA repair, received the Fifth Annual AACR Princess Takamatsu Memorial Lectureship for international collaboration.

CAROL L. PRIVES, the Da Costa professor of biology at Columbia University, was awarded the 14th Annual AACR-Women in Cancer Research Charlotte Friend Memorial Lectureship.

PHOTOS COPYRIGHT 2011 AACR/TODD BUCHANAN.

ASBMB members in industry

In this annual Science Focus feature, we profile a few of our members who are doing industrial research.

BY NICK ZAGORSKI

All American Society for Biochemistry and Molecular Biology members share a passion for the biochemical sciences, but the methods by which these scientific passions are fulfilled are exceptionally varied. This is especially true among members who work in industry. From small startups that many people have not yet heard of to global biotech giants like Merck and Invitrogen and even nonpharmaceutical companies like Kraftand Coca-Cola, ASBMB scientists are making important contributions. In this annual Science Focus feature, we once again profile a small sampling of these industrious individuals to showcase the rich and diverse scope of ASBMB research.

Juan Manuel Domínguez
Manager, Drug Discovery Department, Noscira
Tres Cantos, Spain

noscira

While visitors to Madrid can surround themselves with a culture rich in art, history and architecture, they also can find some newly emerging science culture if they look in the right spots. One such place is found some 10 miles outside the city, in secluded Tres Cantos — the headquarters of Noscira.

One of many small, independent biotech companies springing up in Spain, Noscira is a reflection of Spain's new scientific ambitions.

"Spain does not have a long tradition of venture-fueled biotech companies," notes Juan Manuel Domínguez, who heads Noscira's drug discovery department, "so companies like ours have trouble securing financing. Investors aren't used to supporting an enterprise that, even if highly successful, won't bear fruit for many years."

But if some of the early biotech startups like Noscira, founded back in 2000, can achieve their goals, that can build confidence for future companies.

And as of now, Noscira, which uses natural marine products to identify new therapeutic drugs for Alzheimer's and other neurodegenerative diseases, is on track to provide a boost of that confidence. It's currently exploring the potential benefit of a compound called tideglusib in phase II clinical tri-

Noscira has a library of over 20,000 natural products extracted from various marine organisms, including starfish.

als for both Alzheimer's and progressive supranuclear palsy.

It's a tremendous feeling for Domínguez, who joined Noscira in 2008. "Compared to a large company, working at Noscira (with only around 60 full time employees) offers everyone a true sense of ownership in the whole drug discovery and development process."

Domínguez understands the contrast quite well, having spent 16 years working at GlaxoSmithKline before his move to Noscira (a very short move, as GSK happens to have a drug discovery center in the same town as Noscira).

He joined the global pharma giant straight out of graduate school, earning his doctorate degree in chemistry from the Complutense University of Madrid. "My graduate mentor had many connections with industry people and often took his pupils to visit several companies' facilities, which gave me good opportunity to see what an industry career would be like," Domínguez says. "I thought industry would be a great place to pursue my interests in enzymology, and I had good timing as Glaxo just opened a new center in Spain when I finished my Ph.D."

His early work in Glaxo's biochemistry department involved studying the mode of action for various novel antifungal agents to understand how they specifically targeted fungi but not other eukaryotes. His work retained quite a bit of academic flavor, but he did begin to see some of the differences of working in industry compared to a university.

"I'm not saying it's a good or bad thing, but working at a biotech or pharma does require a scientist to be more pragmatic about his projects," he notes. "So if anyone is thinking about going into the industry sector, they should take into account that sometimes they have to let promising experiments go."

In 2001, following the merger of Glaxo and SmithKline Beecham (which also had a center in Tres Cantos), he moved on to the assay development team. His specialty was developing and miniaturizing assays for hard-to-obtain proteins; during that time he managed to develop a process for assaying substrates of fatty acid synthase — which is very hard to prepare in large quantities — that only required 3 υl sample sizes.

Those skills in protein biochemistry and running assays are valuable for Noscira, which has a library of more than 20,000 marine natural extracts for screening. Equally valuable has been the international exposure Domínguez received in his nearly two decades at GSK; though he has spent most of his time in his hometown of Madrid, Domínguez has worked in laboratories throughout Europe and the U.S. That international interaction has given Domínguez important perspectives on success.

"In the United States, for example, which has a long history in the pharmaceutical industry, I've seen successful places often have matrix management with a strong horizontal leadership," he says. "That is, a senior executive will listen to junior researchers because they have the in-depth knowledge about studies, and this is less common in Europe, where hierarchy is still quite vertical."

But the scientific talent certainly is there, and with a little time, Domínguez thinks the mindset will shift as well. Soon, Spain's homegrown biotechs will be as highly regarded as its many other cultural contributions.

Nancy Robinson
Senior Director, STERIS Corporation
Mentor, Ohio

STERIS

Although people generally do their best to avoid trips to the hospital, at some point in life most everyone will require a surgical or diagnostic procedure. And in those moments, we expect that both our physicians and their equipment be of the best quality.

Nancy Robinson has the satisfaction of knowing that through her work to improve methods to decontaminate and sterilize surgical instruments, the tools used in various surgical procedures will meet the patient's expectation of best quality.

"Some of my colleagues have kidded me that I had fallen from the true faith when I left academia," Robinson says. "But that is not the case; here at STERIS I have found an outlet for my passion of solving technical challenges and my desire to achieve tangible outcomes."

At first thought, a medical device company — as compared to a pharmaceutical company — may seem like an unusual destination for a biochemist looking for a career in the private sector. However, STERIS, where Robinson has been since 1998, is really not too different from a drug company. Both places bring together diverse scientists to solve a biological problem and bring it to market; both involve working through U.S. Food and Drug Administration regulations to ensure that final products are safe and effective; and perhaps most importantly, both groups are about improving human lives.

At STERIS, Robinson carries out research in the Infection Prevention Technologies branch of the health-care business unit, which develops reprocessing equipment such as sterilizers, washer-disinfectors, high-level disinfectants and automated liquid chemical processing systems. (STERIS also has another health-care branch that offers surgical lights, tables and other equipment.)

For the past several years, her team of dedicated chemists and microbiologists, working with a group of talented engineers, has been designing and improving low temperature vaporized hydrogen peroxide sterilization systems called the Amsco® V-PRO™ 1 and the V-PRO 1 Plus Low Temperature Sterilization Systems. Such technology is critical for rapid reprocessing of heat-sensitive instruments that cannot handle the rigors of steam sterilization.

Recently promoted to senior director, Robinson devotes much of her time to carrying out the verification and validation testing of the products and interacting with various global regulatory bodies through the submission process.

For the past several years, Nancy Robinson has been designing and improving low temperature vaporized hydrogen peroxide sterilization systems called the Amsco® V-PRO™ 1 and the V-PRO 1 Plus Low Temperature Sterilization Systems.

It may sound bureaucratic, but Robinson counters that it is quite interesting. "It is very rewarding to interact with both our customers and the medical device manufacturers and discuss how to improve the ease, quality and outcome of their work," she says. "It's also rewarding and a bit challenging to sort through the different global regulatory requirements for our products and devise strategies to most effectively meet them."

Robinson admits, though, that she didn't envision this type of job description back when she re-entered the science workforce in 1994 following a four-year break to raise her children. Previously, she had completed her graduate studies in enzymology and done a commission with the United States Army Medical Research Institute of Infectious Diseases studying the metabolism of a small cyclic peptide toxin called microcystin-LR. (Robinson had received a U.S. Army college scholarship.)

She initially took a postdoctoral position at Case Western Reserve University — where she had also received her doctorate — to study the structure of the cornified envelope, the protective protein coating formed by the upper layers of skin. Robinson's plan was to obtain a permanent position in either academia or industry within four years.

"To that end I was exploring teaching at local institutions, writing grants to develop independent support and reminding colleagues as they would move on to other positions to keep me in mind if anything opened up at their new workplace," she says.

"Things were moving along, and I had just heard from a local university about a potential job when I received a call from a former colleague about an opening at STERIS," Robinson continues. "I was leaning toward academia, but my colleague talked me into coming for a visit."

"After my interview with STERIS, I began to lean the other way."

While Robinson enjoyed basic research, she realized what really drove her in the lab was problem solving and that she preferred tangible solutions to discovery for discovery's sake.

Thirteen years later, she remains excited about working in this challenging and fast-paced industry environment. "I continue to expand my knowledge base every day, I get to work with a great team of colleagues, and I can say I have never regretted my decision to join."

Nick Zagorski (nicozags@gmail.com) is a freelance science writer.

For more information:

Be sure to go to the online version of this article at http://bit.ly/AToday0711SciFocus for a bonus science focus profile of Mary Bossard, a senior fellow at Nektar Therapeutics.

The industrial doctorate

New European graduate program bridges academia and industry.

BY NANCY VAN PROOYEN

Over the past 20 years, the number of scientists who have obtained doctorate degrees has risen more than 40 percent. The growth shows no signs of slowing, since most countries are building up their higher-education systems to compete globally in science and technology. However, in much of the world, many science graduates will not get tenured academic positions. With numerous doctoral degree holders now turning to industry, are traditional graduate programs preparing students for successful pharmaceutical or biotechnology careers?

Over the past 10 years, several universities have started to offer biotechnology master programs that focus on both science and business. However, very few biotechnology doctorate programs exist in the U.S. The University of Virginia offers a doctorate in biotechnology, although students only work with a company two to three months as interns rather than directly connecting their research to a company.

However, in Europe, the outlook is entirely different. The European Commission currently is taking bold steps to train a new crop of graduates prepared to enter industry. Universities around the European Union and several other countries, including Israel, Switzerland, Norway and Serbia, are closely collaborating with businesses under a pilot doctoral program called an industrial Ph.D.

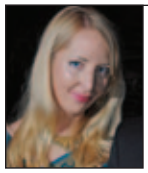
The industrial Ph.D. program is modeled after an existing Danish program that has been in operation for more than 40 years. Other similar successful programs have been started in the UK and France. The goal of the program is to give scientists a more entrepreneurial mindset and skills tailored for both public and private research.

The program requires students to take business classes and create a research project with a focus on development and innovation in a private company. Industrial doctorate candidates divide their time between the academic environment and the private enterprise. Thus, students can be employed with a partnering private enterprise during the project period. Their employers can even be located in different countries from their home institutions. The aim is to build personal networks between companies and research institutions. The program is designed to encourage private industry to play a role in training scientists, and a business focus will allow students to transition smoothly into leadership roles in industry after obtaining their degrees.

There are three overlapping objectives of an industrial doctorate. One is to give students practical tools to manage their research projects at the intersection between a company and a university. The second objective is to give students an appreciation of the commercial aspects of research and innovation. And the third is to introduce students to the nonacademic dissemination of research and the process of securing patents.

The success of the Danish industrial Ph.D. convinced the European parliament to move forward with a Europe-wide program that is expected to incorporate its first batch of 100 scholars in September 2012. The program currently has more than 50 partnering enterprises. The European Commission plans to provide €20 million ($28 million) to fund the program under a special education and funding initiative titled the Marie Curie Action. The ultimate goal of the program is to make research careers more attractive for young people.

Synergy between academics and industry not only will prepare students for translational research but also will make academic research more strategic and technologically relevant. Bioscience laboratories and biotechnology companies with diverse connections have been more successful in publishing research, securing patents, and acquiring grants than those with fewer connections. Moreover, companies with more academic collaborations have flourished while those without have floundered. Overall, the industrial doctorate program is poised to benefit both the students and participating companies and universities.

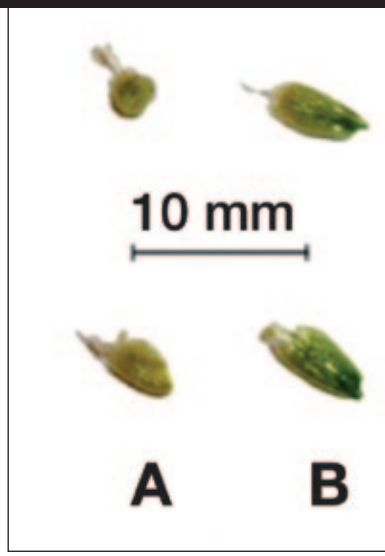


Nancy Van Prooyen (nancy.vanprooyen@ucsf.edu) is a postdoctoral fellow at the University of California, San Francisco.

Pouring energy into biofuels

Many biochemists are working on alternatives to corn-derived fuel ethanol.

BY CHRISTEN BROWNLEE



That line in "America the Beautiful" about amber waves of grain was written as a testamony to our country's abundance and ready opportunity to feed the hungry masses. But increasingly, America's grains are feeding masses of hungry cars, not people. Nearly all gas in the U.S. contains 10 percent fuel ethanol, a product currently made by using yeast to ferment sugar derived from cornstarch. America produced about 13.2 billion gallons of fuel ethanol last year, making this the most common biofuel — fuel metabolically derived from living organisms as opposed to fossil fuels produced over hundreds of millions of years from long-dead organisms — in this country.

But while the corn lobby probably would be thrilled to keep ethanol made from their grain in the top spot, biofuel researchers have other ideas. They're working toward new advances aimed at moving away from corn-derived fuel ethanol, such as engineering bigger and better grasses to pull more fuel from their vegetative tissues rather than their seeds and genetically modifying plants to make removing the sugar polymers that serve as a feedstock for fuels faster and easier. Others are working on modifying plants to produce energy-rich oils preferentially instead of starch or teaching biofuel-processing bacteria new tricks, such as making longer-chain alcohols that store more energy than ethanol, synthesizing biofuels out of proteins instead of sugars, or digesting sugar polymers directly and pumping out biofuels at the same time.

So instead of those amber waves of grain, America may eventually have green waves of switchgrass or miscanthus — or even waving cilia from fuel-making bacteria.

Going green

Although biofuel might seem like a hot topic at the moment, it's really an old idea, explains Daniel Bush, professor and chair of the department of biology at Colorado State University.

"It's just another way of transforming sunlight into a useful form of energy," Bush says.

Plants do much of the work for us, he explains, by creating oils, simple sugars and sugar polymers such as starch and cellulose as products of photosynthesis. We can then process these products into ethanol, biodiesel (diesel fuel made from vegetable oil or animal fat) or other fuels. Though biofuels often have faded into the background during periods with low gas prices, Bush adds, they become more popular with every gas crisis.

Though biodiesel is more common in Europe, ethanol is king in the U.S. Fuel ethanol certainly has its benefits: it adds oxygen to gas, leading to a cleaner burn that produces less pollution, and it increases octane.

However, ethanol also has a number of drawbacks. Crops used most often to produce it can be finicky about where they'll grow. For example, sugarcane, another common source for ethanol, thrives in Florida but not in Michigan, and corn needs rich, pampered soil and not rocky, arid land. Additionally, since the most common sources of ethanol also are food for people, it sets up a competition over the best land between food and fuel.

"It could lead to an unstable market," says Dominique Loque, a research scientist at the Joint BioEnergy Institute in Emeryville, Calif. "Only rich people will be able to drive and eat."

Consequently, many researchers have suggested gathering energy from the vegetative tissues of plants instead of the parts we use for food. Stems, branches, and leaves contain cellulose, a polymer of glucose in the cell wall that holds ample energy for conversion to biofuels. Indeed, potential energy in cellulose is often more than 10 times that available in starch from a given plant. Moreover, these plant organs are frequently a throw-away byproduct of the food industry, so conversion to biofuels could prevent waste.

However, notes Bush, switching from corn kernels to foliage isn't so simple. Though researchers have actively worked on improving corn and other food plants for hundreds of years, the focus has been on the seed, not the greenery. As a result, about half of corn's above-ground biomass is in its ears. If the new biofuel focus is the rest of the plant, Bush says, researchers better get cracking on making new energy crops, such as grasses — significantly bigger.

Katie Dehesh, a professor of plant biology at the University of California, Davis, is coaxing oats to make more oil than starch.

That's one of his lab's projects. With colleagues at Colorado State University and the International Rice Research Institute in the Philippines, Bush is working on identifying genes that are responsible for making the most of rice's green biomass. Rice is a good model for improving other grasses' biomass, he says, since the genomes of all 20 rice varieties have been sequenced. Bush notes that in this work, rice is an experimental model and not a target as a biofuel crop.

"A long time ago, many breeders learned that if you see a very large plant, 50 percent larger than the others, to just ignore it — they put most of their carbon into vegetative growth and have lower seed production," he says. But those big plants are just what he and his colleagues are looking for. The researchers have spent many days walking through rice fields searching for the largest plants produced either through hybrid crosses or mutagenesis. Using modern deep-sequencing approaches, Bush and his colleagues can then locate the gene responsible for the plants' extraordinary size. The team is now close to identifying the first promising gene from that approach.

Bush's lab also is working on another way to make more greenery through bypassing the feedback system that controls a plant's photosynthesis rate. Leaves are the hotbed for photosynthesis, and as plants spin sunlight into sucrose, that product is transported to non-photosynthetic tissues in the plant's vascular system. If production exceeds export, Bush explains, plants shut off photosynthesis until the sweet stuff can distribute to other parts of the plant through its vascular system. Using sugarbeet as a model system, he and his colleagues have engineered plants whose cells have a sucrose transport gene placed behind a constitutively active promoter. Consequently, the leaves are constantly pumping out sucrose — and thus, keeping low sucrose in the leaves and preventing negative feedback on photosynthesis. Over a season, he hypothesizes, this furious activity translates into significantly more biomass per plant.

Another drawback researchers will need to overcome before vegetation rules the biomass roost is that in most plants, energy-rich cellulose is bound up with significant amounts of lignin, the cell wall component that provides mechanical strength. Currently, biofuel producers separate cellulose from lignin with harsh, expensive chemicals and high temperatures. Several researchers, including Loque, are looking for ways to avoid these.

Loque explains that altering lignin content is tricky. Remove too little, and deriving cellulose remains difficult; remove too much, and the plant has no support to grow.

He and his colleagues currently are working on two strategies to surmount the lignin problem. In the first, the researchers are tinkering with where plants deposit lignin. Loque notes that the entire lignin pathway is known and highly conserved. By using promoters throughout the pathway that produce different expression of lignin genes relative to the native ones, the researchers have successfully reduced lignin in undesirable areas while keeping it in necessary places, such as the vessels plants use for nutrient transport.

"In the end, we got plants that look like wild-type, but contain much less lignin," he says.

He and his team also are working on engineering plants that make weaker lignin through genetic modifications that insert ester or amide bonds into the native structure, which has only carbon-carbon or carbon-oxygen bonds. These weak links eventually could reduce the amount of chemicals and lessen the temperatures needed to pretreat cellulosic feedstocks.

Learning about biofuels in Brazil

The American Society for Biochemistry and Molecular Biology is playing a vital role in creating the next generation of biofuels. Last fall, the society co-sponsored a week-long advanced course aimed at inspiring interested graduate students and postdoctoral fellows to join the biofuels revolution. At a small resort in the lush coastal city of Ubatuba, Brazil, 40-odd international participants gathered to attend lectures and participate in intense roundtable discussions.

The aim wasn't to have attendees listen to endless talks, says Bettie Sue Masters, past president of ASBMB and principle organizer of the school. "It was really interactive," she says. In the daily roundtable sessions, participants had the chance to discuss their own work or research aspirations or to solicit lecturers' career advice.

Besides being a terrific chance for young researchers to learn about this burgeoning field, it also proved to be a great way to forge a strong partnership between ASBMB and colleagues in the Brazilian Society for Biochemistry and Molecular Biology and the International Union of Biochemistry and Molecular Biology. These groups are planning to cosponsor future meetings, including one in the fall of 2012 on protein folding and protein-protein interactions.

"It was much better than we ever thought it would be — a valuable experience for everyone involved," Masters says.

Escaping from ethanol

Another drawback of fuel ethanol is that researchers have calculated that, in many cases, it's actually an energy sink rather than a source; the amount of petroleum used to plow and fertilize a cornfield, then transport and process the corn before fermentation, often contains more energy than the resulting ethanol. It's also tremendous waste of the carbon atoms plants work so hard to fix. Only two thirds of a feedstock's carbons are used in ethanol production, explains Katie Dehesh, a professor of plant biology at the University of California, Davis. The other one-third ends up as food for the fermenting yeast and in the air as carbon dioxide.

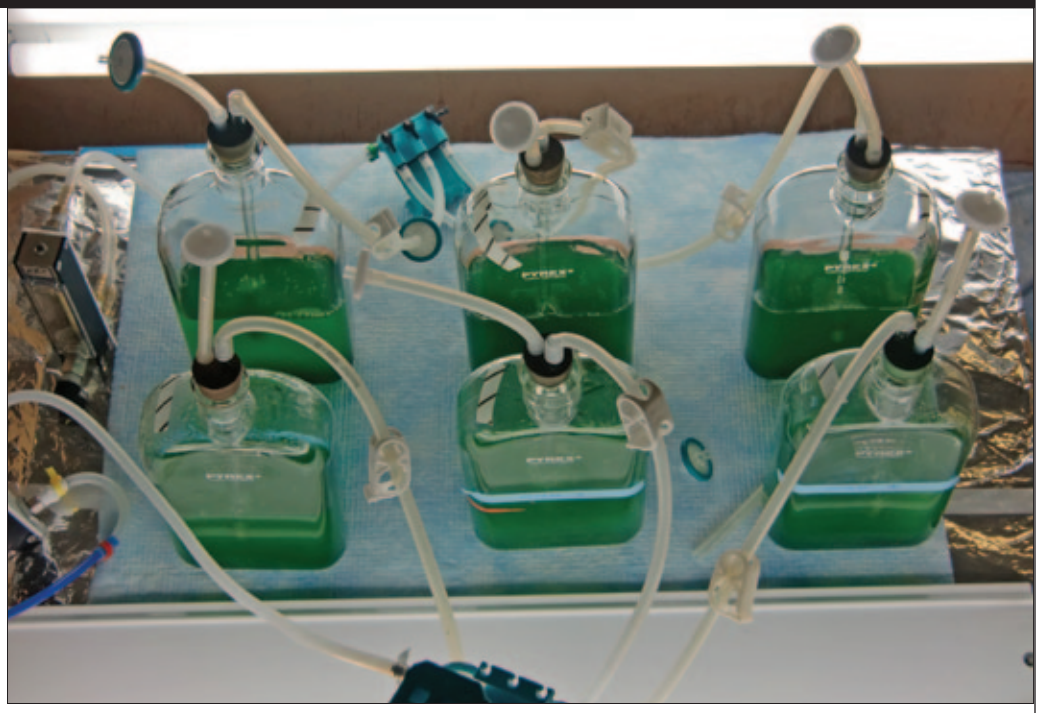
A possible solution is coaxing plants to make more oil than starch. Indeed, many plants already produce significant quantities of oil; it's what fills the frying vats for much-loved fast-food fries. However, using these food crops for fuel oil has the same competitive disadvantages as creating ethanol from corn. Additionally, Dehesh points out, oil is only a minor component of most plants' seeds and is even less abundant in their vegetative parts.

She and her colleagues recently published new research that could offer a possible solution to this problem by redirecting carbon flux toward oils and away from carbohydrates. The researchers used oat as their model organism, since this grain is a rare example of a plant that produces significant amounts of oil in its endosperm at the cost of carbohydrates. Using two varieties of oats — one that produced much more oil than the other — Dehesh's team compared gene activity between the plants during seed development. Surprisingly, the fatty acid pathway that they expected to see upregulated in the high oil producer was actually the same between the two plants. However, the researchers found a variety of differences in the cofactors involved in respiratory metabolism. These cofactors, says Dehesh, appear to be the answer for determining carbon flux.

"I strongly believe that modification of these specific cofactors will provide us with the global key for conversion of starch to oil in any organism," she says. In principle, she adds, there's no need to switch starch for oil in seeds. Rather, genetic engineering could put the activity of these key cofactors in a plant's vegetative tissues, or even in algae or bacteria, changing their metabolisms to spit out more oil.

James Liao, chancellor's professor and vice-chairman of the department of chemical and biomolecular engineering at the University of California, Los Angeles, also is working on moving away from ethanol by using synthetic biology to engineer bacteria that churn out longer-chain alcohols with significantly higher energy density.

Using E. coli as their model organism, Liao and his colleagues leaned on this organism's native amino acid biosyn-



James Liao of the University of California, Los Angeles has engineered photosynthetic cyanobacteria that produce a variety of higher alcohols. PHOTO CREDIT: YIXIN HUO AND XIAOQIAN LI

thesis pathways to create starter molecules for various alcohols. They then strung together genes from various other organisms, including Sacchromyces, Lactococcus and Clostridium, for enzymes to convert these molecules into the desired product. Using this method, the researchers engineered E. coli that produced a variety of higher alcohols, including isobutanol, 1-butanol, 3-methyl-1-butanol, and 2-methyl-1-butanol, from glucose.

Not ones to rest on their laurels, Liao's team followed this research up with another paper, published the next year, that used parts of the same pathway in photosynthetic cyanobacteria. The resulting organism produces isobutyraldehyde and isobutanol by pulling carbon directly from carbon dioxide in air.

In a recent paper, Liao's lab detailed their synthesis of E. coli that produce alcohols from protein — thus far, an unutilized feedstock — by redirecting this organism's metabolic flow of nitrogen.

"We like to keep pushing things further and further," he says.

Jay Keasling, a professor in the departments of chemical and biomolecular engineering and bioengineering at the University of California, Berkeley, also is harnessing the power of synthetic biology for biofuels, both higher-chain alcohols and biodiesel from fatty acids.

In one recent paper, Keasling and his colleagues engineered yeast that make n-butanol, a far cry from the ethanol this organism usually makes. Rather than rely on the amino acid biosynthesis pathway that Liao's team used, the researchers instead modified the acetyl-CoA pathway using genes from five other organisms. The team mixed combinations of individual genes, eventually producing seven different modified strains. One of these successfully produced significant quantities of n-butanol. This year, Keasling's former postdoctoral fellow Michelle Chang, now an assistant professor of chemistry at University of California, Berkeley, significantly improved these yields with some of these same non-native components in E. coli.

Seeking to pack even more energy into their fuel molecules, Keasling's group engineered another set of bacteria to generate biodiesel using a reaction similar to how biodiesel enthusiasts make their own homebrew. First, the researchers tricked E. coli into overproducing the fatty acids that make up its membrane, adding in a plant gene that prevented these hydrocarbons from becoming part of the phospholipid bilayer. A series of non-native genes attached ethanol to the structure, esterifying it much like a home biodiesel maker would. The resulting fuel can be skimmed off the top of the tank and go directly into a diesel engine, Keasling says.

Taking the research one step further, he made another tweak in these bacteria that allowed them to digest hemicellulose, using it as a feedstock for biodiesel production.

Keasling notes that it's still very early times in the biofuel field. His and other academic labs energetically continue to churn out fresh ideas and research, which fuel companies — from big giants to tiny startups — are eyeing with interest. One of these ideas, he says, might eventually end up in the engine of your car.

"We're fortunate, because there's a lot of interest right now," he says. "It's a really great time to be working in this area."

Christen Brownlee (christenbrownlee@gmail.com) is a freelance science writer based in Baltimore, Md.

Meet some of our members in industry

For this issue, we asked several of our members who work in industry to answer some questions about themselves and their research.

BY NICOLE KRESGE

Oliver Chao
Sanofi-Aventis Exploratory R&D
Paris-Chilly Mazarin, France

Q: ***How long have you been an ASBMB member?***

CHAO: You are trying to guess my age? Well, let's say more than 10 years now.

Q: ***What is the focus of your company?***

CHAO: Patient-centered health care and therapeutic development

Q: ***What is the focus of your research?***

CHAO: Actually, the foci of my research: I am in full-blown exploration in the fields of sensory systems, designed-synthetic biology and bio-inspired devices. In addition, I pay special attention to circadian rhythm and neuro-oncology.

Q: ***Why did you go into industry?***

CHAO: When I landed in Paris (relocating with my wife, who's French), it was impossible for non-European citizens to obtain permanent (tenured) positions in the French research institutions. So after a year of a postdoctoral fellowship at INSERM/College de France, when the opportunity to join a pharmaceutical company in the Paris area appeared I did not hesitate. In retrospect, I think I have more flexibility to be involved in wide spectrums of biological sciences because of being in pharma R&D. Naturally, if your scientific interest is very specific or your goal is Nobel-ish, industry may deprive you of your focus.

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

CHAO: As fun as prediction is, the pharma industry or the pharma research paradigm is predictable only in the frame of about two to three years. As far as my company is concerned, I think the general strategy of patient-centered drug discovery is a very wise and feasible goal for pharma researchers to achieve in five to 10 years.

Q: ***With the economy improving, are you seeing any changes in your job or company?***

CHAO: Pharma industry does not really reflect closely the main street/Wall Street pulse. What I believe is that through open-minded adaptation and well-thought-out collaboration, we can face any challenge, any change.

Charles R. Cantor
Chief scientific officer
Sequenom, Inc.
San Diego, Calif.

Q: ***How long have you been an ASBMB member?***

CANTOR: Seems like I've been a member of ASBMB forever – I think I was a member of the American Society for Biological Chemists before the "Molecular Biology" was added. (*Editor's note: Cantor joined ASBMB in 1969).*

Q: ***What is the focus of your company?***

CANTOR: I have three active companies. Sequenom, the company I actually work for, has two focus areas: We are a technology provider of automated nucleic acid mass spectrometers used in a variety of applications from plant and animal genetics to somatic mutation analysis in tumor biopsies. We also are a diagnostic service provider focused on noninvasive prenatal diagnostics and ophthalmology using nucleic acid biomarkers. For diagnostic services we are technology agnostic.

My second company, DiThera, is developing both therapeutic and diagnostic applications of nucleic acid-mediated protein complementation, a method of detecting specific RNA sequences in living cells or manipulating the properties of cells that express these sequences.

And finally, Retrotope concentrates on novel ways to combat oxidative stress in a variety of disease indications. Instead of using antioxidants or other scavengers, we use essential nutrients reinforced by heavy isotopes at key positions to strengthen these potential substrates against oxidative attack.

Q: ***What is the focus of your research?***

CANTOR: I don't do much research myself anymore, but I am still interested in developing new methodologies. Mostly, I make suggestions that are sometimes followed by one of the three companies.

Q: ***Why did you go into industry?***

CANTOR: I found that it was easier to raise money to support risky but potentially high-impact innovative projects in industry than it was in academia.

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

CANTOR: We have a plethora of new tools that affect both diagnostics and therapeutics, but as always, the key obstacle is finding killer commercial applications for these tools.

Q: ***With the economy improving, are you seeing any changes in your job or company?***

CANTOR: Because diagnostics and therapeutics are highly regulated industries, I think they are subject more to fluctuations in the regulatory climate than in the economic climate.

Robert S. McCollum

Research associate
Boehringer Ingelheim Ltd.
Laval, Québec

Q: ***How long have you been an ASBMB member?***

MCCOLLUM: I've been a member since 2000.

Q: ***What is the focus of your company?***

MCCOLLUM: We do antiviral drug discovery.

Q: ***What is the focus of your research?***

MCCOLLUM: I look at biochemical and cellular assays as well as protein purification.

Q: ***Why did you go into industry?***

MCCOLLUM: There are better opportunities at my level (I have a Master of Science).

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

MCCOLLUM: I see more biotherapeutics being developed.

Q: ***With the economy improving, are you seeing any changes in your job or company?***

MCCOLLUM: Changes have already occurred with cutbacks and refocusing of priorities. Reorganization is an ongoing activity.

Yasushi Noguchi

Senior researcher
Ajinomoto Co., Inc.
Kawsaki, Japan

Q: ***How long have you been an ASBMB member?***

NOGUCHI: About four years.

Q: ***What is the focus of your company?***

NOGUCHI: Ajinomoto Co., Inc. focuses on various issues, such as seasoning, processed food, beverages, nutrition, pharmaceuticals and fine biochemicals.

Q: ***What is the focus of your research?***

NOGUCHI: My research has focused on metabolomic profiling for clinical diagnosis including cancers, diabetes and so on. I also do network modeling of metabolic pathways using metabolomics with stable isotopic flux analysis. Using these technologies, we will start a cancer-screening service in Japan this year.

Q: ***Why did you go into industry?***

NOGUCHI: I wanted to engage in projects ranging from research to development to business.

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

NOGUCHI: I think that the correlation between R&D costs and achievements is getting worse in many industries. Therefore, most industries will be willing to be open to innovation in outsourcing research to universities or other ventures, and cutting their internal core-research labs.

Q: ***With the economy improving, are you seeing any changes in your job or company?***

NOGUCHI: At this time, it makes little sense, thinking about just the economy inside my own country. In any case, we will do research for businesses in emerging countries.

Cynthia Tuthill

Senior vice president and chief scientific officer
SciClone Pharmaceuticals Inc.
Foster City, Calif.

Q: ***How long have you been an ASBMB member?***

TUTHILL: I think since 1984 (when I got my Ph.D.).

Q: ***What is the focus of your company?***

TUTHILL: Pharmaceuticals, with a focus on sales in China.

Q: ***What is the focus of your research?***

TUTHILL: Preclinical research for immune-modulating compounds. I don't do the research myself but use collaborations with academic groups or with contract research organizations.

Q: ***Why did you go into industry?***

TUTHILL: I wanted to make new medicines for people, to alleviate suffering.

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

TUTHILL: I see more and more virtual companies like ours who use contract research organizations to do routine studies and academic collaborators to do development and discovery work.

Q: ***With the economy improving, are you seeing any changes in your job or company?***

TUTHILL: Yes. Our sales are strong and we have a good cash balance. Also I notice people are moving around from company to company again, moving up the ladder by moving into new positions in new companies.

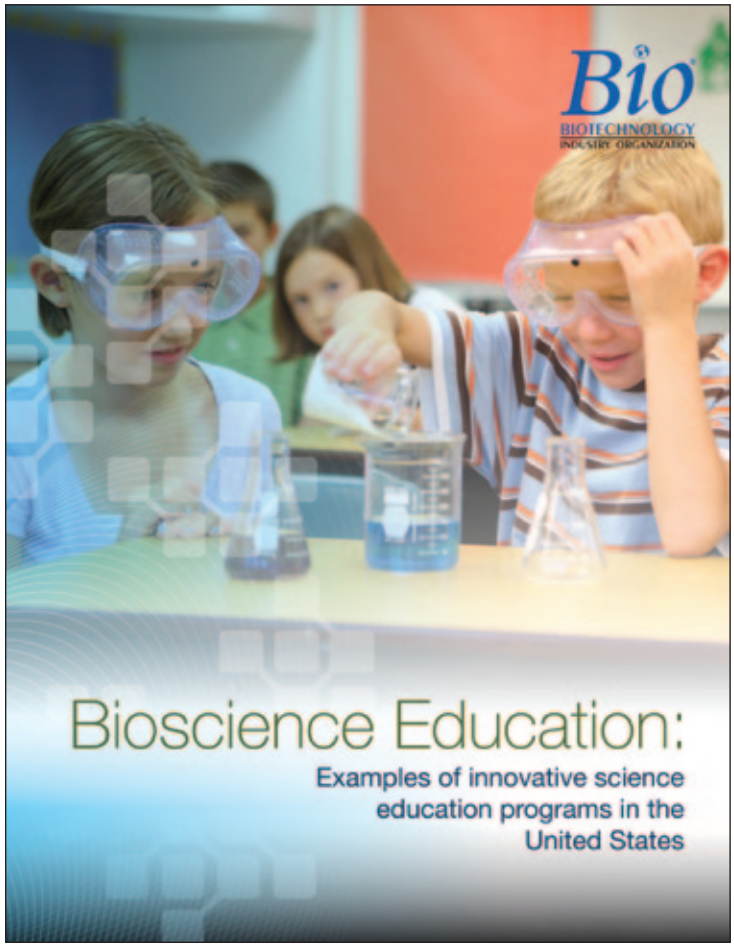
Nicole Kresge (nkresge@asbmb.org) is the editor of ASBMB Today.

Investing in future innovators

BIO releases best practices recommendations for improving STEM education in the U.S.

BY LESLIE W. CHINN

In 2005, in response to a request from a bipartisan group of U.S. legislators, the National Academies of Sciences issued a report titled "Rising above the gathering storm: energizing and employing America for a brighter economic future." The "gathering storm" report, as it commonly became known, evaluated the nation's standing in what it called the "principal ingredients of innovation and competitiveness — Knowledge Capital, Human Capital, and the existence of a creative 'Ecosystem.'" Its findings painted a worrying picture of America's ability to keep pace with the global science and technology market and emphasized that "the most pervasive concern was considered to be the state of the United States K – 12 education, which on average is a laggard among industrial economies."



Show them the science

In recognition of this concern, the Biotechnology Industry Organization, in conjunction with Battelle, a global leader in innovative research, recently released a report containing recommendations for best practices in elementary and secondary science, technology, engineering and mathematics education. The report, "Bioscience education: examples of innovative science education programs in the United States," gives examples of state-administered STEM programs in which BIO sees promise through its ongoing evaluation of bioscience education in the United States.

The BIO report details six areas that have demonstrated effectiveness:

- implementing state-wide bioscience education standards,
- developing special state schools or programs in STEM education,
- encouraging teacher quality and preparation,
- providing opportunities for experiential learning and career awareness,
- supporting mobile lab programs and
- maintaining bioscience education support organizations for schools and states.

In effect, the BIO recommendations are all about exposing kids to science in a coherent yet engaging manner and even encouraging them to think about becoming scientists someday. "Many students leave high school without having learned basic biology principles," the BIO report states, "and even fewer are excited enough by the sciences to pursue them in higher education or as a career."

The report also gives examples of the recommended bioscience education best practices at work, citing specific

initiatives and programs by state. It's no surprise that the states with the highest numbers of effective STEM education programs are Maryland, Massachusetts and California — places that already are hotbeds of scientific innovation. A thriving biotechnology industry tends to make a larger investment in bioscience education, thereby contributing to the human capital component cited in the "gathering storm" report. This type of circular relationship is good for biotech companies, schools and especially the kids who reap the benefits of early exposure to STEM. And because funding bioscience education is especially difficult at present — state and local governments are constrained by tight budgets and other priorities, and the federal American Recovery and Reinvestment Act and America COMPETES Act are set to expire soon — schools are more dependent on the biotechnology industry than ever. But biotech companies tend to cluster geographically; states with a weaker biotech presence tend to lag behind in terms of bioscience education too.

A call to action

According to BIO, comprehensive bioscience education is just one aspect of creating a favorable environment for a thriving biotechnology community. An incubator for innovation, such as a university, where groundbreaking research is performed, often is where small companies begin to take shape. Access to capital also is important so startups can get their feet off the ground. And being business-friendly helps — states that provide tax breaks for small companies, for example, tend to have a more developed biotechnology sector. But a skilled and educated workforce is essential for building the biotechnology industry locally. "Without an increase in children and young adults pursuing the STEM disciplines, the U.S. bioscience industry will be forced to look abroad for competent workers," noted BIO President and CEO James Greenwood in a press release.

Greenwood's statement conveys a sense of urgency about the state of bioscience education in America — as does the BIO report itself. "Where the country leads in scientific and industry development, it is trailing many developed nations in the educational attainment of its workforce," it states. "This poses a very real threat to the nation's leadership position in the coming decade." Even more sobering is the National Academies of Sciences' follow-up report, "Rising above the gathering storm, revisited," which assesses changes in the nation's competitiveness outlook in the five years since the original "gathering storm" document was issued. The 2010 report observes that there has been little improvement in the public school system, particularly in STEM education, and bluntly notes, "The Gathering Storm increasingly appears to be a Category 5."

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For more information:

- The National Academies of Sciences "gathering storm" report: http://bit.ly/NASGatheringStorm
- The National Academies of Sciences "Rising above the gathering storm, revisited" report: http://bit.ly/NASStormRevisited
- The BIO "Bioscience education: examples of innovative science education programs in the United States" report: http://bit.ly/BIOreport

A bioprocessing institute

New Irish facility provides research, training and education for all aspects of bioprocessing.

BY JOANNA FARES

The National Institute for Bioprocessing Research and Training is an initiative led by four of Ireland's top academic institutions: University College Dublin, Trinity College Dublin, Dublin City University and the Institute of Technology Sligo. The driving motivation behind the creation of NIBRT was to bridge the gap between the pharmaceutical sector and academia by developing world-class training programs for students and industry professionals and ensuring the creation of a workforce with the specific skills and competencies needed in industry. In 2006, the Irish government provided seed funds exceeding U.S. $100 million for the project, which now is considered to be a national resource with a catalytic role in the growth and advancement of the biopharma sector. NIBRT's mission has three parts: training and education, research, and providing state-of-the-art multipurpose facilities to house the research and training functions.

A new facility

NIBRT's research labs originally were housed in the UCD Conway Institute of Biomolecular and Biomedical Science pending construction of a new facility in Blackrock, Co. Dublin. The new building was completed in late February, and research staff have now moved in.

The state-of-the art facility houses a small-scale upstream and a downstream bioprocessing pilot plant designed for factory scale-up operations — a concept completely unique to such an institute. The large suites host cutting-edge equipment used during the multistep bio-production process. The upstream plant consists of four bioreactor skids for mammalian cell culture, cross microfiltration and centrifuge systems for product harvesting, and an inoculum preparation lab. These are complemented by UF/DF skids in the downstream plant for product concentration, chromatography skids for the recovery and purification of protein products, and vessels for the virus inactivation step.

Also incorporated in the building are interactive spaces and seminar rooms to host meetings and events that serve NIBRT's educational programs. NIBRT aims to to provide a comprehensive and practical experience, so the facility simulates recognized standard good manufacturing practices. This integrated approach brings together in-depth basic training as well as a hands-on practical experience in its applied industrial context.

NIBRT's new facility is considered to be the most strategic investment to date in Ireland's biotechnology sector and a key industry asset.

The training

NIBRT hopes to provide academic educational modules to students and industrial training tailored to the needs of its pharmaceutical partners. The academic educational programs are geared toward both undergraduate and graduate students. In conjunction with its academic partners, NIBRT offers masters degrees in biopharmaceutical science and bioprocessing engineering. This education model is a core strength of the institute since it prioritizes translational research and knowledge transfer. Students benefit from the combined expertise of academic scientists and industrial partners who work in NIBRT's labs.

The industry training program offers a comprehensive set of fully accredited modules. They include introductory modules that deal with the principles of biotechnology, upstream and downstream technology modules, and facility design and bioprocessing regulatory modules. Courses are highly flexible and are designed to be modified according to the industrial client's needs. Furthermore, training is delivered either at the NIBRT facilities, at the client's site or via distance learning. A list of unique training partnerships with companies such as Pfizer, Centocor, Eli Lilly, and more recently Honeyman and Pall Corporation already have been established.

NIBRT works closely with the client company to identify and analyze specific needs, and then designs customized courses that ensure optimal training relevance. For example, NIBRT joined forces with Pfizer following the establishment of its monocolonal antibody facility in Cork, Ireland, and implemented a graduate certificate in bioprocessing for its operating personnel. As a result, Pfizer was awarded the Continuous Professional Development Company of the Year Award in 2009 by Engineers Ireland.

The Eli Lilly collaboration consisted of delivering training courses in new biopharma operating technologies and aseptic

The National Institute for Bioprocessing Research and Training recently opened a new facility in Blackrock, Co. Dublin.

manufacturing protocols. Another recent training collaboration was the design of an interactive course for Pall Corporation that was targeted to manufacturing operators and intended to ensure thorough understanding of accurate testing of filter integrity, which is critical for efficient and safe pharmaceutical production and regulatory compliance.

Balancing basic and translational research

NIBRT's innovative concept is based on maintaining a balance between fundamental basic research and applicable industrial research. A range of studies are conducted at NIBRT under the supervision of principal investigators with extensive industrial experience. Projects cover key issues in the optimization of bioprocesses. They include investigating protein aggregation during therapeutic product packaging, development of solid glycotechnology for quantitative and detailed structural *N*- and *O*-glycan analysis, development of an Fc receptor platform to evaluate IgG biological activity, assessing the impact of single-use bioreactors on media components and protein product integrity, and quantitative analysis of complex cell culture media and bioprocesses broth.

NIBRT already has a broad array of research collaborations with major biopharma companies such as Roche, AstraZeneca, Merck, BD Biosciences, Eli Lilly, and Waters. The first partnership, announced by NIBRT in 2006, remains a successful ongoing long-term research program with Organon (Akzo Nobel). The project aims to advance the understanding of the regulation and expression of glycosylation enzymes in CHO cell culture and is carried out by Gavin Davey at Trinity College Dublin in collaboration with the NIBRT Dublin-Oxford Glycobiology Lab. The lab, led by glycomics expert Pauline Rudd, has developed a state-of-the-art proprietary high-throughput glycan analysis technology platform. In collaboration with Waters Corporation, the group has built and maintains the world's first database for glycan analysis by ultraperformance liquid chromatography.

NIBRT's expertise in glycobiology has led to an impressive number of industry collaborations. For instance, Agilent's goal is to analyze protein glycosylation in the context of recombinant protein drugs and to study glycan biomarkers of disease (2010 collaboration); Roche is looking to develop and optimize an HPLC glycan assessment technology (2009 collaboration); and Eli Lilly is developing glycan analytical technologies for monitoring cell culture conditions (2008 collaboration). More recently, NIBRT and Rudd's Group joined with the Glycomics by High-throughput Integrated Technologies consortium, which works toward developing novel glycosylation technologies for cancer diagnostics. Outside of the glycobiology area, NIBRT has set up a research partnership with BD Biosciences for cell culture media characterization and optimization.

NIBRT's strong alliances with industry have earned it a reputation of excellence and provide a great example of shifting innovation. The new facility is built to the highest global standards and further anchors NIBRT's role in the Irish life-science industry. NIBRT now aims to establish new startup collaborative research ventures and to help Ireland continue to compete for international biopharmaceutical investments.

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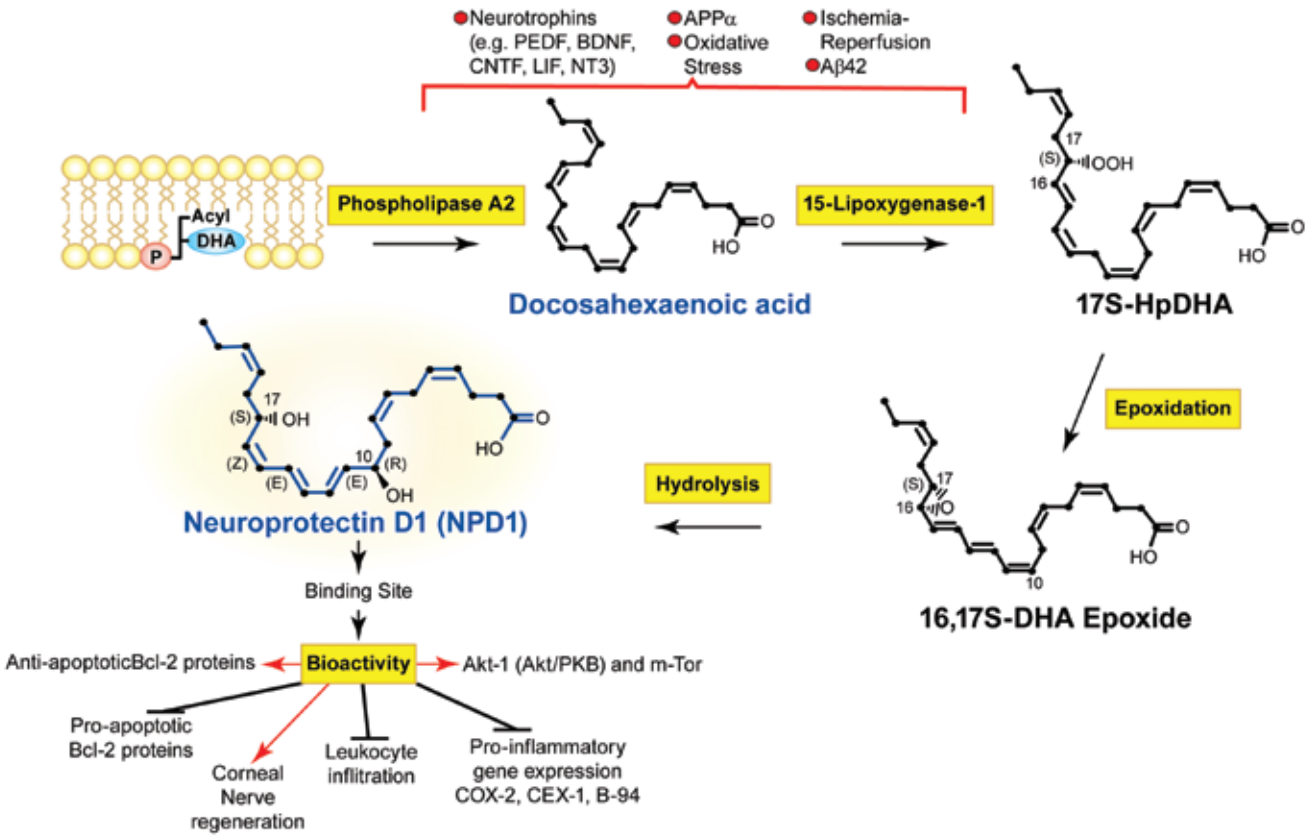
The bioactive mediator neuroprotectin D1

Bioactive derivative of docosahexaenoic acid is a homeostatic cell survival sentinel in the nervous system.

BY MIGUEL F. MOLINA AND NICOLAS G. BAZAN

The complexities of cell function in the central nervous system are sustained by intra- and intercellular signaling networks driven by synaptic activity, neurotrophins, gene programs and other factors. The molecular organization and functional contribution of cellular membranes are pivotal in the myriad of molecular circuitries of the CNS. Docosahexaenoic acid, an omega-3 fatty acid, is concentrated and avidly retained in membrane phospholipids of the nervous system, notably in photoreceptors and synapses. DHA is implicated in brain and retina function, aging, and neurological and psychiatric/behavioral illnesses. The discovery of neuroprotectin D1, the first docosanoid (a bioactive derivative of DHA), is allowing scientists to address fundamental questions concerning



Biosynthesis and bioactivity of neuroprotectin D1. A membrane phospholipid containing a docosahexaenoyl chain at sn-2 is hydrolyzed by phospholipase A2, generating free (unesterified) DHA (22:6). Lipoxygenation (5) is then followed by epoxidation and hydrolysis to generate NPD1 (10R,17S-dihydroxy-docosa-4Z,7Z,11E,13E,15Z,19Z-hexaenoic acid). Thus far, a binding site for NPD1 has been identified in retinal pigment epithelial cells and polymorphonuclear cells.

the biology of omega-3 fatty acids and their significance to brain function and the mechanisms of action in disease models such as stroke, epilepsy and neurodegeneration. The name "neuroprotectin D1" was suggested based on the molecule's neuroprotective bioactivity in oxidatively stressed retinal pigment epithelial cells and its potent ability to inactivate pro-apoptotic and pro-inflammatory signaling (1). 'D1' refers to its being the first identified mediator derived from DHA (1).

The following are disease models and experimental conditions where the protective bioactivity of NPD1 has been found. In all of these instances, NPD1 is made on demand soon after signals are needed to sustain homeostasis. Brain ischemia reperfusion leads to the transient synthesis of NPD1. Since brain damage is proportional to the magnitude of the ischemic insult, we administered NPD1 after experimental stroke with the idea that the amount produced endogenously might be insufficient to exert protection. Thus, we found that infused NPD1 counteracts polymorphonuclear neutrophil infiltration, nuclear factor kappa B (NF-κB) induction, up-regulation of cyclooxygenase-2 (COX-2) expression, decreased infarct size and neurobehavioral recovery (2).

In retinal pigment epithelial cells, the most active phagocytes of the body, NPD1 potently elicits protection against oxidative stress. RPE cells support photoreceptors through the daily shedding, internalization and phagocytosis of photoreceptor outer segment (membrane disc) tips. Notably among neurotrophins, pigment epithelium derived factor, a member of the serine protease inhibitor (serpin) family, is the most potent stimulator of synthesis and selective apical release of NPD1.

DHA deficiency is associated with cognitive decline and possibly Alzheimer's disease. NPD1 abundance was found to be decreased in Alzheimer's disease brains as well as cytosolic phospholipase A2 and 15-lipoxygenase-1 (3). NPD1 bioactivity promotes brain cell survival via the induction of neuroinflammatory downregulation and anti-apoptotic and neuroprotective gene-expression programs that suppress Aβ42 production and its neurotoxicity. Moreover, DHA and NPD1 modulate expression of Bcl-xl (4), Bcl-2 and Bfl-1(A1), anti-apoptotic members of the Bcl-2 gene family, and pro-apoptotic Bcl-2 proteins (3).

Excessive oxidative stress turns on multiple signaling pathways that participate in the pathophysiology of neurodegenerative diseases that lead to cell death. Lipidomic-based analysis has allowed researchers to begin decoding CNS omega-3 fatty acid-derived signals (highlighted by the discovery of NPD1 (2)), defining their bioactivity (Fig. 1) and furthering our understanding of their significance for neuroinflammation resolution, sustenance of synaptic circuitry integrity and cell survival. The experimental manipulation of NPD1-mediated signaling to slow or halt the initiation and progression of neurodegenerative diseases represents an emerging target for pharmaceutical intervention and clinical translation.

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A report from the ASBMB Lipid Division.

The brainy lipid from fish

It's not unusual to find health-food advocates singing the praises of omega-3 fatty acids that are present predominately in cold-water fish. One of these fatty acids, called DHA, has received a great deal of attention for its reported roles in neuronal physiology, pathophysiology, and repair. In this article, Nicolas Bazan highlights some of the reasons for the excitement generated by the discovery of a particular DHA derivative called neuroprotectin D1.

Research and development: a powerful tie bridging many nations

Report looks at steps countries are taking to boost their capacities in science, technology and innovation.

BY MARINA PAZIN

In the aftermath of recent economic hardships and natural disasters, the world appears to many to be a rather dismal place. Yet at least from the perspective of a research scientist, that may not necessarily be the case. It is true that recent economic instability has brought a sense of unease to the research and development arena. But as described by a recent report from the secretary-general of the Organization for Economic Cooperation and Development, even against such a bleak financial backdrop, advances in the globalization of scientific efforts hint that a better future is ahead.

Investing in R&D

Realizing the potential that advances in R&D could have in jump-starting their economies, many countries have made a sustained commitment to invest in R&D. Interestingly, as described in the "OECD Science, Technology, and Industry Outlook 2010," this parameter is multifaceted.

From a financial standpoint, government agencies long have been supporters of R&D, providing both competitively and noncompetitively awarded funding to support long-term endeavors. Intriguingly, many of the countries investigated in the report, including Germany, Belgium and the Czech Republic, have shifted focus in recent years toward supporting infrastructure and encouraging merit-based (competitive) awards.

The financial contribution of the business sector to R&D is becoming more important globally. Among all countries analyzed, Israel stood out as having the highest increase in financial contributions to R&D by its business sector between 1998 and 2008, with Japan, Sweden, Greece, Portugal and Spain following close behind.

Finally, and perhaps less obviously, tax relief in many countries is becoming an important factor in R&D growth. This relief comes in several forms, including additional deductions from taxable income as well as deductions in payable taxes. True to the spirit of incentivizing scientific research, most countries offering tax breaks for R&D promotion increasingly have become more generous in this respect over the years.

Together, the financial contributions outlined above have allowed for broad expansion of research opportunities within the countries analyzed. For example, Slovenia established eight new centers for the advancement of nanotechnologies and health sciences, and Israel developed its own centers for advancement of R&D and innovation (ICORE).

How does a country decide which sector of the broad R&D umbrella to promote? Because the ultimate goal of research is to benefit society, the focus of R&D effort varies across countries, reflecting their citizens' current interests. For example, as part of the American Reinvestment and Recovery Act of 2009, the U.S. allocated $26 billion for the development of clean energy technologies. In contrast, Japan focused its attention on regenerative biology with the goal of developing innovative pharmaceuticals and medical care technologies for its aging population.

Facilitating communication

Besides contributing financially to research and development, many countries have realized that "innovation is not a process easily enclosed by national boundaries" and have made efforts at facilitating communication between scientists. This process is multilayered as well. On the one hand, many countries recently have invested in technologies essential to supporting knowledge announcement, communication and cooperation among research scientists. In this spirit, Denmark is developing what it hopes will be among the best high-speed broadband infrastructures in the world, and both Spain and Finland have opted to do the same.

Additionally, many countries are laying down laws and regulations encouraging transfer of ideas among scientists. In the U.S., for example, the National Institutes of Health require funded investigators to share their research via PubMed Central once it has been accepted in a peer-

reviewed publication. Likewise, many members of the European Union report participation in the EU Seventh Framework Programme for Research and their involvement in European Research Area initiatives to access foreign knowledge and contribute to international research.

Welcoming foreigners

Finally, many countries are changing their immigration laws to facilitate the recruitment of successful talent from abroad. Denmark currently is optimizing procedures for faster acquisition of residence permits for selected foreigners; Norway is allowing foreign talent to start work on site even before immigration applications have been processed; and Austria, under its amended University Act of 2002, has mandated that all R&D-related job postings be listed not only within its local universities but internationally as well.

Investing in talent

It should be pointed out as well that to retain successful scientists within their own borders, many countries are making efforts to improve education and mentorship opportunities for their youth. Canada, for example, recently has developed Synapse-Youth Connection, linking thousands of researchers at the graduate and postdoctoral level with high school students in an effort to support the younger generation in the pursuit of careers in R&D-related fields. The United Kingdom has developed the Science, Technology, Engineering and Mathematics Network program with the same goals in mind. Finally, many countries, including Austria and Finland, have allocated funds for research opportunities for school-age youth in an effort to maintain a successful talent pool at home.

The current times may be hard, but a variety of efforts driving R&D domestically and abroad promise to sustain innovations and ensure a future empowered by technological discoveries.

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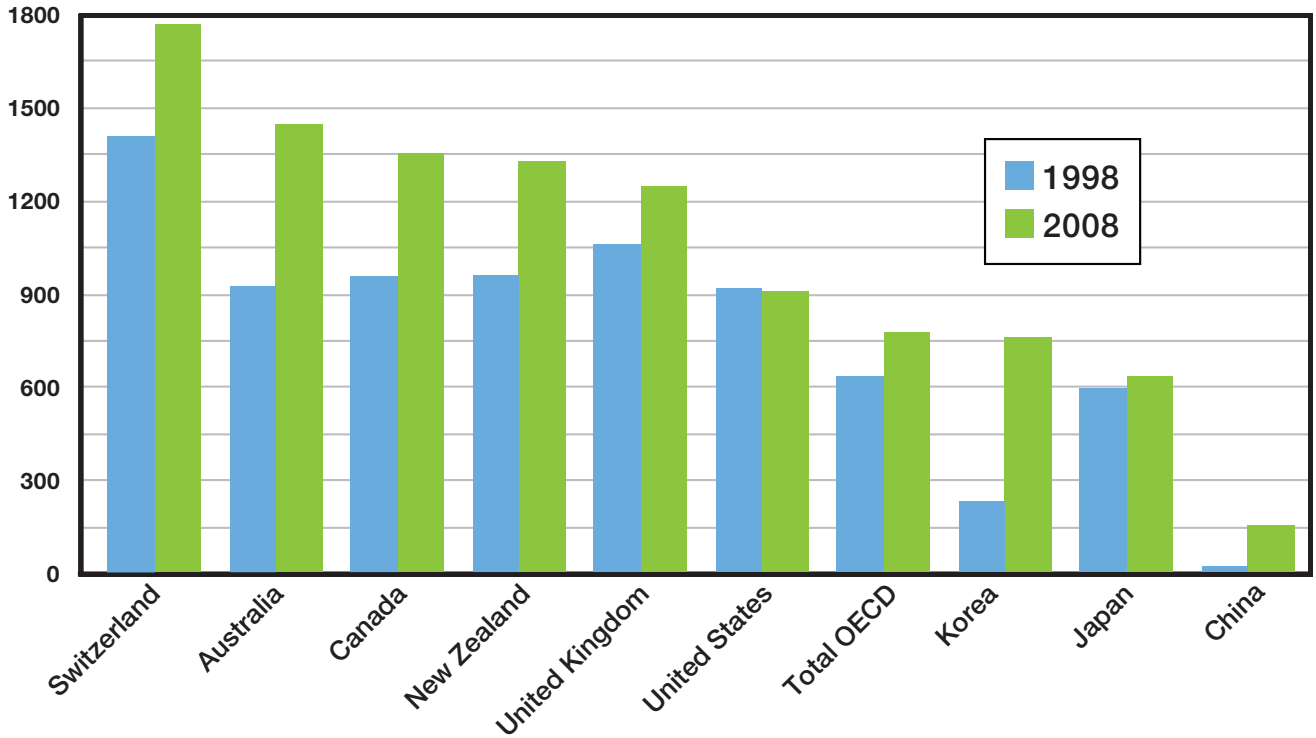
Scientific articles published per million population, 1998 and 2008.



Influencing the future of science

Ways we can help steer the future of science in the right direction.

BY NESTOR O. CONCHA

How do we shape and own our future? Are there a few simple rules to follow?

What we do know is that in the United States and the other mature economies there is a sense of vulnerability. The security of American citizens is not a given: The inadequacies of national security were uncovered by the terrorist attacks of a decade ago. Now the insidious economic crisis and sluggish recovery are sources of anxiety. There is little comfort in the sense of decline in the U.S. and other mature economies relative to the fast growth of rapidly developing economies. These major events in recent history inevitably color the choices made by recent graduates and the education and science funding decisions made by the state and federal governments. There are multiple urgent priorities that our representatives in Congress need to attend, including drafting a plan for the road ahead. Needless to say, whatever plan ends up being implemented, our future depends on the highest level of education and the best science we can produce. How can we influence this outcome? Here are some things we can do.

Advocate for science

In their path to progress, rapidly developing economies are investing in science and technology. In the United States, adequate funding for basic research and education in the sciences and arts is critical to promoting our students and young scientists, even during an economic downturn. To make the conscious decision to support science and education, our authorities and our society as a whole need to be aware of what science can deliver to improve our welfare — that science is an endeavor worth supporting. Poll results indicate that an alarmingly large segment of the population does not believe in evolution or object to climate change. These surveys say as much about those polled as they say about the society they are part off. We, as part of a scientific association and as members of communities, have the opportunity to be the voice of support for adequate education funding and sensible education reform, to be sponsors of the love for science and to urge our government to maintain the highest level of funding for science. This is the only way to preserve and develop the true power that lies in the capacity to innovate, to facilitate new discoveries, and to create new industries and services. We can't be shy about it! We need to be involved and engaged!

Support education and research

Our students are not only competing with their American peers – they now compete with students from other countries as well. More than ever, our students' technical skills need to be honed. Beyond elementary school, higher education institutions and research centers of every kind need to support more high-risk, and potentially high-payoff, transformative research. It is imperative that we redefine the metrics and incentives that will direct funding and resources to education.

> "Change is the law of life. And those who look only to the past or present are certain to miss the future."
>
> *John F. Kennedy*

Communicate and collaborate

No matter where you are in your career, one of the critical professional skills you need to develop is the art of com-

munication and the capacity to establish fruitful collaborations. For some it comes naturally and easy. But the rest of us have to learn and practice these skills. A recent article in Science (1) indicates that papers describing significant scientific contributions have involved an increasing number of co-authors in the last 50 or so years. This clearly suggests that the ability to communicate and form close collaborations is essential to science.

Accept globalization

As more universities open campuses abroad, and as large companies employ more people abroad than at home, being able to collaborate across borders is of the utmost importance. The current trend in many companies of using outsourcing as a means to diversify the risk of costly product discovery and development affects more than just manufacturing jobs. The "smart" jobs are subject to the same forces of competition. In principle, any piece of information can be transmitted via the internet, and therefore the work that produces it can be done anywhere in the world.

There is little workers can do to counteract the basic economic forces that justify relocating production tasks to locations where costs are lower. However, this type of relocation is less likely for innovation engines, the companies that provide the kind of creative jobs that produce highly novel scientific and technological discoveries. To keep the innovation engines from fleeing overseas, you can develop your talents, hone your skills, and remain hungry for the thrill of being the first to discover something. Use your ingenuity to deliver new products and produce unique information and the best science and technology anywhere. Schools need to teach, mentor and coach students in a way that will help schools and industries to stay at the front of the race to innovate. If talent is to be recruited from abroad, we must allow smart immigrants to come and stay in a friendlier place so that all have the chance to flourish and enjoy the great race to be the best. Even though not everyone wins, we all have the opportunity to be winners.

Finally, as Alan Leshner, chief executive officer of the American Association for the Advancement of Science stated in a recent editorial,

> *…[I]nnovation often comes from nontraditional thinking, and many new ideas will come from new participants in science and engineering who often are less tied to traditional ways. That argues for increasing the diversity of the scientific human resource pool, adding more women, minority, and disabled scientists, as well as researchers from smaller and less-well-known institutions. The benefits of increasing diversity for fostering innovation and economic success have been argued well elsewhere. Both research institutions and funders need to attend more to these sources of novel thinking and may have to refine recruitment, reward, and funding systems accordingly (2).*

> "The empires of the future are the empires of the mind."
>
> ***Winston Churchill***

There is a need for a grass-roots movement and social engagement to bring education, science and technology into focus as key strategic values. As President Obama told school children in Philadelphia, "Life is precious, and part of its beauty lies in its diversity. We shouldn't be embarrassed by the things that make us different. We should be proud of them. Because it's the things that make us different that make us who we are. And the strength and character of this country have always come from our ability to recognize ourselves in one another, no matter who we are, or where we come from, what we look like, or what abilities or disabilities we have."

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A report from the Minority Affairs Comittee.

Peering below the surface

Some tips for reading letters of reference.

BY PETER J. KENNELLY

The letter of reference frequently offers the first, and potentially only, opportunity to humanize the evaluation process, to delve into the realms of motivation, character, creativity, perseverance, responsibility, independence, initiative, leadership, respect for others, and integrity. In a world where potential mentors and employers place increasing emphasis on complementary skills, letters of evaluation offer insights beyond the metrics of the vitae and into personality and character.

Since the people who author these letters of evaluation also serve on search and admission committees, you would expect them to know what the reader is looking for. Yet all too often letters of evaluation can be surprisingly generic in form and uninformative in content. There is information to be gleaned, however, even from a poorly written letter, particularly when multiple letters are available to compare and contrast.

One letter, three agendas

Today's litigious atmosphere has contributed significantly to the monotonous homogeneity so frequently encountered in contemporary letters of evaluation. Other factors include the increasing sterility of teacher-student interactions that has accompanied the steady growth in class size and the intrusiveness of social media on campus. But in the final analysis, the letter of recommendation has been plagued by an inherent ambiguity since its inception: Whose letter is it? Whose interests take priority?

Certainly the members of the search, admissions or awards committees who request the letters, and to whom the letters are in fact addressed, would appear to have a strong claim as the party whose interests should be paramount. The recipient expects to receive a letter that offers a comprehensive, balanced description of the applicant's professional accomplishments and ability capped off by an objective overall ranking consistent with the text. The reader would expect to find comments regarding the applicant's professional potential, command of relevant knowledge and techniques, independence and initiative, communications skills, ability to work with others, and so forth. No one is perfect: In addition to highlighting the applicant's strongest attributes and significant accomplishments, a reader-directed letter will contain a few thoughtful and constructive comments on areas where the applicant may lack experience and training or need further work.

Many evaluators, on the other hand, cast themselves in the role of advocate. Rather than providing an independent evaluation, the author sees himself or herself as an agent charged with aiding the applicant in reaching his or her goals in much the same way a realtor works with a homeowner to sell his or her property. Any response to a request for numerical ratings or a relative ranking — a common feature of graduate school and fellowship applications — will be skewed heavily toward the very highest values. The signature of the advocate-author is a stridently positive tone juxtaposed against a striking unevenness in coverage. While most authors generally will say very little when they struggle to find positive things to say, the advocate-author adopts a more extreme all-or-nothing interpretation. Hence the letter will seem incomplete as some aspects of the candidate's abilities and accomplishments will be described in great detail, whereas comments on some related topics will be nowhere to be found.

In some cases, the evaluator may have let some personal agenda intrude into his or her evaluations. Since one relatively painless way to divest oneself of a weak performer is to have him or her secure another position elsewhere, an evaluator may be tempted to paint an overly rosy portrait. Conversely, the desire to hang on to a well-trained and productive member of their research group may tempt some principal investigators to hold back in their evaluations. In both cases, the key indicator will be a disparity between the descriptors used and the documented productivity of the candidate. For example, if a trainee is described as the leader and intellectual driving force behind a particular project yet consistently is buried in the "et al." portion of the author list on the relevant papers, suspect over-selling!

Some authors are animated by a vivid fear of legal retribution should a candidate's search prove unsuccessful. Their letters contain repeated stipulations that the other evaluators are more qualified to comment upon the

applicant's skills and abilities. Letters in this genre tend to be relatively brief and dominated by vague, innocuous descriptors that neither inform nor inflame.

Multiple letters are key

Always request multiple letters. Pattern recognition is one of the more reliable ways to tease out information about a candidate whose individual letters of evaluation are frustratingly vanilla. If multiple evaluators fail to devote any space to some obvious topic, odds are that they share significant reservations in this area. Similarly, if multiple evaluators state that an applicant's grades are not reflective of his or her performance and abilities, it is a good bet that this is indeed the case.

The identities of the evaluators selected by the candidate also can be revealing. One can feel positive and reassured when each evaluator unhesitatingly describes his or her relationship to the applicant in specific terms. Other positive signs are that the trainee initiated contact or met regularly with the investigator in question. A person who asks other trainees to write letters instead of experienced and trained leaders may be technically quite competent but personally insecure and immature. Omission of the applicant's last mentor or supervisor from the list of evaluators suggests that you proceed with caution.

In describing the candidate's strengths, do the evaluators illustrate their points with specific examples? Supporting anecdotes should flow easily from someone who has substantive, personal knowledge of the candidate. The order in which specific strengths are presented also can be a telling indicator. The mention of some fundamental characteristic — for example, "an extremely talented experimentalist" or "an original and innovative thinker" — suggests a very high overall opinion of the candidate, whereas "a great command of the literature" suggests a person struggling to find something positive to say about someone whose abilities and goals may be mismatched. On the other hand, in my experience, very few authors include statements like "I would gladly hire the candidate back in future" or "the candidate would be welcome anytime as a member of my research team" unless prompted, so when this phrase is freely volunteered, it should be noted carefully.

Learn to recognize avoidance

When an evaluator is convinced, based on his or her own direct interactions with a trainee, that the candidate is strong or even exceptional, in most instances the enthusiasm is palpable. As you read the letter, you get the clear sense that the evaluator is having trouble keeping it to a reasonable length – that he or she simply can't say enough. While letters for good or solid candidates may lack the same energy, they tend to be unhesitatingly direct in tone. On the other hand, any behavior suggestive of avoidance, such as difficulty in selecting a first strength, generally is indicative of an author struggling to find some way to make the evaluation sound better.

A classic model of avoidance is the letter that spends three paragraphs describing in great detail the trainee's project, its progress and outcomes. The first paragraph talks about the student's rotation project. The second relates in painstaking detail progress at the bench and in class during years one and two. The next paragraph relates the experiments that constitute the heart of the thesis. Finally, after negotiating a full page or so of narrative, the reader suddenly finds himself or herself faced with a concluding paragraph that covers the candidate's specific qualities in three sentences or so. The end. Whenever I see such a letter, I get the impression that the author set a goal to write something long enough to suggest a positive opinion. Once that critical length was reached, usually a full page, the author could now safely move to the denouement, which he or she dispatched in a few short sentences. This structure is ideally suited to the agenda of the author focused first and foremost on providing no opening for a litigator.

Where do we go from here?

Reviewing a candidate's credentials should be done in a holistic fashion. Your goal is to reconstruct stories of the candidates' educational and professional development to date and obtain a feel for their future trajectories. Learn to read between the lines of letters of recommendation. Identifying outliers and unearthing underlying trends can help bring a candidate's abilities and qualifications into focus, leading to better matches of trainee with mentor and applicant with position.

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A report from the Education and Professional Development Committee.

THE JOURNAL OF LIPID RESEARCH

Tributes and methods: the July JLR

BY MARY CHANG

Honoring a lipid pioneer

The July issue of the Journal of Lipid Research contains a very special tribute to the first editor-in-chief of JLR. Daniel Steinberg of the University of California, San Diego, has written an "In Memoriam" piece on the late and distinguished Donald B. Zilversmit, who passed away at the age of 91 in September 2010. What is known today as the Journal of Lipid Research started as a humble idea — an initial application to the National Institutes of Health from Zilversmit to publish a handbook on lipid methods.

In the retrospective, Steinberg discusses some of Zilversmit's groundbreaking research and novel notions. For example, one proposal, made in 1973, was that chylomicrons, a class of large lipoprotein molecules, might be significant in the process of atherogenesis — a concept that has since been supported by clinical studies. In his illustrious career, Zilversmit pioneered research into the turnover rates of phospholipids and made significant contributions to our understanding of glucose and glycogen metabolism. One particularly important contribution to the field of lipid research was his careful quantification of lipoproteins and their components as they entered the artery wall.

Zilversmit was a beloved member of the lipid community and will be sorely missed.

New and interesting methods

It seems rather fitting, for a journal that began as a methods handbook, that JLR has three remarkable methods papers in its July issue. In the first, Stephen F. Previs and colleagues at the Merck Research Laboratories confirm the advantages of using heavy water (^2H_2O) to quantify cholesterol synthesis in African green monkeys, suggesting the same technique could be used in humans.

The second methods paper comes from M. G. Ghosn, of the University of Houston, and colleagues who show that optical coherence tomography, a noninvasive and nondestructive near-infrared imaging technique, can be used to measure the rates at which molecules as small as glucose or as large as a lipoprotein permeate through arterial tissue.

And finally, in the third paper, Xuntian Jiang, of the Washington University School of Medicine, and colleagues explain their development of a sensitive and specific liquid chromatographic-tandem mass spectrometric method for quantifying two specific cholesterol oxidation products that are associated with Niemann-Pick type C1 disease, a rare and fatal neurodegenerative disorder. Jiang and colleagues describe a novel assay for diagnosing NPC1 that is both highly sensitive and quick.

Mary L. Chang (mchang@asbmb.org) is managing editor of the Journal of Lipid Research.

jbc THE JOURNAL OF BIOLOGICAL CHEMISTRY

Molecules and music on the mind

BY ANGELA HOPP

If Solomon Snyder's scientific life had its own musical score, it would have mystery, joy and many crescendos. It would be fast and full.

"For me," Snyder writes in a recent issue of the Journal of Biological Chemistry, "research is largely about the unfettered pursuit of novel ideas and experiments that can test multiple ideas in a day – not a year."

Those swift and nimble movements onward yielded a number of greatest hits for Snyder, a neuroscientist at the Johns Hopkins School of Medicine.

His group's feats include the discovery of the opiate receptor, the discovery of opiatelike peptides in the brain,

A musical family: Solomon Snyder with daughters Judy (guitar) and Debby (flute) and wife Elaine around 1980. Snyder continues to play daily and has served on the board of the Baltimore Symphony Orchestra for two decades.

and the characterization of the actions of neurotransmitters and psychoactive drugs. He helped start Nova Pharmaceuticals and Guilford Pharmaceuticals. He won the Lasker award. Hopkins' neuroscience department is named in his honor. He has more accolades and honorary degrees than can be named here. He has been busy.

But how does someone who acknowledges not having a knack for science in his youth manage to develop such a research repertoire? In his JBC "Reflections" article, Snyder explains that it all started with his love of music.

Snyder was taught how to play the guitar by Sophocles Papas, a close friend and, in Snyder's words, disciple of famed classical guitarist Andrés Segovia. Snyder manned Papas' guitar shop and taught lessons on weekends while pursuing a pre-med degree at Georgetown University in Washington, D.C. At the time, he wanted to become a psychiatrist.

In 1958, Dan Brown, then a young research associate at the National Institutes of Health, came into the guitar shop for lessons. Brown happened to need a lab technician, and Snyder fit the part. He ended up working in the lab during summers and breaks.

Just a few years later, Snyder wrote his first paper, "The mammalian metabolism of L-histidine. IV. Purification and properties of imidazolone propionic acid hydrolase" (1). It was published in the JBC and "accepted with no revisions, the only time that's ever happened," he writes.

While the Doctors Draft Act rerouted Snyder's pursuit of practicing psychiatry, his summer lab's proximity to that of Julius Axelrod's[i] proved advantageous. He moved across the hall in 1963, and that's when the tempo really picked up.

"Working with Julie was exhilarating," Snyder writes. "Each of us in the lab pursued multiple projects with a surprisingly high yield of successful outcomes. The two years in Julie's lab constituted my sole full-time research training, but the impact of his inspirational mentorship on me, as on all of his students, was transformative."

To find out more about Snyder's work and life, read his complete "Reflections" article, "Mind molecules," in the June 17 issue of the JBC.

Angela Hopp (ahopp@asbmb.org) is managing editor for special projects at ASBMB.

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FOOTNOTE

[i] Axelrod's work on the neurotransmitters epinephrine and norepinephrine won him the Nobel prize in 1971.

Web Extra

For a YouTube slideshow of excerpts and photos from Solomon Snyder's "Reflections" article, visit http://bit.ly/SnyderReflection. Note that the song playing in the background (by composer Jonathan Leshnoff) was written for and performed by Snyder. Fittingly, it is titled "Shir Shel Shlomo," which is Hebrew for "Song for Solomon."

The key to success: believe in yourself

An interview with Saurabh Sen, a research scientist at Lucigen Corporation.

Saurabh Sen (ssen@lucigen.com) was born and raised in India. He received a masters degree in biotechnology from the Indian Institute of Technology, Bombay. In 2000, he started his doctoral research at the University of Helsinki, Finland, and earned his degree in 2005. He then did postdoctoral fellowships at the Washington University School of Medicine and the University of Alabama at Birmingham. He currently works at Lucigen Corporation.

Getting a job offer in industry is pretty hard during these tough economic times, which makes getting three offers a very impressive feat. However, Saurabh Sen was able to do just that after completing a postdoc at University of Alabama at Birmingham. He finally chose to work for Lucigen Corporation, a biotechnology company delivering advanced molecular technology, tools and services to life scientists by inventing solutions to difficult problems in DNA cloning, amplification and protein expression. Below, Sen gives some practical advice and talks about his current job.

ASBMB: ***What were the key factors involved in your successful job applications?***

SEN: To answer in few words: perseverance, tenacity, thorough preparation for the interview and luck. The combination of these factors helped me to land my job offers. The first time always is the toughest, and frankly speaking, it was not easy for me either. But at the end of the day, when three different employers expressed their willingness to welcome me on board, I was glad that I could present myself in the most deserving manner. The job search is a full-time job, and people get kind of disheartened when replies do not pour in. My simple advice is to keep trying: unless you knock on the door, it won't open up magically. Also, make use of every networking opportunity that comes your way.

ASBMB: ***From your experience, do web-based job applications always go straight to the recycle bin?***

SEN: No, they definitely do not. Actually, all of my successful job applications were web-based, and all the offers that I received were through internet-based applications. I know that it's a common notion, but the cover letter and résumé do not always go straight to the recycling bin when you apply online. The trick is to use key words in your résumé that match the job description. The candidate also should have at least a 60 to 75 percent match with the skill sets listed in the job description. Otherwise, the application probably won't land on the hiring manager's desk.

ASBMB: ***Can you give some tips on preparing for a job interview?***

SEN: Sure. I won't get in to the dos and don'ts — you can read those anywhere. My suggestion is to just be yourself when you do an interview, be it an initial telephone interview or an on-site interview. Be calm, composed, and show enthusiasm when answering questions. And always think before you speak. No arguments, no controversial statements, be truthful, always have a positive attitude and be yourself. Make a positive impression on the interviewers with your personality, flexibility, adaptability, enthusiasm and resourcefulness. Demonstrate your affinity for teamwork, your leadership skills, your problem solving abilities, your capacity for thinking outside the box and your aptitude for taking calculated risks. Success will be yours if you believe in your virtues and in yourself.

And always try to present something extra that is valuable to the prospective employer — this will make you stand out from others. In my case, I have a unique mathematical formula (see figure) that I use to describe my personality traits and have found that, in the majority of situations, my prospective employers have been amazed by it.

ASBMB: *What do you think is the biggest challenge in landing a job in industry?*

SEN: I think the biggest challenge is to find the perfect fit between the candidate and the job requirement, to match the skill sets and to pick the smartest candidate. Thus finding a job that serves as a perfect marriage between the employer and the employee is a win-win situation for both. Apply to jobs where you really are a good fit and not based on assumptions that you might be a good fit. Apply selectively, prudently, and keep an eye on the new openings daily. Be flexible, adaptable and open to new ideas.

ASBMB: *Why did you decide to work at Lucigen?*

SEN: That was a difficult decision. The major driving force to choose Lucigen over the others was the challenging project they offered me on G protein-coupled receptors. It is a tough project, but the challenges and uniqueness of the project keep me going.

Having worked with GPCRs during my graduate studies and through my first postdoc, I know how tough these receptors are to deal with. To transform a GPCR project into a success story is my dream. These receptors are the broadest target in the pharmaceutical industry. More than 50 percent of the currently available prescription drugs target GPCRs, making them the most sought-after drug class.

One of the things that I love best about working at Lucigen is the chance to participate in innovative and exploratory research projects, marketing efforts and business development. Being a small company, we are a well-built, cohesive family — all working together to do good science and deliver novel products to the scientific community (and in turn bringing in more value for what we do).

Saurabh Sen's mathematical formula for describing his personality traits.

ASBMB: *Are you still involved in bench work?*

SEN: Of course. I love the bench. People have different opinions about the industrial environment and how research programs are operated in an industrial setting. I devote a significant fraction of my time to cutting-edge experiments at the bench. It's fun, and that's what keeps me going.

ASBMB: *Was your transition from academia to industry easy?*

SEN: Well, for me it was rather smooth sailing. I had a little bit of industrial experience (nine months) before my graduate studies, and that sort of laid down the foundation for me to come back to industry again. I did not find any significant challenges or hurdles that acted as barriers to my transition. Many people find it difficult to adapt to industry coming from academia, and I believe it is more the mindset that plays a crucial role in the process. One thing is for certain — in an industrial setting, an individual doesn't have the luxury to do much offshoot exploratory research; the focus mainly lies on the corporate goals and milestones that need to be achieved annually. If you are ready to embrace that, I don't see any problems with the transition.

ASBMB: *Can you describe a typical day at work?*

SEN: For me, a typical day at work involves thorough execution of my planned agendas, and, as always, I am ready to take up new challenges. It includes checking my e-mails and calendar when I arrive at work, looking for any meetings that I may have during the day and planning experiments accordingly. Completion of my planned experiments, data analysis, updating my notebook and planning the next day's experiment generally is what I strive to accomplish by the end of the day. Coming to work every morning with the challenge of discovering a novel solution for an unsolved scientific problem keeps me on my toes for the whole day.

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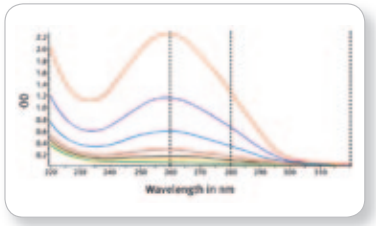

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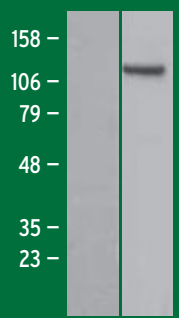

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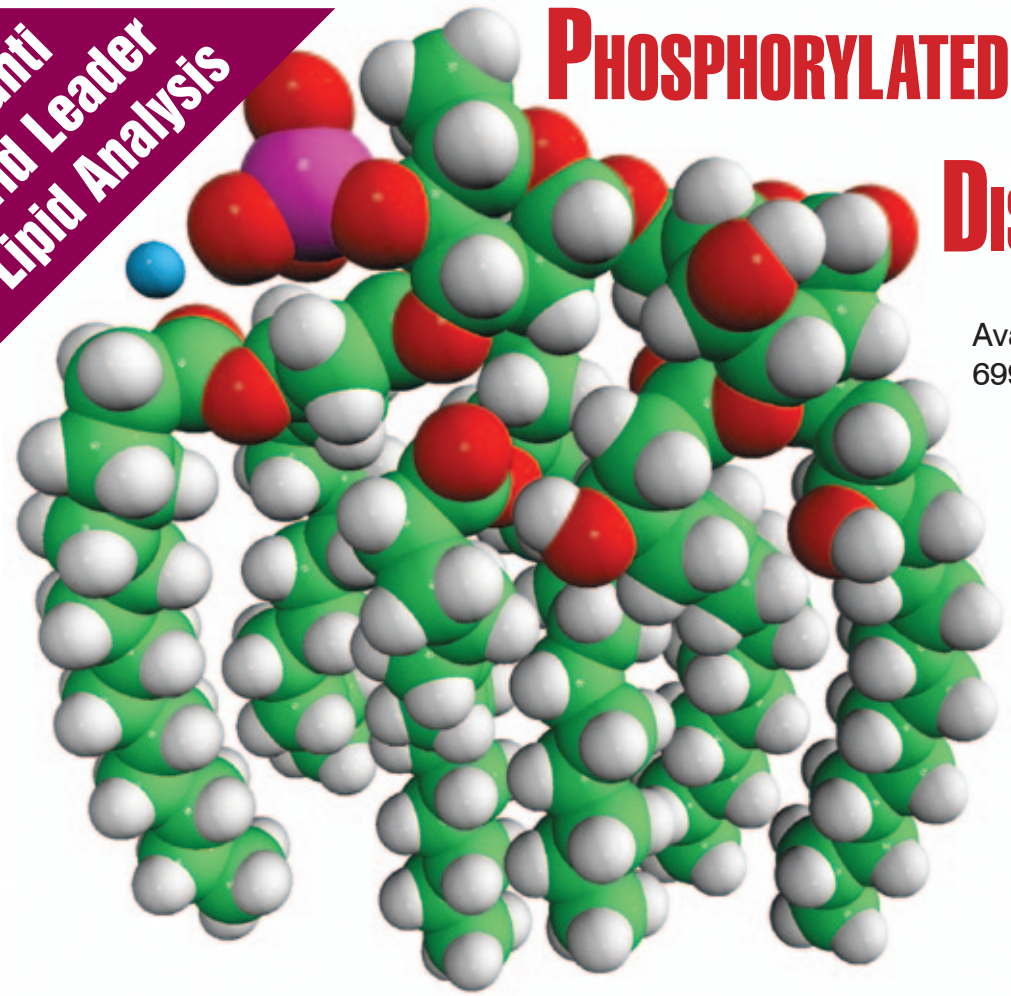

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