ASBMB today

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MY SPOUSE AND THE MOUSE
The next installment in the Derailed but Undeterred essay series

VIRGINIA LEE
Notes on a career in science

American Society for Biochemistry and Molecular Biology

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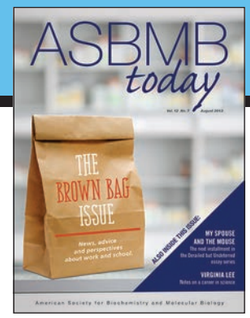

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ASBMB today

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ASBMB Today

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NIH to begin mass retirement of research chimpanzees

PHOTO CREDIT: NATIONAL INSTITUTES OF HEALTH
Pumpkin is a 24-year-old chimpanzee living at the Alamogordo Primate Facility in New Mexico.

The National Institutes of Health will begin retiring many of the nearly 1,000 captive chimpanzees to the Federal Sanctuary System, leaving roughly 50 for future experimentation needs. The move comes as the NIH begins to implement the recommendations of an Institute of Medicine report regarding the necessity of chimpanzees for biomedical research. Read more about this from ASBMB's science policy fellow, Chris Pickett, at asbmb.org/asbmbtoday.

Unearthing hidden gems in the ASBMB archives

The first Source Files post features John J. Abel of Johns Hopkins University, who founded the Journal of Biological Chemistry in 1905 with Christian Herter. The next year, he founded ASBMB (then the American Society of Biological Chemists). Abel served as the society's second president in 1908.

Discovery: It's what you're about. But ferreting out the prized, charming and peculiar pieces of your field's history isn't exactly something you have a ton of time to do, which is why we decided to do it for you in a new website called Source Files. There, you'll find figures and photos from our archives that struck our fancy. Sometimes serious, sometimes not, these brief posts are meant to make more discoverable the stories our journals and society have told over the decades. Visit Source Files at asbmbsourcefiles.tumblr.com. Send suggestions to asbmbtoday@asbmb.org.

Spreading the word about health disparities

The Prairie View A&M University College of Nursing in the Texas Medical Center in Houston hosted the 11th annual Disparities in Health in America Summer Workshop in mid-June. The six-day continuing-education program, offered to healthcare professionals, social workers, students, community members and civic leaders, this year had the theme "Working Towards Social Justice." Lovell A. Jones, who won the American Society for Biochemistry and Molecular Biology's Ruth Kirschstein Diversity in Science Award in 2012, served as the program chairman. See a slideshow of photos from the event at asbmb.org/asbmbtoday.

president's message

Imagining a sustainable biomedical enterprise

BY JEREMY BERG

The opportunities for research in biochemistry and molecular biology and related areas to have impact both on basic knowledge and on human health, energy and other essential areas are tremendous, almost unprecedented. Yet at the same time, the system, broadly defined, for conducting such research is struggling with many challenges. In academia, principal investigators are spending much of their time writing and reviewing grant proposals rather than conducting research. Many faculty members are dependent on the success of such proposals not just to facilitate their research but also for their continued employment. At the same time, universities and other institutions are increasingly dependent on the success of these proposals for their financial viability. Many talented young people who have embarked on careers in biomedical fields find themselves in long periods of training that may be too narrow to prepare them for the range of career opportunities that may be of interest to them. Interactions between academia and the pharmaceutical and biotechnology companies are of increasing interest to both groups, but the frameworks for these interactions are often cumbersome and challenging to set up and may not optimally support the goals of the participants. The federal government is both a major financial supporter of biomedical and biological research and the source of regulations that affect academia and industry. The financial support has not kept up with inflation over the past decade and has been eroded substantially by the enactment of sequestration in the present fiscal year. The regulations, while developed with the best of intentions, may not strike the optimal balance between prevention of undesirable events and time and financial burdens that decrease productivity. Finally, an analysis of trends indicates that many of these problems are getting worse rather than better so that the status quo is not sustainable.

It is easy to imagine a sustainable future in broad strokes. Note that building a sustainable enterprise is not just a matter of gaining increased financial support. The fact that federal support for research has not even kept pace with inflation for a decade has exposed structural defects in the system, but these defects existed independent of the level of support. With that said, we must make the strongest possible case for continued and increased support for research because of the great dividends these investments will pay to society in terms of knowledge; improvements in health, energy and other fields; and both short- and long-term economic development. Our focus on sustainability is most certainly not a matter of conceding that subinflationary budget increases are inevitable or are good policy. Indeed, a clear vision for a sustainable enterprise is likely to be most important as a driver for and in the presence of increased investments.

In a sustainable enterprise, researchers would still compete for funding through peer-review-based processes, because this has proved to be an effective means for allocating resources to the most important ideas. However, in a sustainable environment, the process would be more efficient so that less time was spent writing and reviewing proposals, freeing

Sustainability can be achieved only by encouraging the major stakeholders to engage in serious and thoughtful self-examination and then bringing them together to develop policies and programs that will set the system in the right direction.

up time actually to do the research. Young scientists would come out of their training at an earlier stage and well prepared for the exciting range of career paths in biomedical research. Academia, industry and government would interact almost seamlessly to harness basic research advances into applications and products that would benefit the public. Of course, moving toward such a future is much more complicated than simply describing it. These are systemwide issues with many conflicting goals and needs that must be meshed through balance and compromise. It is not the case that many of these issues would vanish if only there were more money available to the system. Sustainability can be achieved only by encouraging the major stakeholders to engage in serious and thoughtful self-examination and then bringing them together to develop policies and programs that will set the system in the right direction.

The American Society for Biochemistry and Molecular Biology Public Affairs Advisory Committee has been focused on the issue of moving toward a sustainable biomedical research enterprise for the past year. The approach involves three major stages. The first stage has been to develop a white paper (http://bit.ly/15CmbNP) that lays out these issues in some detail and raises important questions that must be considered to form a foundation for defining answers. The white paper includes three major sections, each of which is described by a position statement.

Stakeholder interactions and cultures: The ASBMB's position is that a sustainable biomedical research enterprise requires a new era of meaningful and substantive working relationships among the major stakeholders.

Training and workforce: The ASBMB's position is that a sustainable biomedical research enterprise requires a highly skilled scientific workforce that is balanced in expertise and numbers across the biomedical research network, from knowledge creation and discovery to products and economic benefit.

Academic research funding: The ASBMB's position is that stable federal support for basic biomedical research is irreplaceable and essential for a sustainable biomedical research enterprise. The major stakeholders must coordinate efforts to explore new collaborative research funding mechanisms at their interfaces to balance the workforce and repair and restructure the research network. A positive feedback loop is required wherein stable basic research funding creates knowledge that is translated into economic success by industry, thereby feeding back to government to fund additional science.

The purpose of this white paper is to serve as a conversation starter with a broad group of stakeholders. The first important group of stakeholders is the membership of the ASBMB. We are reaching out to other scientific societies, groups and key individuals to get their input as well. The goal is not to continue to polish the white paper but rather to identify and prioritize issues for further analysis and action.

The second stage will occur at the annual meeting in April in San Diego. The PAAC is organizing a panel discussion with representatives and thought leaders from different sectors to continue the process of prioritizing and start to examine possible steps for action. We plan to put some of the most important questions in the white paper to the panel for their reaction and to allow ASBMB members and other attendees at the Experimental Biology 2014 conference to engage with the panel and with each other on these topics.

The third stage will be to follow up to develop action items to address the highest priority issues. This process will involve broader groups of stakeholders across the various sectors. Some of these action items may involve single issues that need to be addressed urgently. However, since the underlying issues are fundamentally systems problems and many potential changes and programs will interact with one another, the most successful path forward likely will involve an integrated suite of proposed changes.

The PAAC, and in particular a special issues subcommittee chaired by Lee Gehrke with considerable input from incoming PAAC chairman Bob Matthews, has spent substantial time and effort producing the white paper. I thank them for their work. Please take the time to read the white paper and send any comments to me at president@asbmb.org. We hope we have captured the most important issues but need your feedback, and now is the time to get issues on the table.

A quote often attributed to Henry Kissinger but actually from Wallace Sayre, a political science professor at Columbia University, states that "academic politics is the most vicious and bitter form of politics, because the stakes are so low." The present situation is a clear violation of Sayre's Law. The stakes are very high — for academia, for the larger biomedical research enterprise, and for the nation. We must get past wringing our hands and move forward with a thoughtful plan for action.

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

Turning controversy into action

BY CHRIS PICKETT

High-profile science controversies such as the Supreme Court's ruling on patents on complementary DNA (1) and the release of the draft High Quality Research Act (2) have left some scientists concerned about how well government officials understand science and how science is done. While it may be easy to lament these turns of events, the reality is that science-related controversies offer crucial opportunities for scientists to speak up, join the public conversation and try to steer public opinion and policy in a direction that favors research.

Having the executive, legislative and judicial branches of government full of career scientists might yield policy decisions that are more agreeable to researchers, but a large influx of scientists into our government is not on the horizon. Thus, high-ranking government officials will continue to depend on scientists and their advocates to communicate the vital aspects of science and its administration. The justices of the Supreme Court are not experts in biology, yet they will continue to be asked to rule on the legality of various aspects of biological research. Most U.S. senators and representatives never have applied for research grants; however, they still are tasked with oversight of science-funding agencies and their granting practices.

If we are to improve the environment for conducting research in this nation, then the gene patent ruling, the HQRA and other such events should illustrate that science communication must be a constant process that continually improves upon itself. In legal cases, scientists must continue to teach their advocates not only about the nuances of basic science but also about how to communicate those nuances effectively to judges and justices. In Congress, scientists must continue to inform lawmakers about the importance of science and how science is conducted as well as how to write legislation that benefits the scientific enterprise instead of damaging it.

The American Society for Biochemistry and Molecular Biology works exhaustively on behalf of its members to engage the federal government at multiple levels to improve the working environment for scientists. But we can't do this alone. To improve the public's and government's understanding of science, we need your help! You, the constituent, have the ear of your elected representatives to inform them of the important scientific research in your district and state. You, the neighbor, have the unique opportunity to discuss scientific progress with the people you live near and see every day. The scientific community needs you, the scientist, to step forward and fulfill the important roles of science communicator and advocate.

Get involved

Are you interested in meeting with your elected representatives to discuss the issues confronting biological and biomedical research today? The ASBMB is continuing its August meeting campaign, and you can take part!

Step 1: Email Ben Corb, the ASBMB director of public affairs, at publicaffairs@asbmb.org to express your desire to meet with your elected representatives during the August recess.

Step 2: Complete a very short district-meeting questionnaire.

Step 3: Contact the offices of your elected representatives to set up meetings or have an ASBMB representative set them up for you.

Step 4: Receive ASBMB meeting materials that will ensure your meetings are a success!

Step 5: Conduct your meetings and begin fruitful, long-lasting relationships with those offices.

To see how other district meetings have gone, check out the testimonials from last year's class of at-home advocates (3).

Chris Pickett (cpickett@asbmb.org) is the science policy fellow at the ASBMB.

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Baumann, Lima become HHMI investigators


BAUMANN


LIMA

Two ASBMB members were among the 27 researchers named Howard Hughes Medical Institute investigators this summer. Peter Baumann of the Stowers Institute for Medical Research studies various aspects of chromosome biology, including telomere maintenance, as well as reproduction in unisexual vertebrates. Christopher D. Lima of Memorial Sloan–Kettering Cancer Center is a structural biologist studying macromolecules involved in post-translational modification by ubiquitinlike proteins and the pathways contributing to RNA maturation and RNA decay. As HHMI investigators, Baumann and Lima will be paid their full salaries (plus benefits) and be given research budgets for five years.

Lima image courtesy of Memorial Sloan–Kettering Cancer Center

Rockefeller's Young named Shaw laureate


YOUNG

ASBMB member Michael W. Young, a professor and the vice president for academic affairs at The Rockefeller University, was named one of the winners of the 2013 Shaw Prize in Life Sciences and Medicine. The announcement made earlier this summer in Hong Kong recognized Young's work on circadian rhythms in collaboration with Jeffrey C. Hall of the University of Maine and Michael Rosbash of Brandeis University. The annual prize, now in its 10th year, is worth $1 million, and the three winners will split it. A ceremony will be conducted in September.

Davis named founding faculty for Quinnipiac med school


DAVIS

J. Nathan Davis, an associate professor of medical sciences at Quinnipiac University, has been named one of the founding faculty members of the university's Frank H. Netter M.D. School of Medicine. The medical school, located in the Center for Medicine, Nursing and Health Sciences on Quinnipiac's North Haven Campus, will open its doors to its first 60 students this month. Davis, formerly of the Louisiana State University Health Sciences Center Medical School, will teach biochemistry. "I am very pleased to have Nathan as a member of our founding faculty," said Bruce Koeppen, the school's founding dean. "He brings to the School of Medicine extensive expertise related to tumor biology, cell biology and biochemistry, all of which will help us develop our curriculum in these important areas."

Tomic–Canic joins NINR advisory council


TOMIC-CANIC

Marjana Tomic–Canic, a professor of dermatology and the director of the Wound Healing and Regenerative Medicine Research Program at the University of Miami medical school, was one of five people recently appointed to the National Advisory Council for Nursing Research, the principal advisory board of the National Institute of Nursing Research. As a member of the board, Tomic–Canic will provide recommendations on the direction and support of research on nursing practices and will review grant applications and extramural programs.

In memoriam: Stefan Andersson


ANDERSSON

Stefan Andersson, a research professor at the University of Houston's Center for Nuclear Receptors and Cell Signaling, died in early June at age 59. Anderson, who joined the university in 2009, studied steroid hormone action in women's reproductive health. Raised and educated in Sweden, Andersson previously worked at the University of Texas Southwestern Medical Center at Dallas and Merck & Co.

Members' age-related disease projects win BrightFocus grants

Seven ASBMB members in July won grants from the BrightFocus Foundation, which supports research on brain and eye diseases related to aging. The awards, issued to 53 researchers total, amount to $7.2 million. The ASBMB members were:

David A. Harris, Boston University School of Medicine

Joachim Herz, University of Texas Southwestern Medical Center

Lee-Way Jin, University of California, Davis

Stephen Strittmatter, Yale University School of Medicine

Curtis Brandt, University of Wisconsin

Michael H. Elliott, University of Oklahoma Health Sciences Center

Beatrice Yue, University of Illinois Medical Center

Full descriptions of the winning investigators and their projects can be found at http://www.brightfocus.org/brightfocus-2013-research-grants.html.

NCATS issues awards to repurpose shelved compounds

ASBMB member Strittmatter is among recipients


STRITTMATTER

The National Institutes of Health announced in June that it had awarded $12.7 million to nine academic research groups matched with pharmaceutical companies to explore new uses for some of the companies' shelved compounds. One of the awards was issued to ASBMB member Stephen M. Strittmatter and his team at Yale University School of Medicine.

Strittmatter, along with Haakon Berge Nygaard and Christopher H. Van Dyck, will explore the use of a compound from AstraZeneca called saracatinib, or AZD0530. The team recently characterized, using a mouse model, a pathway in which beta amyloid damages neurons in Alzheimer's disease; they found that inhibiting the Fyn kinase in that pathway reduced symptoms. The new study will test the use of saracatinib as a Fyn inhibitor, first in mice and later in humans, for safety. Previously, AstraZeneca tested the compound in humans with cancer.

Another group based at Baylor College of Medicine will study saracatinib in a lung disease called lymphangioleiomyomatosis.

The award program, called Discovering New Therapeutic Uses for Existing Molecules, is led by the National Center for Advancing Translational Sciences and is funded by the NIH Common Fund. In late May 2012, NCATS made available information about more than 50 shelved compounds and solicited proposals for new uses from academic researchers. Those proposals were peer-reviewed, and then cooperative agreements between the winning institutions and the pharmaceutical companies were forged.

During a news teleconference on June 18, NCATS officials indicated that they'd aimed to fund about six projects through the program but ended up having enough money to fund more, because the funding requests from the winning proposals were lower than expected.

NCATS Director Christopher P. Austin said during the telephone briefing, "These companies have invested between $10 (million) to even $100 million in these drugs to get them to this point. We around here talk about football. This is an analogy of the drug-development process … Some of these drugs have been taken all the way to the 10-yard line or the 5-yard line, and we're hoping that we can have a new special team come in and even run a play or two and have a touchdown formation. So we're really hopeful one of these will result in the end zone really soon."

NEW AND DEPARTING ASBMB COUNCIL AND COMMITTEE MEMBERS

Welcome!

Steven McKnight, *President-Elect*
Karen Allen, *Secretary*
Squire Booker, *Council Member*
Brenda Schulman, *Council Member*
Gregory Gatto Jr., *Council Member*
Takita Felder Sumter, *Minority Affairs Committee Chair*
Hinh Ly, *Education and Professional Development Committee Member*
Bob Matthews, *Public Affairs Advisory Committee Chair*
Gerald Carlson, *Public Affairs Advisory Committee Member*
Preston Hensley, *Public Affairs Advisory Committee Member*
Wesley Sundquist, *Public Affairs Advisory Committee Member*
Julie Hudson, *Public Outreach Committee Member*
Susanna Greer, *Public Outreach Committee Member*
Teresa Evans, *Public Outreach Committee Member*
Shannon Colton, *Public Outreach Committee Member*
Jeffrey Benovic, *Publications Committee Chair*
Alex Brown, *Publications Committee Member*
Blake Hill, *Publications Committee Member*
Anne-Frances Miller, *Publications Committee Member*
Thomas Poulos, *Publications Committee Member*
Lila Gierasch, *Nominating Committee Member*
Karen O'Malley, *Meetings Committee Member*
Geeta Narlikar, *Annual Meeting Program Committee Co-chair*
Enrique de la Cruz, *Annual Meeting Program Committee Co-chair*

Thanks for your service!

Suzanne Pfeffer, *Past President*
Mark Lemmon, *Past Secretary*
Levi Garraway, *Past Council Member*
Jonathan Weissman, *Past Council Member*
Squire Booker, *Past Minority Affairs Committee Chair*
Weiping Jiang, *Past Education and Professional Development Committee Member*
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Ann Marie Pendergast, *Past Publications Committee Member*
Frances Sharom, *Past Publications Committee Member*
Carol Fierke, *Past Annual Meeting Program Committee Co-chair*
Patrick Sung, *Past Annual Meeting Program Committee Co-chair*

ASBMB Annual Award WINNERS

ASBMB MERCK AWARD
Benjamin F. Cravatt
The Scripps Research Institute

ASBMB AWARD FOR EXEMPLARY CONTRIBUTIONS TO EDUCATION
Harold B. White III
University of Delaware

ASBMB YOUNG INVESTIGATOR AWARD
Samie R. Jaffrey
Weill Medical College of Cornell University

AVANTI AWARD IN LIPIDS
Sandra L. Hofmann
University of Texas Southwestern Medical Center at Dallas

BERT AND NATALIE VALLEE AWARD IN BIOMEDICAL SCIENCE
Michael M. Gottesman
National Cancer Institute

DELANO AWARD FOR COMPUTATIONAL BIOSCIENCES
Michael Levitt
Stanford University

EARL AND THRESSA STADTMAN DISTINGUISHED SCIENTIST AWARD
Aviv Regev
Broad Institute

HEBERT A. SOBER LECTURESHIP
Dana Carroll
University of Utah School of Medicine

HERBERT TABOR RESEARCH AWARD
Bruce Stillman
Cold Spring Harbor Laboratory

MILDRED COHN AWARD IN BIOLOGICAL CHEMISTRY
Lila M. Gierasch
University of Massachusetts–Amherst

RUTH KIRSCHSTEIN DIVERSITY IN SCIENCE AWARD
Freeman A. Hrabowski III and Michael Summers
University of Maryland, Baltimore County

WALTER A. SHAW YOUNG INVESTIGATOR AWARD IN LIPID RESEARCH
Mary L. Kraft
University of Illinois at Urbana–Champaign

WILLIAM C. ROSE AWARD
Lynne E. Maquat
University of Rochester Medical Center School of Medicine and Dentistry

ALICE AND C. C. WANG AWARD IN MOLECULAR PARISITOLOGY
Ken Stuart
Seattle Biomedical Research Institute

Retrospective

François Jacob (1920 – 2013)

BY JAMES E. DARNELL JR.

The death of François Jacob at age 92 on April 19 should serve as a reminder in this age of virtually instant whole-genome sequencing and 20-plus-person publications that the present-day understanding of gene and cellular regulation rests on the earlier deep thinking and superb critical experimental skill vested in single individuals. Jacob, of course, was spectacularly endowed with both these capabilities. His partnership with Jacques Monod (1) uncovered how inducible genes are controlled in bacteria through synthesis of an unstable intermediate between genes and protein synthesis. This then led to Jacob's discovery of messenger RNA with Sydney Brenner and Matt Meselson (2).

IMAGE COURTESY OF INSTITUT PASTEUR

Jacob's childhood, adolescence and World War II experiences have been preserved for us through the use of a third remarkable trait. He was to me and to legions of others perhaps the finest writer to come out of 20th-century science. "The Statue Within," first published in French in 1987, has been celebrated by nonscientists and scientists not only as an invaluable autobiography recounting momentous science but also as great art. One is left with the conviction that Jacob easily could have been a highly successful writer.

He tells of the very important influence of his grandparents, at whose house he spent his summers as a child. The grandfather, a four-star French general (perhaps the only Jew to achieve such a high rank), furnished the young boy with books and apparently welcome instruction about the classical and European historical worlds. In a few engaging pages, Jacob portrays an adoring mother and somewhat stern father for whom he went through a bar mitzvah and immediately thereafter, at least to himself, disavowed religion.

At 18 (and, one gathers, more or less by default) Jacob began medical studies, but Hitler's invasion of Poland in 1939 and quick conquest of France drove Jacob out of medicine at the end of his second year and into the Free French Forces assembled by Charles de Gaulle in England. As a member of the medical corps, Jacob fought both in North Africa and, after D-Day, in Europe, where he was wounded seriously, ending his plans to become a surgeon. France may have lost a potentially gifted surgeon, but the world gained one of its premier scientists.

Deciding that a research career appealed to him after the war, Jacob worked for a brief period on tyrothricin to finish off a thesis for his M.D. Tyrothricin is an antibiotic discovered by René Dubos at the Rockefeller Institute (now The Rockefeller University) that is too toxic for use except topically. Jacob finally had the courage to ask for admittance as a fellow at the Pasteur Institute. He was accepted and in 1949 took the comprehensive introductory course required of all fellows. Because he had become interested in genet-

ics, he approached André Lwoff to serve as his mentor but was rebuffed initially. On his second or third try, he was finally accepted by Lwoff to begin a research career in 1950. Lwoff and two postdoctoral visitors, Lou Siminovitch and Niels Kjeldgaard, just had discovered UV induction of prophage in lysogenic bacteria (3), and Lwoff offered this as a project on which Jacob, now 30 years old, should begin. Jacob divulges in "The Statue Within" that he did not know what "prophage" meant, a fact he kept to himself. He learned his trade quickly and with great delight, working with the lysogenic bacteriophages in Pseudomonas pyocyanea. After a brief and successful training period, he formed a close friendship with Élie Wollman. The two began an imaginative use of bacterial conjugation and chromosome transfer in E. coli. An early surprising result was the discovery of zygotic induction of prophages. When a lysogenic donor (male) transferred its chromosome into a nonlysogenic recipient (female) cell, phage production and lysis occurred. Later, chromosome transfer was the basis of the famous PaJaMo (4) experiments that were key to proposing the existence of an unstable messenger RNA. The clincher here were experiments using ^{32}P-labeled cells (including, of course, their labeled RNA) that the three designed and began in Paris (5) and that Pardee and his student Monica Riley in Berkeley carried to completion (6). Radioactive decay in the labeled RNA with consequent loss of already induced enzyme (β galactosidase) forming capacity suggested that an unstable RNA had to be renewed constantly. Thus the messenger idea was born. Within a year Jacob, with Sidney Brenner and Matt Meselson, had demonstrated bacteriophage T4 messenger RNA.

Jacob described vividly his intense discussions with his partner Jacques Monod both in "The Statue Within" and in a commemorative essay in "Origins of Molecular Biology: A Tribute to Jacques Monod" (7). These descriptions document two great minds at work, revealing Jacob's ability to translate each logical "physiologic (biochemical)" problem Monod introduced into an experimental genetic answer. These conversations not only produced the messenger proposal but also led to the discovery of all the functional genetic sites and the role of repressor proteins that govern regulation of the genes in operons. This story should instruct all students of biology, young and old, in the use of logic in biological discovery.

James Watson's and Francis Crick's great deduction of the structure of DNA 60 years ago this spring often and correctly is said to be the watershed moment that first led to all the remarkable progress in modern biology. But Jacob, together with his Pasteur colleague Monod and his original mentor Lwoff, brought life to the molecule containing life's instructions.

James E. Darnell Jr. (darnell@mail.rockefeller.edu) is the Vincent Astor professor emeritus and head of the Laboratory of Molecular Cell Biology at The Rockefeller University. He completed a stint as a postdoc with Francois Jacob from 1960 to 1961.

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ASBMB TODAY LOOKS BACK

We have had the privilege of publishing over the years dozens of Retrospective articles about the great men and women who have contributed to our current understanding of biochemistry and molecular biology. This summer we launched a special collection of those remembrances and biographies on our website. Visit www.asbmb.org/asbmbtoday and click on "Collections" to see ones you might have missed or could use in the classroom.

Retrospective

Adolphus P. Toliver (1931 – 2013)

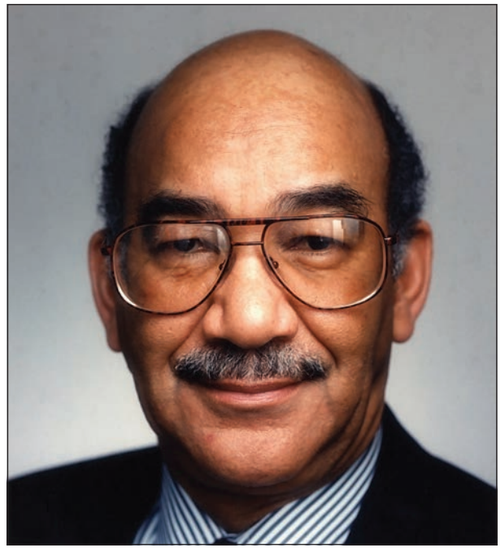
BY HINDA ZLOTNIK

With the passing of Adolphus P. Toliver, the scientific community has lost a friend, a great mentor, a change agent and a leading proponent of the minority programs at the National Institutes of Health.

Toliver, the Minority Access to Research Careers Branch chief from 1994 to 2012 at the National Institute of General Medical Sciences, died March 26.

Previously, Toliver had served as the executive secretary (scientific review administrator) of the biochemistry study section of the NIH Division of Research Grants (now called the Center for Scientific Review). Prior to joining the NIH, Toliver was a member of the faculty at University of California, Davis.

He earned a bachelor's degree in biology from Washington University in St. Louis and master's and doctoral degrees in molecular biology/biochemistry from Purdue University in Indiana. His postdoctoral studies at Kansas State University were supported by an American Cancer Society fellowship.



A special gift for mentoring

Known to friends and colleagues as "Tol," he was born and raised in Saint Louis in the era of segregation. He was a smart student and a self-learner, but at an early age he never thought he would become a scientist. A mentor he had when he worked in a clinical laboratory was the one who recognized his talent and encouraged him to study. This mentorship by a person "who did not look like me," Tol said, inspired him profoundly and left a lasting influence on his ideas and views on mentoring.

Throughout the many phases of Tol's scientific career, he had a special gift for identifying and developing talent. Many scientists owe part of their successes to him, a demonstration of one of his most outstanding qualities: being a great mentor. His mentoring moments, as many can attest, occurred during formal and informal meetings while he was conversing with students, administrators and scientists. It often is said that a great mentor is someone who takes an unselfish interest in an individual and helps him or her grow. Tol's numerous mentees, such as Dwight Lewis, Shiva Singh, Shawn Drew Gaillard, Alberto Rivera-Rentas and Kamilah Ali, recall that he was generous with his advice and feedback but also persistent until he saw the results he expected. His friendly and relaxed personality allowed him to engage people and communicate in a frank yet helpful way. He was fair and trustworthy, and he was an astute communicator. But more importantly, he was always available to all those he considered his friends and mentees.

An accomplished career

Beyond his mentoring, Tol was a change agent at the NIH, where he spent most of his scientific career. He strived to increase the diversity of the biochemistry study section by inviting young and emerging professors — men and women from all backgrounds — to be part of the review team. His aim was to allow them to learn the NIH peer-review system and improve their grant-writing skills. He was superb at this and at ensuring that a project received the best evaluation possible. As executive secretary, he also conducted a careful

scientific assessment of the rapidly evolving field of biochemistry to justify the creation of new study sections in two emerging areas, molecular and physical biochemistry. As a result of this major accomplishment, Tol helped lead the scientific community through the revolutionary period that gave birth to molecular biology and permanently influenced the scientific landscape.

As chief of the MARC Branch at NIGMS, Tol made other seminal contributions. He was instrumental in changing the MARC Honors Undergraduate Training Program to the MARC Undergraduate Student Training in Academic Research, or U*STAR, a program that emphasized his vision for curricular improvement and state-of the-art research training.

He refocused the BRIDGES program while functioning temporarily as its acting director, created the Postbaccalaureate Research Education Program, encouraged professional societies to apply for funding to increase the participation of underrepresented students in biomedical and behavioral research, and established the Annual Biomedical Research Conference for Minority Students. He was especially proud of this meeting, because it achieved one of his dreams: to have a high-quality scientific meeting for minority students training in research. ABRCMS is now in its 13th year and is the largest professional conference for minority students planning to pursue advanced training in science, technology, engineering or mathematics. Last year, ABRCMS attracted about 3,300 attendees, including 1,700 undergraduate students.

Tol was truly one of a kind, and his legacy is monumental. He worked with and influenced an entire generation of biochemists. His lasting dream of a more diverse and well-prepared scientific workforce is being achieved through the numerous people he mentored, especially the many current and former MARC students who are pursuing research careers. His insightful comments and sensible advice as well as his humor and tact will be missed by those who were fortunate to know him.

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MY SPOUSE AND THE MOUSE

BY HARVEY J. ARMBRECHT

In my wife, it began at age 58 with pronouns. Linda began referring to our female pets as "he." No big deal. We joked about it. But gradually more serious symptoms appeared – short-term memory loss, the inability to concentrate, confusion in social situations and finally hallucinations. She ultimately was diagnosed with Lewy body disease, a relative of Alzheimer's disease with no cure.

In the mouse, it begins at 12 months with memory loss. The mouse has reduced ability to learn and remember as measured by aversive T-maze testing. In this case, the mouse is the SAMP8 mouse, a spontaneous animal model for early memory loss, which is accompanied by Alzheimer's diseaselike pathology. This memory loss has been characterized extensively by a group headed by my division director, John Morley, at the St. Louis VA Medical Center and St. Louis University School of Medicine. Unlike in humans, in the SAMP8 mouse there is a cure. The age-related memory loss is related to an increase in β-amyloid in the hippocampus. The Morley group showed that reducing the β-amyloid load by injection of a specific antisense oligonucleotide reversed the memory loss. Treated SAMP8 mice could now remember as well as normal mice.

My involvement with the SAMP8 mouse began in the summer of 2009, about the same time that Linda began to show neurological symptoms. The Morley group had performed a series of gene array experiments and needed a biochemist to interpret the results. That was me. My job was to analyze gene expression in the hippocampus of these mice. We were interested in the differences in SAMP8 mice and the effect of the oligonucleotide treatment. By the end of 2009, I was involved heavily in pathway analysis of the array data. At the same time, Linda's symptoms were getting worse. I had the sinking feeling that I was involved with memory deficits at home as well as in the lab.

In early 2010, Linda was having more severe memory loss and hallucinations. A complete physical and neurological exam revealed nothing. Finally, a geriatric psychiatrist diagnosed her with Lewy body disease based on her symptoms and psychological testing. Suddenly, I became a consumer of the medical literature rather than a contributor. I did a PubMed search for "Lewy body." From a biochemical standpoint, I found out that the protein implicated in Lewy body pathology is α-synuclein. Over-phosphorylation of serine 129 is implicated in α-synuclein aggregation and pathology. Very interesting. Now what about treatment and cures? With impatience, I skipped over all the animal models. This was unusual for me, as I had used animal models all my life in my research. I wanted human treatment and cures. The literature search revealed that there was none, only palliative care.

As things were getting worse at home, they were getting better in the lab. We found highly significant differences in the inositol phosphate signaling pathway, a pathway previously implicated in memory formation. The oligonucleotide treatment also produced significant changes in this pathway. These results suggested that modifying downstream targets of the inositol phosphate pathway might enhance memory in the SAMP8 mouse. This prediction since has been verified, with possible implications for targeted therapy. We had visions of papers and grants.

We presented the results of our SAMP8 studies at the international Alzheimer's meeting in Honolulu in July 2010. My son flew in from out of town to stay with Linda while I was away. I was on a roller coaster of emotions. As a scientist, I was elated; as a husband, I was despondent. It felt strange to attend a scientific conference addressing a disease that was afflicting my wife. I divided my time between basic science sessions and sessions on caregiving. The setting in Honolulu captured my conflicted mood perfectly – human pathology inside the convention center and great natural beauty outside of it.

It has been three years now. Linda has been relatively stable. Her hallucinations are now well controlled by medication. Due to her condition, she cannot drive or work – huge losses. However, she still has her sense of humor and determination. Her days are taken up with occupational therapy, water aerobics and outings with friends. We travel frequently to visit our grandchildren. We enjoy each other one day at a time.

In the lab, we submitted several grants based on the gene array data. They were all the victims of falling paylines. The SAMP8 mouse is not a traditional model for Alzheimer's disease, and oligonucleotide administration is not a typical treatment. It is not a good time for innovation. Personally, I retired in March 2012, partly to spend more time with Linda. I still come in to the office almost daily. I am working to get the SAMP8 array data published. It is important work, and, because of Linda's condition, I have a personal interest in seeing it published.

What about the future? In the Hollywood ending, our research in the mouse would lead a cure for Linda. I don't expect a Hollywood ending. To begin with, the SAMP8 mouse is not a model for Lewy body disease. The SAMP8 pathology is linked to β-amyloid, while Lewy body disease is linked to another protein – α-synuclein. But even if there is no Hollywood ending, being a biochemist gives me hope. I have hope that future medical research will develop an animal model of Lewy body disease that will be used to develop treatments – perhaps not for Linda, but for people down the road. I hope that our work on restoring memory in the SAMP8 mouse will contribute to that. But being a biochemist also gives me hope beyond that. To me, the marvelous life processes that we study point to a greater reality beyond us. I have hope that what cannot be made right in this world will one day be made right in the world beyond. And in that world, Linda will again use pronouns perfectly, and no mouse will have memory problems.

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Reviewing is a business transaction

BY ELEFTHERIOS P. DIAMANDIS

I work at least 12 hours per day. I also spend two hours at home answering e-mails. Almost every day, one of these e-mails is a request for a review. My success in science is haunting me! People know that I am an expert in a few things, and they are asking me to review papers all the time. Let us count. I get 300 requests for review per year. Each review requires three to four hours to complete, and if I were to accept those I would devote one to two days per week to this.

One reason for doing a review is that others are reviewing my papers, so I should contribute to the pool. If I publish 20 to 30 papers per year, and I review the same, I am on par. But as I just mentioned, I do not have the time. And who would ever care if I did a review? Reviewing is not a highly recognizable activity, and it requires a lot of time. I could see my administrator saying, "Why are you wasting your time reviewing other people's papers and not concentrating on what you are paid for?" I know I will not get a promotion by reviewing other people's work. If I do win the reviewer-of-the-year award from a journal, I have a feeling that my colleagues will say, "Look at him: He is wasting his time, and he is rewarded for it."

"I could use this money to buy back some personal pleasure. For example, I could buy a billiards table, a pinball machine or a fancy treadmill without having to ask my wife's permission to do so."

I believe that the current practice of reviewing is wrong. This is an important service requested by journals (many of them publish for profit), but they want it for free. Reviewers of highly successful and profitable journals do not get a share, despite being part of the success. As time goes by, as journals proliferate and as people become busier, their appetite to review any paper, for any journal, diminishes greatly. The only way I can see a revival of this activity is to consider it as a business transaction.

If journals want my time, they should pay for it. With a four-hour slot per paper and $50 per hour as a modest remuneration, a review is worth $200. Prospective reviewers will be more inclined to do a very good job if they know that they will be paid. More importantly, retired scientists with great expertise and a lot of free time will be keen to participate to make some money on the side. If I do 20 reviews per year at $200 per review, I will make $4,000. I could use this money to buy back some personal pleasure. For example, I could buy a billiards table, a pinball machine or a fancy treadmill without having to ask my wife's permission to do so.

Who would pay for this service? There are two parties interested in the process, the author and the journal, and they should split the cost equally. If the process is futile (the paper is rejected), they both lose, and if it is fruitful (the paper is accepted), they both win. The reviewer wins too. I do not think a $200 reviewing expense for an author is a high one, considering that publishing in an open-access journal costs between $1,000 and $2,000. I suspect that conversion to this system will make everybody happy. Editors will not have to beg reviewers to do the job for free, and they likely will get a good service in terms of speed and quality.

Bottom line: Reviewing should be a paid service governed by the laws of supply and demand. I am glad some companies and publishers are beginning to implement these or similar ideas (1).

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REFERENCE
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Perceptions matter

Would reviewer compensation undermine public credibility?

BY PETER J. KENNELLY

When I hear scientists propose that reviewers be compensated, I do not dismiss the idea out of hand. After all, I typically review 30 to 50 manuscripts a year, so at $50 or $100 a pop … After all, a good reviewer brings years of training and experience to the evaluation of scientific work and spends quality time reading, reflecting and generating feedback on a manuscript. Many publishers directly profit from my voluntary contributions to the vetting of research papers, so why not stop the exploitation of my public spirit and let me share the wealth?

While there is some merit to the idea of compensating professionals for their service, there is peril as well. Peer review is one of the cornerstones of science. We differentiate ourselves from the vast array of consultants, advisers, forecasters and other experts because we put our ideas and experiments to the test both at the bench and among our peers. If people perceive that the peer-review system has been compromised, our community stands to lose much of its ability to inform and enlighten. We become just another set of so-called experts.

"If people perceive that the peer-review system has been compromised, our community stands to lose much of its ability to inform and enlighten."

We tend to credit those individuals foolish enough to take on thankless tasks of no apparent personal benefit voluntarily and repeatedly with positive, even altruistic, motivations. The perceived thanklessness and onerousness of uncompensated peer-review service enhances, admittedly with essentially circumstantial evidence, the perception that referees attempt to be objective and fair.

The idea that scientists are being paid to give the thumbs up or thumbs down on each other's work would offer potent ammunition for skeptics and critics of all kinds. For those who believe the peer-review system is fundamentally flawed, the equation "money = corruption" will seem as logical as "2 + 2 = 4." The suspicion that a reviewer might alter his or her standards, even unconsciously, in an effort to curry favor with editors for financial gain is a recipe for disaster. Certainly those who are pushing the replacement of peer-reviewed journals by unvetted research blogs would seize immediately on reviewers for hire as a cudgel for advancing their agenda.

In the end, science derives its credibility and funding from the perception that the work we publish is the product of a system that employs, as one of its integral components, a mechanism for objective, self-correcting quality control. While there are some publications and institutions that do compensate reviewers, in considering the idea of making reviewer compensation universal, it is not really important whether scientists think it is a reasonable idea. What is really important is how it will play with John and Mary Q. Public and the persons they elect to public office.

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Got a beef? Ready to rile? We welcome your submissions and suggestions for our new Point/Counterpoint feature. Contact ASBMB Today Editor Angela Hopp at ahopp@asbmb.org.

NOTES ON A CAREER

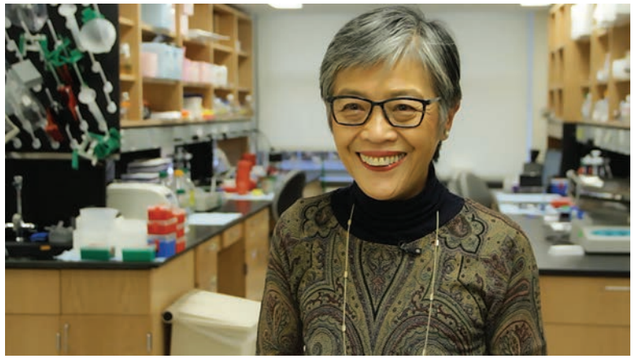
How Virginia Lee charted a successful path from the piano bench to the lab bench.

BY RAJENDRANI MUKHOPADHYAY

"I never really had a role model," says Virginia M-Y Lee, director at the Center for Neurodegenerative Disease Research at the University of Pennsylvania, pausing to reflect on her unusual career path. "I made decisions based on a number of factors – of where I wanted to go and live, what I wanted to see and what I wanted to learn. Then I just went and did it."

This attitude of getting things done without following preset directions could be credited for Lee's scientific success. Over the course of three decades, Lee and her husband, John Trojanowski, co-director of the center, have spearheaded efforts to identify some of the proteins involved in Alzheimer's, Parkinson's, frontotemporal dementia and amyotrophic lateral sclerosis, known as ALS or Lou Gehrig's disease. "Science is so exciting now. I would have never imagined, as a high-school girl or even as a postdoc, where I am right now," says Lee. "It's a very interesting journey for me."

Indeed, it is an interesting journey, especially when one realizes Lee didn't have a conventional entry into a scientific career. For there was a time in her life when Lee was training to be a concert pianist.



"COULDN'T WAIT TO GET OUT"

Lee was born in Chongqing in southwest China in the 1950s and moved to Hong Kong when she was 5 years old. "We lived as an extended family – lots of aunts, uncles, cousins and brothers," recalls Lee. In the chaos of a large family, Lee says, no one paid much attention to her. Her father, a restaurateur with businesses in Hong Kong and on the U.S. West Coast, was rarely around. When Lee was about 11, most of her relatives, including her mother, left Hong Kong for the U.S. "I stayed behind with one of my brothers and my paternal grandmother to finish high school," says Lee.

She attended a Chinese primary school, where the classes were taught in Chinese, and spent a year in a Chinese high school before she moved to a high school where the language of instruction was English. "It was a difficult switch," says Lee. "But I was competitive. I looked around at my classmates and thought, 'I'm not as good in English as they are. But science is a new language for everyone.' We were all on an even playing field."

Besides science, Lee excelled at something else. Her mother insisted that she learn the piano, for which Lee demonstrated aptitude. When the time came for her to take the next step after high school, her mother told her to apply to the prestigious Royal Academy of Music in the U.K. Lee did as she was told, but she also had an ulterior motive. "Hong Kong is a very small town. I couldn't wait to get out," she says. "I just was thrilled to have the opportunity to get out of Hong Kong and go someplace else and explore."

Lee arrived in London in 1962, eager to learn about the British people and their norms and customs. "When you go to a foreign country, one thing for me, always, is you want to learn more about the people," she says. "There is no point being in a foreign country if you stick to your own community."

As she adjusted to her new life, however, she acknowledged she had a problem. Lee found the eight hours of daily piano practice to be maddening and felt she lacked sufficient talent to make it big. "I realized it's difficult to make a career out of piano, unless you are really outstanding," she says. "I think if I had been playing the violin, my career might have been different, because it's easier to be a member of an orchestra than a soloist. Piano doesn't give you much choice in that matter."

So Lee persuaded her mother to allow her to attend college to study science. Her mother's stipulation was that Lee had to keep up with her music training while attending the University of London's undergraduate chemistry program. But after plugging away at the Royal Academy of Music for two years, "I quit," says Lee. "My heart wasn't in it." From then on, Lee threw herself into science.

PHOTO COURTESY OF VIRGINIA LEE

Virginia Lee is interviewed by a local Fox affiliate in September during the University of Pennsylvania's "5K for the IOA," a race raising awareness and support for the university's Institute on Aging.

Because she had found chemistry "a bit too dry," Lee decided to steer toward biochemistry for her master's degree in the late 1960s. "I wanted to learn something that is more relevant to life," she says. She did her master's under Nobel laureate Ernst Chain's supervision at Imperial College. The first day at the engineering and technology institution still stands out in Lee's mind: "That first day was a real shocking experience. I was in this hall with 3,000 people. I looked around and thought, 'Holy moly, there is not a single woman in this room.'"

COMING TO AMERICA

As she got closer to finishing her master's degree, Lee considered her next move. She hadn't lived with or even been near her parents since she was 11, and she decided it was time to get to know her mother better. "My mother was living in L.A., and I thought, 'San Francisco is close enough, so I can visit her a lot but I can still live on my own,'" says Lee. "That's why I made that choice to go to UCSF. It turned out to be a good solution. I did get to see her a lot, but I still could do my own thing and go to graduate school."

At the University of California, San Francisco, Lee worked with C.H. Li, "who was one of the great biochemists in purifying pituitary hormones," she says. Li's achievements included isolating luteinizing hormone, synthesizing human growth hormone and identifying beta-endorphin and insulinlike growth factor 1. Lee learned about endocrinology, biochemistry, pharmacology and biophysics.

Still stricken with wanderlust, Lee in 1973 moved to the Netherlands after she completed her Ph.D. for a yearlong postdoctoral stint at the University of Utrecht. It was at this juncture that Lee became curious about the brain, as her work on pituitary glands turned her attention toward it. "I thought the brain was a fascinating organ, because it regulates so many things," she says. "Also, not much is known about it, so I was just fascinated."

But the scientific fit at Utrecht wasn't a good one, so Lee decided she needed to get back to the U.S. It just so happened that a friend from graduate school was doing a postdoctoral fellowship at the Pasteur Institute in Paris. Lee regularly hopped on the train and visited her friend on weekends. At the Pasteur Institute, she met Michael Shelanski, who was wrapping up a sabbatical and preparing to set up a research group with Lloyd Greene at the Children's Hospital at Harvard University. Shelanski, an expert in Alzheimer's disease who is now at Columbia University, asked Lee if she'd be interested in joining his group in Boston as a postdoctoral fellow. "I said, 'OK,' and off I went," says Lee.

BOSTON

In 1974, Lee once again was in a new place to do research and explore. But this time, life had more excitement than usual in store in the form of John Trojanowski. He was then an M.D./Ph.D. student training in pathology, and he's been Lee's life and scientific partner for more than 30 years now. Lee had noticed Trojanowski at a seminar in 1974 at Harvard and around town on other occasions ("with another girlfriend," notes Trojanowski). But it was only on April 30, 1976, at the bar in the Copley Plaza Hotel (now the Fairmont Copley Plaza), that Lee finally got a chance to strike up a conversation with him. They realized they had lived in the Netherlands at the same time, he in Rotterdam and she in Utrecht, and that they had attended the same concert at London's St. Martin in the Fields, an Anglican church that hosts one of the U.K.'s longest running free musical series.

Trojanowski says his first impression of Lee was that she was a "ravishingly beautiful woman who was extremely bright and very engaging, a woman of her own views and opinions." Soon, they were a couple, and they married in 1979. "We love to be with each other," says Trojanowski. "We also fight like hell."

Their arguments, especially about science, are legendary, to the point that Shankar Vedantam devoted a part of a chapter in his 2010 book "The Hidden Brain" to their disagreements. Lee and Trojanowski both hasten to add that they've lately toned down their public sparring.

"I think we've scared a number of people," says Trojanowski with a chuckle. He tells a story of when Lee's niece Suzette spent a summer with them to do a high-school research project in the 1980s. "We went to see 'Evita' in New York, and we were going to buy tickets. Somehow, we got into a huge fight in Times Square and jumped out of the car, screaming and yelling at each other," recounts Trojanowski. "Her niece went home and said, 'They are going to get divorced! You can't believe how much they fight!'"

PHILADELPHIA

Shortly after the couple married, a job in the biotechnology sector beckoned Lee to Philadelphia. Smith, Kline & French, now GlaxoSmithKline, offered her a position to build up its neuroscience research portfolio. Trojanowski was in the middle of his neuropathology training at the Massachusetts General Hospital. "We had our first big fight then, because I wanted to stay at Mass General," says Trojanowski. He also had doubts about Philadelphia. "The mayor at the time was a guy named Frank Rizzo, who, when asked about his politics, said he was to the right of Genghis Khan," says Trojanowski. "Boston, at the time, was on the economic rise. Philadelphia was in the doldrums."

But in a signature move of their life together, "we discussed, compromised and came up with the best decision for the way forward for the both of us," says Trojanowski. The couple moved in 1980 to Philadelphia so that Lee could take up the job offer, and Trojanowski transferred to the University of Pennsylvania medical school and later accepted a tenure-track position there.

Yet Lee's new pharmaceutical job turned out to be a disappointment. She found she wasn't being allowed to study neuroscience. "I was in a very compromised position. I was in misery," she says of the year she stuck it out in that job. The university came to her rescue. There wasn't a tenure-track position available, but Trojanowski's boss was able to offer Lee a research-track position, which she accepted.

But she was immediately beset by doubt. Although she had bagged an RO1 grant from the National Institutes of Health, Lee wondered if she needed a backup plan. "At that time, Ronald Reagan was going to privatize the NIH," says Lee. "If there was no NIH, there would be no funding for research. My husband can deliver babies. What would I do?"

So Lee applied to the Wharton School of Business at Penn to get an M.B.A. Her thinking was that the M.B.A. would let her step up the corporate ladder in the pharmaceutical industry. "But then the science really took off," says Lee. "I never looked back."

The M.B.A. training comes in handy in running a research team of up to 50 people. Lee and Trojanowski work with clinicians and help them store their data and bank samples, run a drug-discovery program, and pursue basic science research. Organizing and managing all that requires implementing an infrastructure, which Lee says her business education taught her to do. But more importantly, Lee says, the M.B.A. has helped her think like a small-business owner. "Running your own lab is like running a mom-and-pop shop," she says. "You

get money. You have to pay bills. You have to order supplies and so on. On the small scale, it's not as important, but when it's on the large scale, any kind of business training and organization skills, as well as knowing about finances, is important to running a big lab."

SCALING GREAT WALLS

When they both started at Penn, Lee had a project on the effects of nerve growth factor on PC12 cells, and Trojanowski was studying axonal transport and endocytosis. In 1983, the two collaborated on a project for which Trojanowski did electron microscopy on the filamentous inclusions that formed when NGF interacted with PC12 cells, and Lee did the biochemistry of the receptor-NGF interaction. They had so much fun working together that they considered building a joint research program. Neurodegenerative diseases beckoned.

"We knew nothing about the identity of neurofibrillary tangles or senile plaques or any of these disease proteins in neurodegenerative diseases," says Lee. They recognized that Alzheimer's disease was going to become an increasingly important illness in society (see the April 2013 ASBMB Today cover story). Lee and Trojanowski knew they could tackle the complex disorder from different angles. Trojanowski, as a neuropathologist, had access to brains from patients who consented to autopsy. Because he was responsible for making the final diagnosis of what killed a patient, he would know which brain samples were from patients with Alzheimer's disease.

Then there was Lee, the biochemist who came to realize she had something special to bring to Alzheimer's research. "In the 1980s, I was asked to serve on study sections because there weren't that many women at that time. 'Asian' was also still considered to be a minority," she says. "I was three to four years into my faculty position and I was already on study sections." There, she realized that the people studying neurodegenerative disorders were M.D.s. "They are not well-trained in basic science," says Lee.

So she and Trojanowski decided to make it their goal to isolate systematically and identify the disease proteins in neurodegenerative disorders, starting with Alzheimer's disease. Before they launched their project, they asked senior faculty for their opinions. "All of them, except for one person, said, 'This is a crazy, stupid idea. Alzheimer's is a wasteland. You'll ruin your careers,'" recalls Trojanowski. "The only one who was supportive was Vince Cristifalo, who started the Institute on Aging." (Trojanowski is now the director of the institute.)

Even family members had doubts, Trojanowski recalls: "Virginia's father is a no-nonsense businessman. He said, 'Look, John and Virginia, you're not going to solve this in your lifetime.' I said, 'Jack, when the Great Wall of China was built, people who were putting the very first bricks in the ground knew they wouldn't live to see the end of the wall being built as a defense structure. You just have to believe what you're doing is important and will be impactful over time.' He said, 'OK, I get it.'"

In 1991, in a Science paper, a team led by Lee and Trojanowski demonstrated that the cytoskeletal protein tau is a building block of neurofibrillary tangles, one of the characteristics of Alzheimer's disease. Over the years, they and colleagues have identified α-synuclein as a protein in Lewy bodies, a hallmark of Parkinson's disease, and TDP-43, the protein involved in ALS.

In the past decade, hints of a theme have emerged from their work and that of others, says Lee. In the fall of 2012, their group demonstrated that misfolded versions of α-synuclein, the protein implicated in Parkinson's disease, can be transmitted from cell to cell in mouse models, adding weight to a hypothesis that a common mechanism of neurodegenerative disorders could involve the passage of misfolded proteins through the central nervous system. In the 1980s, "it was only a dream that there would be a common mechanism," says Lee. "I think in the next 10 years or so, the field as a whole will prove there is a common mechanism for the progression" of neurodegenerative disorders.

Trojanowski admits they've grown increasingly workaholic with age. "We are science addicts," he says. Lee still plays the piano over the Christmas and New Year's break, but once the holidays are over she is ready to throw herself back into science. "There's a time and a place to do certain things," Lee says. "As long as I can work and keep up with the pace, I would like to contribute. If there is some disease-modifying therapy for Alzheimer's and Parkinson's in my lifetime, I would be delighted. If I contribute to it, that would be even better."

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Venom-based therapies

Healing in the midst of pain

BY PUMTIWITT C. MCCARTHY

Have you ever had the unfortunate experience of being stung by a jellyfish? The painful chemical cocktail that the jellyfish has released is venom. Many animals, not just jellyfish and snakes, use venom to weaken their prey. However, venom has turned out to be an unexpected source of therapeutics against many diseases. Here, we take a look at some of these creatures and how their venoms have been used and may be used in the future as therapies.

Pumtiwitt C. McCarthy (prancy@gmail.com) just completed a postdoctoral fellowship at the U.S. Food and Drug Administration. She is now an assistant professor of chemistry at Morgan State University. *Image courtesy of Lenny Photos.*

THE GILA MONSTER

IMAGE COURTESY OF H. ZELL ON WIKIMEDIA COMMONS

The Gila monster, or Heloderma suspectum, is one of only two types of lizard in the world that produce venom. Gila monsters live in desert areas of the western United States. The lizard releases its venom through a bite but in a way much different from that of a snake. Snakes use quick, short bites to inject venom into their victim. Gila monsters, on the other hand, bite down longer and harder, and venom is released through grooves in the lower jaw. Some of the symptoms of a bite can include pain, swelling, nausea and low blood pressure. The venom is not just one peptide or protein – rather it is a mixture of components. Gila venom contains serotonin, hyaluronidase, phospholipases, phosphodiesterases and proteases, which could contribute to all or some of the symptoms. However, the toxicity of Gila venom is mainly due to a compound called gilatoxin.

Gilatoxin is a glycosylated serine protease. It contains a series of peptides that show bioactivity with different cellular receptors. One of these peptides, exendin 4, was found to have nearly 50 percent sequence similarity to human glucagon-like peptide 1. GLP-1 is a 29-amino-acid hormone that increases insulin production from pancreatic cells. The peptide binds to a G-protein-coupled receptor on the surface of pancreatic cells, leading to an intracellular signaling cascade. The result of this cascade is an increase in cyclic AMP production. Higher cAMP levels signal pancreatic cells to produce more insulin, which causes a decrease in overall blood sugar. A compound that increases insulin production is a useful tool to treat Type 2 diabetes in patients who do not secrete enough insulin naturally. The 38-amino-acid peptide exendin-4 was shown to have the same effect on insulin as GLP-1 and last even longer. In the early 1990s, John Eng, then at the Bronx Veterans Affairs Medical Center, was the first to publish data about this property of gilatoxin. The compound was licensed to a pharmaceutical company for further development as a diabetes drug in 1996 with the generic name exenatide. One version of the drug was released in 2005 and another, longer-lasting version was released in 2012.

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CONUS SNAIL

The conus snail resides in the coral reef in the Philippines, Australia and Indonesia. The snail typically feeds on fish, worms and even other snails. It injects its venom using a harpoonlike projection from its mouth. There are more than 500 species of snail, with each one estimated to produce more than 100 different toxin molecules in its venom. These molecules are peptides, called conotoxins, usually between 10 and 30 amino acids in length. Conus snail venom is known to affect voltage and ligand-gated ion channels, neurotransmitter receptors, and cell-surface proteins involved in signaling. All of these interactions prevent firing of nerve impulses, which can lead to muscle paralysis.

The field of cone snail research was pioneered by Baldomero Olivera. Olivera had an interest in cone snails from his days collecting shells as a child in the Philippines. When he established his own lab, he decided to focus on studying the conotoxins more closely. Olivera's career changed with the fateful discovery of the omega-conotoxin MVIIA from Conus magus. This 25-amino-acid toxin was discovered by a high-school student in his laboratory in 1987. Omega-conotoxin specifically blocks neuronal voltage activated Ca^{++} channels without affecting other subtypes. Not only is MVIIA specific, it is potent. The toxin is estimated to be 1,000 times more powerful than morphine – with no dependency. It was licensed in 2004 as ziconotide. The drug was targeted to provide pain relief to those with extreme pain, such as patients with HIV, cancer and neurological disorders. Interestingly, it seems that conotoxins may not be exclusive to snails. A toxin from Conus marmoreus was recently found in the wings of the butterfly Hebomoia glaucippe using a combination of two-dimensional electrophoresis and mass spectrometry. Amino-acid sequence analysis indicated that the toxin glacontryphan-M found in H. glaucippe is identical to the one found in Conus. This toxin may be involved in the butterfly's defense against an array of predators.

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PIT VIPER

IMAGE COURTESY OF FAUNA PRO ON WIKIMEDIA COMMONS

The effects of the venom of Brazilian pit viper Bothrops jararaca are so extreme that plantation workers bitten by the snake were known to pass out soon after being bitten. In the 1960s a Brazilian researcher, Mauricio Rocha e Silva, sought to gain a better understanding of the effects of the venom. His laboratory purified the venom for its studies. When one of Silva's postdoctoral fellows, Sergio Ferreira, began working with Sir John Vane of the Royal College of Surgeons in London, he brought some of the purified pit viper venom with him. Vane was already at

work studying the angiotensin I and II. These proteins are part of the renin-angiotensin hormone system for blood pressure regulation and water balance in the body. Secretion of renin starts a cascade of proteolytic cleavage events, which leads to production of angiotensin II. Angiotensin II is produced by the enzyme action of angiotensin converting enzyme, or ACE, a powerful molecule that can cause blood vessels to tighten and constrict. This leads to an increase in blood pressure. Vane discovered that pit viper venom can act as an ACE inhibitor. This property of the venom accounts for the victims' symptoms; inhibition of ACE causes a steep decrease in blood pressure, leading to fainting.

Because pit viper venom had such remarkable effects on blood pressure, it had potential for use in patients with high blood pressure. Further development of the compound for therapeutic use required a first-of-its-kind collaboration between academia and industry. Vane gave his compound to two pharmaceutical researchers. These scientists further isolated the exact compound responsible for the inhibition activity. They also were involved in determining ways to modify the structure of the compound to make it more potent and increase bioavailability. These studies were some of the first forays into rational design of pharmaceutical agents. Optimization of the compound led to approval of the ACE-inhibitor drug captopril in 1975.

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VENOM-BASED THERAPIES FOR THE FUTURE: THE BLACK MAMBA AND THE PLATYPUS

The black mamba, Dendroaspis polylepis, is considered the deadliest snake in the world. It lives in southern and eastern Africa. In a recent multi-institutional study in France, compounds from the black mamba's venom, known as mambalgins, were shown to block acid-sensing ion channels, or ASICs, on neuronal cells. Two 57-amino-acid mambalgins were found during a screen in search of compounds that inhibit ASICs. The level of blocking observed was comparable to the effects of morphine. The groups plan to continue their studies better to understand the role of mambalgins in pain sensing.

For the duck-billed platypus, Ornithorhynchus anatinus, looks can be deceiving. The creature seems cute and cuddly from afar, but in reality it can inflict a painful bite. The effect of its venom is extremely painful and long-lasting. Platypus venom contains many components, including a class of compounds known to form cation channels in lipid bilayers quickly. Recently a series of novel peptides were discovered based on this activity with neuroblastoma cells. Researchers plan to characterize these peptides further.

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In this issue:

Going M.D./Ph.D. vs. going 100% Ph.D.

BY CODY WESTON

Author's note: This article, which was adapted from a post on my blog, was conceived after a student who has a strong interest in a research career in neuroscience asked for my advice. Thus, it was written with someone who is more interested in research than clinical care in mind.

I will begin by saying that a research career is absolutely possible with an M.D. alone, but I think it's not a very advisable route, considering the out-of-pocket expenses and lack of formal training in forming and answering scientific queries.

As you may know, the stated goal of most M.D./Ph.D. programs is to create physician-scientists who aim to do 80 percent research and 20 percent clinical time. Therefore, they are well-suited for people with a strong research interest rather than a primary interest in care.

What's more, clinical time can be defined in a number of ways. With an interest in neuroscience, for example, you could use your M.D. to become a neuropathologist and help the clinical side by analyzing patient samples without having to interact directly with patient populations if you prefer.

If you're deciding between an M.D./Ph.D. approach and a Ph.D. approach, the M.D./Ph.D. programs may be somewhat more competitive, but they are not significantly more difficult than M.D. programs if you have a strong research background.

Below, I've outlined what I think are the key considerations in deciding whether to go for a dual degree or a single degree.

Pros of an M.D./Ph.D. program

- **Career security:** The clinicians always will be in demand, regardless of research funding climate.
- **Grant demand:** An M.D. lends a clinical credibility to research proposals that often makes grants more attractive to funding institutions.
- **Institutional demand for physician-scientists:** At the faculty and postdoctoral phase, you will be a more desirable candidate in many cases if you possess the versatile education of a physician-scientist.
- **Flexibility:** This applies both during and after the program. Most M.D./Ph.D. programs do not require you to pick your program right away. This means that you can enter wanting to be a neuroscientist and change course to become a biochemist or pharmacologist if your interests change. After the completion of your program, you can continue into residency with or without a research emphasis; you can proceed directly into a postdoc and become a pure scientist that just happens to possess a background in clinical medicine; or you can take a still different course in industry, government or consulting. Related to this, it's worth noting that you avoid some of the turf battles between M.D. clinical scientists and Ph.D. translational researchers if you decide to work with patients or patient samples, because your education will give you substantial authority in both realms.
- **Better understanding of clinical problems:** There are an infinite number of research questions to be asked. There is a finite amount of time in a career. With a medical education and regular access to patient populations, you're more likely to understand the questions relevant to improving the health and happiness of the population. This point is less relevant if your passion is for pure scientific understanding, but it was a factor that drove me toward this career path.

Cons of an M.D./Ph.D. program

- **Length:** An M.D./Ph.D. program will take eight years on average, compared with a Ph.D. program, which ought to be done in five to six years.
- **Purity of purpose:** There's only so much time in the day. It's impossible to be all things to all people, and choosing a single doctoral degree gives you license to focus on your research with fewer outside concerns.
- **Program availability and admissions:** It's still competitive to get into natural science Ph.D. programs, but there will be more slots available for Ph.D. programs than for dual-degree programs, so you stand a better chance of attending a more elite institution or one that's better suited to your needs.
- **Opportunity costs:** It's worth considering that the extra time and mental energy spent in developing a clinical foundation could be poured directly into developing your research career. It is possible that choosing a Ph.D. program rather than a dual-degree program could lead you to become better versed in your area of study sooner, giving you an edge over a less-focused person.

An important consideration is that your decision isn't set in stone, either. Some M.D./Ph.D. students begin as Ph.D. students and transition into the program. Other people attend medical school or graduate school after completing another program if their interests have changed. Still others begin as M.D./Ph.D. students and drop half to become a medical or graduate student during the process when they discover that the rest doesn't appeal to them as much as they thought.

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Faculty Perspective

THE EVOLUTION OF BIOMEDICAL SCIENCE AND YOU

BY LOUIS B. JUSTEMENT

The choice of whether to pursue an M.D./Ph.D. versus a Ph.D. presupposes a sincere desire to incorporate research into a future career. However, there are many additional factors that must be considered when weighing these two options.

One of the most important issues to consider is the evolution of biomedical research and how the two training paths will affect one's competitiveness in the biomedical research workforce of the future.

Whereas biomedical research has had a longstanding tradition that relies on investigator-initiated research in individual laboratories, there is now a shift in the nature of biomedical research that increasingly involves team-based, large-scale, translational initiatives with an emphasis on the significance of the research in terms of the development of new therapies and improved treatment of diseases.

Based on this, it is important to assess future career options in terms of the role that a given career will have in the evolving biomedical workforce. This should include an assessment of the necessary knowledge-based and skill-based competencies that will be important for future career success.

The M.D./Ph.D. track provides critical training that enables individuals to effectively bridge issues pertaining to the current state of medicine with initiatives in biomedical research in a bidirectional manner. Ideally, the knowledge gained through M.D./Ph.D. training facilitates one's ability to inform basic biomedical research initiatives based on recognized needs in the clinical arena and conversely

to translate the findings from biomedical research into improved therapies. Thus, M.D./Ph.D.s have the unique ability to engage in team-based, translational research based on their foundational training in human physiology and biomedical research.

Those who pursue the Ph.D. also play an important role in team-based, translational research by virtue of their intensive training in one or more theoretical or technical aspects of biomedical science. The Ph.D. track affords them the opportunity to specialize in a theoretical area of science and to gain additional in-depth experience in one or more areas of technology, such as bioinformatics or high-throughput analytical approaches that are being used more extensively. Thus, Ph.D.s can contribute to team-based, translational research initiatives based on their expertise in a particular area of biomedical science as well as through their expertise in advanced technologies that are critical for promoting the evolution of biomedical science and the practical translation of knowledge into therapies.

Regardless of whether one chooses to incorporate aspects of medicine or technology into a research career, there are essential competencies that will be required in either instance, including excellent oral and written communication skills, the ability to work with and manage others in a team, professionalism and a solid ethical foundation.

Taking time to think about the evolution of biomedical science and how you will fit into that process will play an important role in helping you make the right decision.

Louis B. Justement (Lbjust@uab.edu) is the associate director of the Medical Scientist Training Program and a professor in the microbiology department at the University of Alabama at Birmingham.

Faculty Perspective

PLENTY OF OPTIONS FOR STUDENTS WITH ALL DEGREES OF INTEREST IN RESEARCH AND MEDICINE

BY DAVID M. ENGMAN

There are many different careers for physician-scientists and many different ways academic physician-scientists combine research, patient care, teaching and administration. The percentage of time spent in each activity typically changes throughout a career. Most of us who are interested in science and medicine actually would find a number of different careers to be rewarding and enjoyable. With this in mind, it might be useful to approach the question of which type of degree to pursue as follows:

For students who have always aspired to practice medicine but did not enjoy research in college, going to medical school makes the most sense. There are a number of opportunities to do research in medical school, and it is good to do so both to give research another chance and because research experience makes a person a better doctor.

Students who never have had an interest in medical practice but always have been curious about how things work (health) or do not work (disease) should pursue a Ph.D. If they want to conduct biomedical research and want some training in clinical medicine without devoting all the years required to become a practicing physician, there are Ph.D. programs that provide clinical education for their students (e.g., the Howard Hughes Medical Institute Med into Grad Programs, http://www.hhmi.org/grants/institutions/medintograd.html).

Students who are scientists at heart and who have a high, moderate or unknown interest in clinical practice are best suited for M.D./Ph.D. programs. These programs provide rich, integrated courses of training and protected time to develop research and clinical skills.

There are some rare individuals who have a seemingly innate understanding of how to do research successfully and typically have significant research experience and accomplishment. For them, an M.D. program with additional research in medical school and especially during a residency or fellowship might make sense.

Finally, there are the so-called late bloomers, people who train as physicians or as scientists and then discover that they are interested in the other career or a combined career. There are numerous pathways for late bloomers to pursue alternate or combined careers and a number of training programs and funding mechanisms for doing so. As with all major life decisions, it is advisable to discuss the options with as many people as possible who are actively engaged in the different possible careers.

David M. Engman (d-engman@northwestern.edu) was director of the Northwestern University Medical Scientist Training Program from 1995 – 2011 and is a pathologist-scientist combining clinical diagnostic molecular biology and basic and translational research in tropical parasitic diseases.

A blog, a CV and a domain name

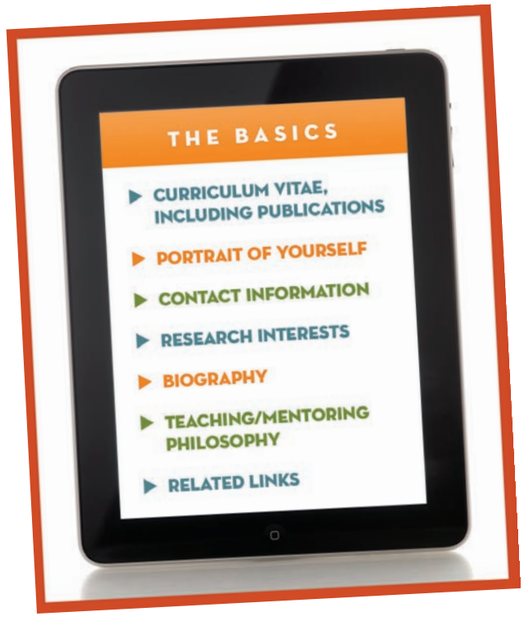
All you need to impress your next employer?

BY SAMUEL FURSE

You probably have been told that in the increasingly competitive world of research science, selling yourself effectively is what makes the difference between being offered a job and not. An underused medium for putting yourself out there in a way that can be planned and under your control is the personal blog site.

The term "blog site" in this context means a website that includes factual blogging by the site owner, his or her professional biography, and related information. Such sites are independent and not institution-based.

For aspiring researchers, there are many advantages to having such a site. It is a good way for people to find you online without having to make too much effort; a Google search of your name will do, even if you have little Google juice to start with. A professional and memorable domain name is also a good way to set the tone of the site. The format www.[forename][surname].com can provide an infinitely more suitable alternative to other online presences, such as Twitter or Facebook, which may not be appropriate for professional purposes. You also can present an online curriculum vitae that puts you in the sort of light in which you want potential employers to see you.



A personal blog site is also a way of providing continuity from the end of postgraduate training until a long-term job comes along. During the postdoctoral stage, your professional e-mail address might change about every two years. A site of your own gives you a permanent address that is useful, professional-sounding and linked to a site that reflects well on you. This shows that you are serious and capable.

The blog provides an opportunity for you to stick up for otherwise neglected areas of research (lipids, in my case) or just something you want to showcase. The blog also prevents your website from being a webpage with just your basic details on it — a pale imitation of LinkedIn.

As it is your blog site, you can choose both the subject and the tone for your blogging. You may even like to use more than one — general audience, general scientific audience, specialist and so on. Whatever you choose, blogging can be a great way to establish a commitment to an area of research, start intellectual debate or just chew through the literature.

With this scope for choice and showcasing, there does come responsibility. It is not possible to predict or control quite who will see your site. This means that it ought to be legally sound but also inoffensive to a wide audience (not just to your mother).

A basic but good example of how this can be important is how well the website text matches that in your job applications. If your research interests posted online do not concur with those in a cover letter, for example, that might raise questions about your commitment to the job for which you have applied.

To create a good impression to any reader, your website ought to be polished in appearance and content. This can be time-consuming and expensive,

especially if you do not possess the required Web design skills. I have no experience with designing websites, so when I was putting mine together I was ready to pay friends in ale and hard cash to ensure my site was properly constructed. Be warned, however, that website design is a continuous process: Browsers and hardware are updated constantly, and how and what you want to use the website for may change in a way that cannot be predicted during the initial design process.

A sober head is needed for the aesthetics of the site as well. A good rule is to ask whether a color-blind person with English as a second language could read it on his or her smartphone. If not, the site will probably not be that easy for everyone else. So, during the design process, it is worth experimenting with typesetting and layout to see what works.

There are some simple rules to avoid the bigger pitfalls. My No. 1 rule is to avoid typefaces that have characters that are similar, as they can be confusing for getting across scientific notation or data. For example, in the font Arial, uppercase "I," lower-case "l" and the number "1" can look very similar, especially to a reader who is not yet enthralled by what you have to say or who is reading it on a small screen with poor resolution. Equally important, complicated typefaces like Edwardian script or similar can be a real and instant turn-off. It is worth making the effort to have a recognizable site, but remember to keep it simple and readable.

The notion of carefully checking to avoid inconsistencies between your site and job application documents is worth applying to the text as well. I employ a proofreader for virtually all the text on my site to ensure that it is typo-free. Proofreaders cost money, as do most of the other aspects of the site if you are to do them properly.

One last point is that you have to ensure you are able to commit to the project for the long term. If the site disappears because your host has taken it down, it will be almost as though it never existed. Equally, if the site becomes out of date, it probably will be noticeable and might not reflect as well on you.

Despite the complexities, I do recommend this mode of self-presentation. It is a flexible and effective way to market yourself – so much so that the cost and the need for careful thought in the design are clearly outweighed by the value the site brings. I learned much of this through experience, and I have no doubt there is more to learn. However, that in itself is something I regard as an added, if unintended, consequence of a personal blog site. Good luck!

Samuel Furse (S.R.Furse@uu.nl) is a postdoctoral researcher in chemical biology at the University of Utrecht. Visit his blog site at www.samuelfurse.com/lipids and follow him on Twitter at www.twitter.com/samuelfurse.

Editor's Note
CRAFTING AN ONLINE PRESENCE

Throughout the 2000s, I taught a course called Print and Digital Media Writing to communications students at the University of Houston. During my first five or so years of teaching, at which time I also worked full time at the Houston Chronicle news desk, I focused almost exclusively on teaching news and feature writing.

But by 2007, I'd witnessed round after round of layoffs at work, and several of my former students who were print-journalism hopefuls had failed to snag jobs at newspapers – not even at low-paying ones with very small circulations in the middle of nowhere. The newspaper industry was downsizing, and there simply weren't enough gigs (or decent-paying ones) out there anymore.

In mid-2007, I left the newspaper industry (thankfully by choice) to do science communication at the university full time – and I completely changed the way I taught my Print and Digital Media Writing class. Sure, I still taught students about news value, quotes, balance and fairness, and storytelling, but I also taught them how to sell themselves so that they could compete in the job market of the day.

They learned how to establish a presence on Twitter, then still in its infancy, and how to use it professionally. They learned how to design and write résumés that showed how their education and training could benefit employers in multiple fields. I encouraged them to start their own blogs and to pay careful attention to how thought leaders and influencers conduct themselves online. I stressed the difference between a private persona and a public persona.

If you're still with me on this trip down memory lane, this is what I'm getting at: Today, even though I'm no longer at the head of a classroom, I still teach communication. As editor of ASBMB Today, I coach writers, almost all of them scientists, at different professional stages, and I still offer the same advice when it comes to showcasing their skills and work samples and engaging in online discourse to advance their careers.

Creating an online presence — be it a blog, a Twitter account, a portfolio of your work or a simple re-creation of your curriculum vitae — is pretty important today, regardless of your field. I'm convinced that scientists can benefit from creating and maintaining online personas. But you don't have to take my word for it.

Encouraged by peers and altmetrics to keep going

Adam Byron, a postdoctoral research fellow at the University of Edinburgh, has kept up a personal site for several years. In the early days, it contained the same information as his CV. Today, he says, it's "a means to engage the wider community and communicate thoughts about my science and my career."

He continues: "I've found it a great way to promote my work, most notably in combination with Twitter, which I use extensively."

Byron, who displays his figures when they're published on journal covers and posts press releases about his group's work on his blog, wasn't sure at first how the online endeavor might go over. His friends and colleagues encouraged him, though, so he just kept at it.

"(M)ore recently, with the introduction of alternative metrics, this has really begun to change. For example, I can now monitor how often my publications – which I promote through my website, Twitter, LinkedIn, Mendeley and others – have been cited or retweeted (using ImpactStory.org)," he says. "This is fantastic because it reveals the impact my research is having both on scholars and on the wider public. It is clear that without this promotion through my blog, my work would be less widely read."

ImpactStory.org catalogues how often your work — papers, datasets, slides, etc. — is cited, bookmarked, downloaded and tweeted.

Byron says he feels certain his online presence is building, to at least some degree, name recognition; he hopes that will work in his favor as he moves closer to running his own lab one day.

Taking the lead as a PI and building your (or your lab's) brand

"I would definitely recommend every scientist have their own independent online presence, no matter what the career stage," says Dave Bridges, who recently became a principal investigator at the University of Tennessee Health Science Center.

In fact, Bridges is such a believer in putting forth an online persona that he aims to give each member of his research group a page on the lab website. "I think it's important for everyone to be both allowed and empowered to have their own voice both within a group and outside of it," he says. "I would even go so far as to think of a research group as a collaboration of – occasionally dissenting – voices, rather than as a single voice."

Bridges envisions giving his trainees spaces where they can comment on recent additions to the scientific literature and communicate the work they've done: "I like the idea of providing this forum to them on a lab website, because I can enforce that and centralize what our group is up to, but I think it would be good for everyone to also be able to have their own separate independent online presence."

Samuel Furse, who has written for us in this issue about the benefits, pitfalls and workload of creating a website with a blog component, points out that having an online space provides "continuity from the end of postgraduate training until a long-term job is arrived at."

Furse, today a postdoctoral researcher at the University of Utrecht, notes that his professional email address has changed several times as he has moved to different institutions, but his email address associated with his personal website has remained the same.

Furse uses his site as a space where he can "stick up for otherwise neglected areas of research," which in his case is lipids.

This tactic is in line with advice offered in a Forbes column titled "5 Reasons Why Your Online Presence Will Replace Your Resume in 10 years." In it, writer Dan Schawbel insists, "Your online presence communicates, or should communicate, what you're truly and genuinely passionate about."

Your own personal newsroom

Having worked as a public information officer on the science beat at the University of Houston, I have seen the Internet empower institutional communications offices to distribute research findings widely without being at the mercy of the media. Online newsrooms and social media have given PIOs greater control of their messaging than ever before.

What I find even more interesting, meanwhile, is how individual investigators are using their online personas to spread their messages entirely on their own.

One of the most common complaints among investigators is that their work, when it is communicated by the media, is sensationalized or misinterpreted. I am optimistic those instances will become fewer and farther between as an increasing number of researchers take it upon themselves to communicate the facts and the implications of their work.

Everyone I talked to emphasized that the economic and technological barriers of maintaining an online presence are minimal, thanks in large part to the ever-growing number of free blogging platforms that do most of the heavy lifting. But website maintenance and blogging do require time, which is at a premium for investigators at all stages.

"What used to be seen as shameless self-promotion is now an essential component of any scientist's professional skill set," says ASBMB Public Outreach Coordinator Geoff Hunt. "If you aren't fluent in online communication, then you're behind the times."

Angela Hopp (ahopp@asbmb.org) is editor of ASBMB Today.

HOW OTHER SCIENTISTS ARE DOING IT

Before you begin forging an online presence, it's best to study how others are doing it. Here's a sampling of scientists (at and away from the bench) who use their real names.

Jeremy Berg, ASBMB president and University of Pittsburgh School of Medicine
Twitter: @jeremymberg

Dave Bridges, assistant professor at the University of Tennessee Health Science Center
Twitter: @dave_bridges

Bethany Brookshire, scientist-turned-writer
Twitter: @scicurious
Blogs: http://blogs.scientificamerican.com/scicurious-brain/ and http://www.slate.com/authors.bethany_brookshire.html

Adam Byron, postdoc at University of Edinburgh
Twitter: @adambyronnews for news updates and @adambyron for personal tweets. Blog: http://adambyron.com

Steve Caplan, associate professor at the University of Nebraska Medical Center and author
Twitter: @caplansteve
Website: http://www.stevecaplan.net/

Clay Clark, professor at North Carolina State University
Twitter: @biochemprof
Blog: http://blogs.biochem.ncsu.edu/

Glen Ernst, research scientist at the Lieber Institute for Brain Development
Twitter: @geernst
Blog: http://cenblog.org/just-another-electron-pusher/

Samuel Furse, postdoc at University of Utrecht
Twitter: @SamuelFurse
Blog: http://www.samuelfurse.com/lipids

Terri Kinzy, professor at Rutgers University
Twitter: @kinzytg

Elizabeth Petro, graduate student at Johns Hopkins University School of Medicine
Twitter: @ElizabethJPetro
Blog: http://solargecko.blogspot.com/

Amanda Lewis, assistant professor at Washington University at St. Louis School of Medicine
Twitter: @Lewis_Lab

Eric Scerri, University of California, Los Angeles
Twitter: @ericscerri
Website: http://ericscerri.com/

Mark Stewart, graduate student at University of Alabama at Birmingham
Twitter: @MD_Stewart

Bill Sullivan, associate professor at the Indiana University School of Medicine
Twitter: @wjsullivan
Lab homepage: http://www.sullivanlab.com/

How to find the right lab rotation

BY K.D. SHIVES

Some of you reading this will be starting graduate school this coming fall. Congratulations! You are just beginning what will be one of the most difficult and rewarding processes of your life. Those of you going into Ph.D. programs likely will do rotations in various labs during your first year before settling into the lab where you will do your thesis research. Choosing this laboratory is extremely important, as you will end up spending more time with these people than your family, and establishing good working conditions is critical to finishing your dissertation in a timely fashion.

Here is some advice that I wish I had gotten before embarking on the laboratory rotation selection process that will help with yours:

Find a rotation lab before the semester starts.

It is important to have a first rotation arranged well before the semester begins. Depending on the size of your institution and area of interest, it may be difficult to get spots with popular labs unless you arrange it over the summer. Otherwise you may find yourself in a position where you have to take a rotation in a lab that is not appropriate for you.

Find a lab with funding.

The funding situation in academia under the current economic climate is less than ideal. Many labs are struggling to maintain consistent funding as budgets remain static or are outright decreased. This directly affects how many students an investigator can take on. Try to find a group with a good funding history and current funding if at all possible. (See sidebar.)

Talk to lab members other than the principal investigator.

You will be spending most of your time with the day-to-day members and not the PI. Ask the research assistants, other graduate students and postdocs what the lab is like and try to get their input as well. Ask about the lab-management style: Is the PI a micromanager or very hands-off? What conditions do you work well in? You cannot discount how important it is to work well with your lab mates. While you may not become the best of friends, a relationship built on mutual respect will get you through graduate research without too much pain.

Read at least one recent publication from the group.

This is a good way to get familiar with recent work from the lab as well as the common techniques used by the group. This is also a good starting point for meeting with different investigators, as you will be familiar with their work and better able to discuss your rotation options and potential projects within the lab.

Read the grant.

Really. Just read it. It is a long and boring document, but it is the heart of the modern academic research group. What the lab wants and needs to accomplish for funding purposes is all right there in the grant and provides an invaluable guide to what you will be doing in a group. Reading the grant can clarify the aims of a lab and give a very clear picture if the research is in your area of interest and appropriate for your thesis research. It's also a valuable experience if you've never read a successful grant before and are unfamiliar with the format.

With these basic guidelines in mind, you should be able to find multiple labs that will be good fits for you personally and support your thesis research. Good luck, and happy hunting!

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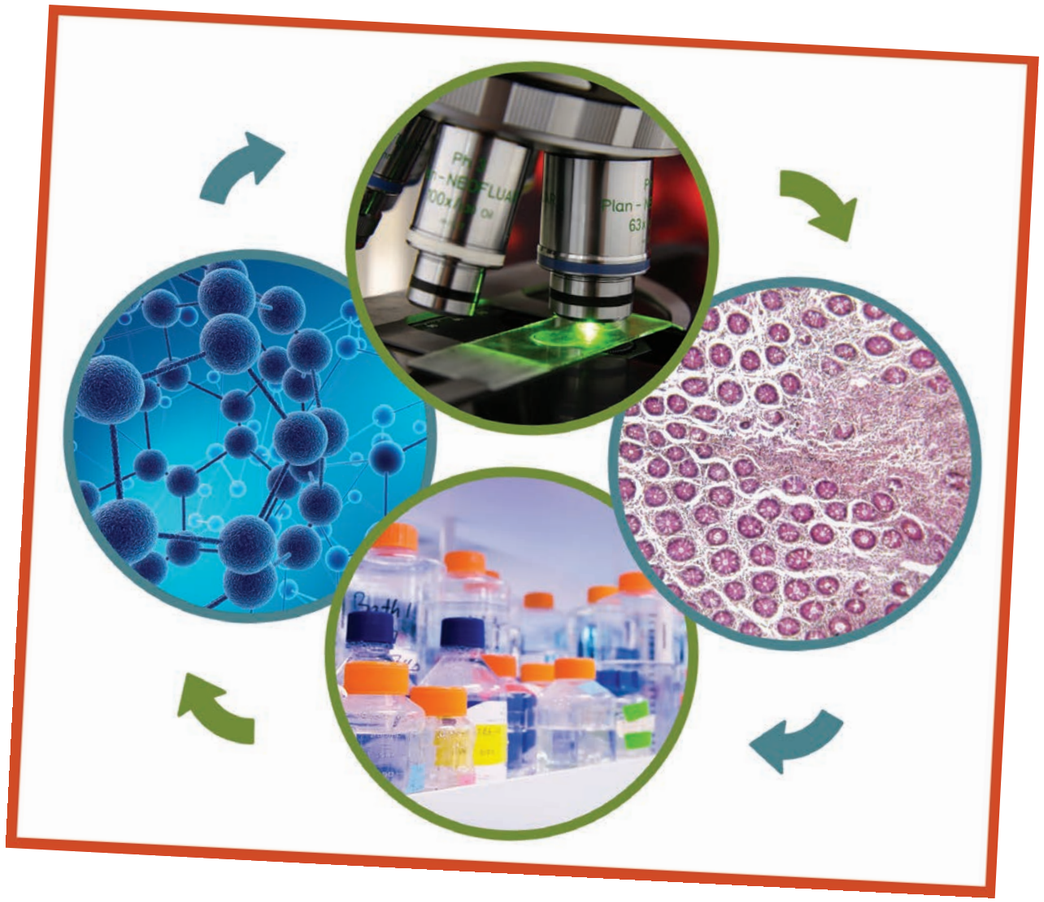
HOW TO BROACH THE FUNDING ISSUE WITH PROSPECTIVE PIS

Right now, federal funding for scientific research in the United States is at a disheartening all-time low and may remain that way for some time. For new grad-



uate students, this poses potentially significant issues, as joining a laboratory depends largely on it having the funding to support your thesis research. Put simply, less funding means fewer resources to support graduate students. You don't want to end up in a lab with a poor funding situation, as the principal investigator may have to shut down his or her research program if the funding situation does not improve.

So how do you politely ask a PI whose lab interests you whether he or she has enough funding to support you? This can be an awkward exchange, as it is usually frowned upon simply to say, in an e-mail to someone you have not yet met, "Hi. Do you have funding?"

To broach the subject tactfully, you can ask indirectly about the funding situation by burying it a few lines into your introductory e-mail. After a few lines of introducing yourself and explaining your interest in a lab rotation with this person, you can segue into the topic of funding. A simple statement, such as "If you have the space to take on a student, I would enjoy speaking with you further about rotation options," will let the PI know, without being uncomfortably direct, that you are aware of funding limitations in taking on new students.

However, if during the course of your rotations you find that you have a few labs with funding to choose from, don't be afraid to do a rotation in a lab that can't take you for financial reasons. You can use these as opportunities to learn new and interesting techniques that you can take with you through the rest of your graduate experience.

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Choosing the right journal for your work

Senior scientists offer advice for young investigators

BY LESLEY WASSEF

Getting published is one of the most important aspects of science. You and your lab members have done a lot of work and have produced the results. You have a good story to tell, and you want to publish it. But to which journal should you submit your manuscript? One with a high impact factor? One with editors you know? One you like to read? One in your field? One that is new?

Young investigators sometimes just let their principal investigators decide without understanding how they came to the decision. However, the time will come when those young investigators will be the PIs and will have to decide for themselves.

A young investigator myself, I took advantage of being part of the Rutgers Center for Lipid Research and asked a number of PIs for their advice on how to choose a journal.

Do your homework

George Carman, whose lab investigates phospholipid metabolism and signaling in yeast, made it clear that the decision is "based on the research you want to publish and the scope of research published by the journals." He insisted that "you must read the scope and instructions to authors for all the journals you are considering."

He offered this example: "You wouldn't send a vitamin A paper to the Journal of Alligator Studies, unless, of course, your work on vitamin A impacts alligator physiology. All kidding aside, if your work deals with vitamin A metabolism, you might consider a journal with a broad scope dealing with biochemistry, metabolism, physiology or nutrition."

In addition, he said, consider whether your work has mechanistic data or describes an effect of something.

Judith Storch, who investigates lipid traffic in cells with particular emphasis on long-chain fatty acids, monoacylglycerols and cholesterol, added that "for your work to be seen, you want it published in the journal that the major players in your field would be reading."

So the journals under consideration need to be of good quality, but does a high impact factor verify the quality of a journal?

Storch said she has seen how things have changed over time. "With keyword searching, you would think that where you publish should have become less important. However, it has become more important to some people because of the impact-factor craze. But what should be important is what journal has the right information or the best science."

Constructive criticism

Many people are afraid of reviewers' critiques. However, I was encouraged when Storch suggested submitting to journals where you will "get the best quality review possible." This provides you with "great questions and suggestions from reviewers" that you may not have thought of. This, in turn, will assist you in amending the paper so that it is more concise and could provide input for the following paper or study.

> **"Don't sell your work short. Ask yourself, 'What is the crux of my article? And where are similar articles being published?'"**
> – Sara Campbell

Sara Campbell, an assistant professor who investigates exercise, obesity and gut, said it's OK to ask for recommendations from your peers and even editors of other journals. Editors know what is needed for publication and will provide useful advice that you may not have considered before, she explained.

Furthermore, Campbell says, "Don't sell your work short. Ask yourself, 'What is the crux of my article? And where are similar articles being published?'" she said. This is important, because you want your work to be seen by people in your field. But "don't be afraid to branch out to a journal you have not tried." Your work

may have something novel that other journals might find interesting and relevant to their scope, she said.

Takeaways

So where should I publish my next manuscript? There is no strict protocol to follow. However, I do know that in my area of study a majority of manuscripts are published in certain journals. Therefore, I will make a list of journals in my field and perhaps ones that cover a broad range of topics.

I will make sure I understand the scope of the journal and decide whether my manuscript fits within that scope. In addition, I will be sure to study the instructions for authors.

I don't want to waste my time and submit to a journal that does not find my work relevant. Although it would be nice for my manuscript to get accepted during the first round (we all wish this), I will read the reviewers' comments and use that information to fill in the gaps in the manuscript to make it more complete and appropriate for the journal's audience.

Then, if my first-choice journal does not accept it, I'll reassess the crux of my story, revisit the candidate journals' scopes and try to find a better match.

Lesley Wassef (lesleywassef@yahoo.com) is a research associate in the Food Science and Rutgers Center for Lipid Research at Rutgers University.

ON A RELATED NOTE

Evaluating impact:

• The American Society for Biochemistry and Molecular Biology is one of the many organizations that have signed on to the San Francisco Declaration on Research Assessment, which, broadly put, urges institutional administrators making hiring, promotion and tenure decisions to consider a broad spectrum of indicators of researchers' contributions to the scientific enterprise. For more information about the declaration, visit http://am.ascb.org/dora/.

Other viewpoints:

• In 2011, then-ASBMB President Suzanne Pfeffer wrote an editorial in ASBMB Today titled "Impact factors – what the H?" Link: bit.ly/gzCaXN

• In 2007, Vincent C. Hascall, Johan Bollen and Richard W. Hanson wrote an editorial in ASBMB Today titled "Impact factor rankled." Link: http://bit.ly/eP5TAV

The brains behind Coursera's neuroscience offering

BY ANGELA HOPP

Coursera, one of the outfits offering massive online open courses, has provided almost four dozen life sciences classes since its launch in April 2012. Henry Lester, professor of biology at the California Institute of Technology, earlier this year wrapped up a Coursera class of his own design. At the start of Lester's "Drugs and the Brain" in late 2012, about 60,000 students were enrolled. In the end, about 4,400 students received certificates of accomplishment, denoting satisfactory completion of the course requirements. ASBMB Today's editor, Angela Hopp, completed the course and later talked to Lester about his motivations for teaching it, the challenges he encountered along the way and the advice he'd give those tossing around the idea of one day teaching a MOOC. His responses have been edited for length, style and clarity.

Q: Tell us about the origins of your "Drugs and the Brain" course.

In the late '90s, the Caltech faculty decided that all Caltech grads need to have taken a course in biology – a pretty easy decision. The burden fell to those who could actually teach a required course in biology for nonbiology majors. Several tried teaching Biology 1, with lots of objections from the chemistry, physics and math undergraduates who felt that biology was simply memorization-rich and could not be derived from first principles.

Around the year 2000, I was serving on the National Advisory Mental Health Council. I offered to take over Biology 1, transforming it into a course that would convince Caltech undergraduates in chemistry, physics, engineering and mathematics to become neuroscientists so that they could find solutions for neural diseases. Many of us think that these are a major problem of the 21st century. So I conceived of a course in the neuroscience of disease.

At dinner, I told my family about this plan. My children, who were high-school students at the time, screwed up their noses and said, "Dad, this won't work. We are late-stage teenagers. So are Caltech freshmen. We all think that we're immortal. We have no interest in disease. Come up with a different plan." I went to my room and sulked. At dinner the next night, I said, "I have a different plan. I'm going to teach a course called 'Drugs and the Brain.'" My wife and children each put two thumbs up.

So I taught "Drugs and the Brain" to Caltech freshmen for seven years. Beginning in 2008, I modified this course to become a general "Introduction to Neuroscience" course for biology majors, taught with Ralph Adolphs. Ralph and I allow video recordings of our lectures for the benefit of the students. When Caltech made an agreement with Coursera, the vice provost for instruction asked whether I would take the trouble to adapt those videos for Coursera. As usual in people's lives, you have no idea how much work is involved.

Q: How much prep time was required for the course?

Beginning in June of 2012, I modified the material for the online course. Each of the 52 10-minute minilectures required six to eight hours. It's not actually a Caltech course yet, although it overlaps heavily with "Introduction to Neuroscience." Some of my introductory neuroscience course students took the online course for extra credit.

Q: It looks like more than half of the "Introduction to Neuroscience" class at Caltech participated in the "Drugs and the Brain" class on Coursera to earn that extra credit. What kind of feedback did you get from those students?

The feedback was very positive and advised us to structure the course so that it would be a full Caltech course, independent of our "Introduction to Neuroscience" course. I intend to expand "Drugs and the

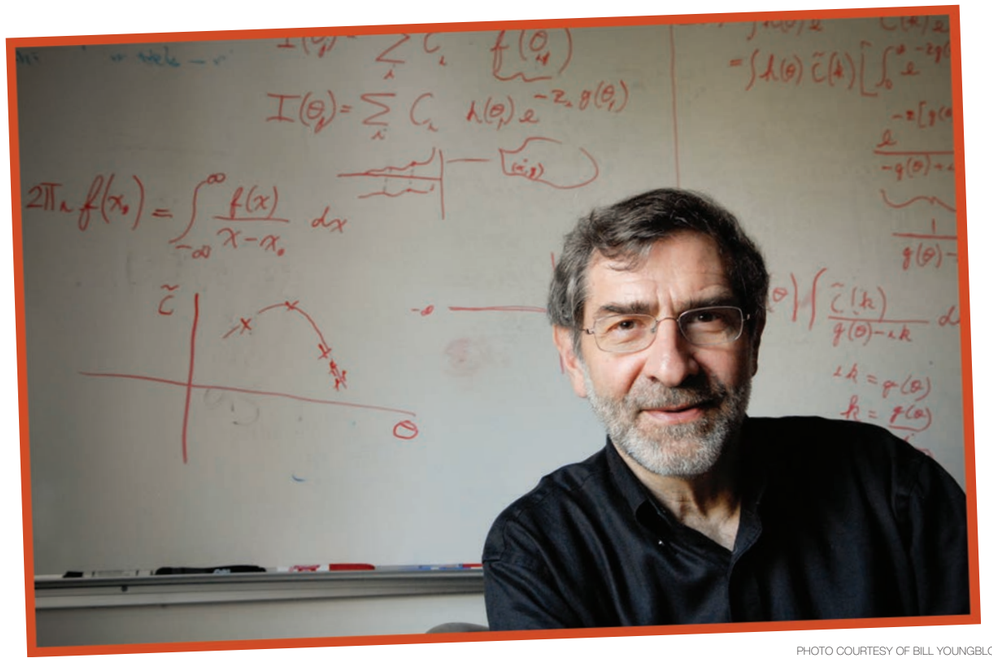

PHOTO COURTESY OF BILL YOUNGBLOOD

Brain" and make it into a simultaneous online/Caltech course.

Q: How did you determine when you should weigh in on discussions being held in the forums?

I set up a special forum for feedback on my lectures. That forum was informally known as "Mistakes in Henry Lester's Lectures." I carefully monitored that forum. I learned that there was at least one person more expert than myself on every topic, with the possible exception of my most recent paper on nicotinic receptor biophysics. (Editor's note: Lester also weighed in on other forums but credits Ph.D. student Crystal Dilworth for skillfully doing the heavy lifting.)

Q: About one-fifth of the "Drugs and the Brain" students reported that they had friends or family members with a brain condition of some sort, and some indicated in the forums that they had them themselves. How did that influence your course?

I think this is wonderful, and I was glad to see that the students regulated themselves in the sense of discouraging and not asking for confidential medical information and advice. It was helpful to have some students who had personal experience and very helpful to have other students who had professional experience.

I was amused at one student who requested information on generalized anxiety disorder – and who repeated this question three times simultaneously in three different forums. Another student said, "You know, I'm having trouble concentrating on just the video window on my computer, and it's even worse on my phone. And could you please include material on (attention deficit hyperactivity disorder)?"

Q: Did you have experience with online-learning environments before you joined Coursera? How did you prepare?

No, so I had to learn production value and introductions and transitions from the wise counselors at Coursera and from our own digital media experts at Caltech.

Q: What were some of the most important points you took away from more than 2,000 comments that students contributed to the post-course survey?

For academic professionals, the quantum of professional achievement is the good paper published and the good career launched. I was not initially certain how either of those goals would fit into an online course. But I was gratified to see the amount of attention that a couple of dozen students paid to a field I'm trying to launch called "inside-out neuropharmacology." Pleasingly, a couple of dozen students mentioned in the feedback that they found that this was the most exciting and interesting part of the course. So, as for the professional impact of teaching a course, it really did work in this instance.

Other Caltech colleagues ask, "Well, should I write a textbook, or should I teach a MOOC?" The now-obvious answer is this: "Write the draft of your textbook. Teach a MOOC with it. You'll receive intense and complete feedback to improve the textbook."

Q: According to your post-class survey results, less than one-third of the students enrolled in "Drugs and the Brain" were based in the United States. Do you feel like that will influence how you teach it in the future?

There are going to be two fundamental issues … The first is language. I think that will solve itself with automatic translation programs and with study groups. The second is not as easy, and that is time zones. Three, four, five years from now – when the technology and communications and bandwidth are much better than at present – we're still going to have to figure out how to deal with people for whom it's the middle of the night. How can they communicate with people who are at their afternoon best here? I think that it does interfere with the quality of discussions and will eventually limit real-time video chats like Google Hangouts.

Q: Do you have any advice for those who might be thinking about putting on a Coursera course?

My modus operandi was "Keep it as rigorous as you like intellectually but as simple as possible logistically."

Another way to think about a MOOC distinguishes research on teaching from teaching of research. Research on teaching studies what works best for imparting knowledge and what gets students excited. The folks at Coursera and other places have a vast amount of information on that topic, and I have been really interested in what can be learned.

The question of how you teach a person to do research is also complex, and some ASBMB members are very interested! That's going to involve writing and interactions with the course staff in ways that we're only beginning to think about now.

Angela Hopp (ahopp@asbmb.org) is editor of ASBMB Today. Follow her on Twitter at www.twitter.com/angelahopp.

"Drug and the Brain" overview

Week 1. Introductory concepts. Drugs, drug receptors, neuroscience. Resting potentials. Equivalent circuits.

Week 2. Drugs open and block ion channels. Dose-response relations. Desensitization. Epilepsy drugs. Drugs activate and block G-protein pathways.

Week 3. Drugs block neurotransmitter transporters. Recreational drugs. Nicotine addiction.

Week 4. Drugs for neurodegenerative diseases.

Week 5. Drugs for psychiatric diseases. Developing new drugs.

By the numbers

Below are some findings from the post-course survey, which was completed by 4,353 students.

Top 10 student locations

1. U.S. (1,358)
2. Spain (256)
3. Brazil (221)
4. U.K. (210)
5. India (165)
6. Canada (160)
7. Russia (126)
8. Australia (122)
9. Portugal (119)
10. Germany (110)

Students with degrees and professional certifications

- 44% reported having undergraduate degrees in the sciences or humanities
- 26% reported having master's degrees
- 10% reported having Ph.D.s
- 7% reported having medical degrees
- 75% reported having professional certifications in fields other than the health sciences

AARP's annual ranking of workplaces for employees over 50

Health systems and research institutions claim top five spots

BY ANGELA HOPP

Multiple medical- and research-related institutions landed on AARP's list of best workplaces for employees age 50 and older this year. Here's a snapshot of the top five, all of which have biomedical ties.

National Institutes of Health (Bethesda, Md.)

Listed at the No. 1 slot in the AARP Best Employers for Workers Over 50 was the National Institutes of Health, which has been recognized four times now by the annual program. AARP and its co-sponsor, the Society for Human Resource management, noted that 47 percent of NIH employees are age 50 or older. The organization emphasized the NIH's flexible work schedules, paid time off for caregiving and fitness programs, including one for workers 50 and older.

Scripps Health (San Diego)

The nonprofit Scripps Health, which includes four hospitals and 19 outpatient facilities, came in at No. 2. AARP pointed to its staged retirement programs for workers 55 and older and its use of recruiters and employment websites specifically aimed at older workers and retirees. Employees over 50 represent 36 percent of the Scripps workforce.

Atlantic Health System (Morristown, N.J.)

Retirees of the Atlantic Health System, ranked at No. 3 by AARP, can work up to 999 hours each year and still collect their retirement benefits. They also get discounted meals at AHS hospital cafeterias. Like Scripps, AHS uses employee-placement agencies and websites that focus on older workers. Thirty-eight percent of the system's workforce is 50 or older.

The University of Texas MD Anderson Cancer Center (Houston)

Part of the largest medical center in the world, the University of Texas MD Anderson Cancer Center was ranked at No. 4. MD Anderson covers 100 percent of full-time employees' medical premiums and covers 100 percent of retirees' medical and prescription premiums. Like the three institutions above, it dedicates an administrator to retiree relations.

Mercy Health System (Janesville, Wis.)

Coming in at No. 5, Mercy Health System offers a program called Senior Connection that makes admission to MHS facilities smoother and offers a variety of other benefits, including Medicare and insurance claims assistance. The Work-to-Retire program gives employees between 50 and 54 (with five years of service) more flexible schedule options, and those 55 and up (with 15 years of service) work seasonally while keeping their benefits. Like all of the institutions above, MHS also offers many types of free health screenings and programs.

Angela Hopp (ahopp@asbmb.org) is editor of ASBMB Today. Follow her on Twitter at www.twitter.com/angelahopp.

Rap Genius

Science between the lines

BY JEREMY DEAN

"Now here we go dropping science, dropping it all over
Like bumping around the town like when you're driving a Range Rover
Expanding the horizon and expanding the parameters
Expanding the rhymes of sucka MC amateurs."

– Beastie Boys,
"The Sounds of Science"

I grew up a literary child in a scientific household. Both my parents, Ann and Jurrien Dean, worked at the National Institutes of Health. Dinner-table conversations consisted of foreign-sounding words and phrases like "chromatin," "hematopoiesis," "globin gene switching," and something that seemed more like it came from the realm of science fiction than actual science: the zona pellucida! (It's basically a force field, right?) As the after-dinner discussion turned to the lab, I turned from the table to the laboratory of great literature and most often to works of magical realism created by Toni Morrison and Gabriel García Márquez.

My intellectual isolation as a humanist has not gotten easier with age, especially after earning a doctorate in English – now I, too, am incomprehensible to most. All my younger siblings have entered the sciences for their professional careers: I have a brother in an M.D./Ph.D. program in neuroscience at Vanderbilt Univesity, a sister attending Brown University's medical school this fall and a brother majoring in chemistry at Harvard University. And I have married a behavioral biologist, Karin Akre, now a postdoc at Duke University.

Recently, though, my career has allowed me to collaborate with my growing family in interesting and unexpected ways. Since receiving my degree last fall, I have been exploring an alternate academic path working for a startup called Rap Genius as its "education czar." Rap Genius lets users read and write line-by-line annotations not only for their favorite rap songs but also for great works of literature and historical documents. Lately, we have been making forays into the sciences. Classic scientific works like Darwin's "On the Origin of Species" have been added to the site's interactive archive (1), as have more recent NIH reports (2), but we also are working with less accessible texts in an effort to use the Genius platform to engage students and the broader public with scientific research.

When I started working for Rap Genius this spring, my wife suggested that she use the platform in her Principles of Animal Behavior course at the University of Texas at Austin. The idea was that the difficulty of reading a complex academic article for the first time in an upper-division college course could be eased by having students read that article together as a class, share the responsibility of research and discuss the text as they read. We purposefully chose an article from the journal PLOS ONE for this proof of concept because we knew the content to be in the public domain. Not only did more than 80 students in Karin's course collaboratively annotate Varenka Lorenzi, Ryan L. Earley and Matthew S. Grober's "Differential responses of brain, gonad and muscle steroid levels to changes in social status and sex in a sequential and bidirectional hermaphroditic fish" on Rap Genius, bringing the text to life with their own research, but without any promotion or prompting, random visitors to the site clearly read through the article as well. One commented, "I legit spent 2 hours reading this. Rap genius. what are you doing to me?" (3)

But the ultimate Science Genius crossover occurred a few weeks ago when my father forwarded me the e-newsletter for the American Society for Biochemistry and Molecular Biology that mentioned the society's submission to a PBS science-rap contest. (Congratulations on an honorable mention, by the way.) The contest was prompted by a program that Rap Genius co-organized with Christopher Emdin of Columbia Teachers College in the New York City Public Schools in which students write raps based on their science curricula (4). The ASBMB's rap was about the knockout mouse (5) and is now fully annotated by the society on Rap Genius, as are the songs of other finalists in the competition (6).

We invited the producer of the ASBMB's video, outreach coordinator Geoff Hunt, up to New York recently to be a judge in the Science Genius program's Final B.A.T.T.L.E.S. alongside Wu-Tang's GZA and Jennifer Bogo, senior science editor at Popular Science, among other dignitaries from the fields of hip-hop and science. The winner of that contest was Jalib, also known as Jabari Johnson, of Urban Assembly School, who rapped about scientific and life lessons learned from physics class (7). The whole evening, though, was a testament to how popular culture and scientific knowledge can come together in powerful ways, engaging young people with academic content and engaging the scientific community with a broader public.

Our plan at Rap Genius is to launch a variety of annotation channels for different intellectual communities so that one day there will be a separate site called Science Genius, which will be an interactive archive for everything from raps about science to laboratory journal club articles. I especially believe that social reading platforms like Genius will offer scholars the opportunity to expand their audiences beyond their immediate colleagues.

Imagine scholarly articles with layers of annotation that guide the lay person through the research findings. Or abstracts that are broken down by a scholar to help explicate his or her work. One example of an annotated abstract ("Forecasting the impact of storm waves and sea level rise on Midway Atoll and Laysan Island within the Papahānaumokuākea Marine National Monument – a comparison of passive versus dynamic inundation models") is from the U.S. Geological Survey (8).

We no longer need to imagine rap songs about complicated scientific ideas; the ASBMB and the students in the Science Genius project have schooled us with the knowledge they dropped in rhyme.

Whether you are down with the mathematics of rhyming, the science of beats or the "k-nowledge" of rap music more broadly, we invite the scientific community to share and collaborate on knowledge making at Rap Genius.

Jeremy Dean (Jeremy@rapgenius.com) is chief of education at Rap Genius.

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ASBMB's Geoff Hunt, who recently produced a rap (that won an honorable mention from PBS) about the knockout mouse, went to New York to judge the Science Genius program's Final B.A.T.T.L.E.S. Hunt joined at the judges' table Wu-Tang's GZA, Popular Science's Jennifer Bogo and others involved in hip-hop and science. For photos from the event, see this article online at www.asbmb.org/asbmbtoday.

jbc THE JOURNAL OF BIOLOGICAL CHEMISTRY

A deeper look into cholesterol synthesis

BY SWATHI PARASURAMAN

The human body needs cholesterol to maintain membrane fluidity, and it acts as a precursor molecule for several important biochemical pathways. Its regulation requires strict control, as it can cause problems if it's produced in excess. In 1964, Konrad Bloch received a Nobel Prize for his work elucidating the mechanisms of cholesterol synthesis. His work eventually contributed to the discovery of statins, drugs used today to lower blood cholesterol levels.

The biosynthesis of cholesterol is a complex process with more than 20 steps. One of the first enzymes is 3-hydroxy-3-methylglutaryl-CoA reductase, also known as HMGCR, the main target of statins. As links between intermediates in cholesterol synthesis and various diseases are being discovered continually, more information about the regulatory role of the post-HMGCR pathway is needed.

In a recent minireview in the Journal of Biological Chemistry, Laura Sharpe and Andrew Brown of the University of New South Wales describe multiple ways various enzymes other than HMGCR are implicated in the modulation of cholesterol synthesis. One such enzyme is squalene monooxygenase, which, like HMGCR, can be destroyed by the proteasome when cholesterol levels are high.

The minireview also explains how pathway intermediates can have functions distinct from those of cholesterol. For example, intermediate 7-dehydrocholesterol usually is converted to cholesterol by the enzyme DHCR7 but is also a vitamin D precursor. To synthesize the enzymes necessary to make cholesterol, SREBPs, short for sterol regulatory element binding proteins, have special functions. Along with transcriptional cofactors, they activate gene expression in response to low sterol levels and, conversely, are suppressed when there is enough cholesterol around. Additionally, SREBPs control production of nicotinamide adenine dinucleotide phosphate, or NADPH, which is the reducing agent required to carry out the different steps in the pathway.

Lipid carrier proteins also can facilitate cholesterol synthesis. One example is SPF, or supernatant protein factor, which transfers substrate from an inactive to an active pool or from one enzyme site to another. Furthermore, translocation of several cholesterogenic enzymes from the endoplasmic reticulum to other cell compartments can occur under various conditions, thereby regulating levels and sites of intracellular cholesterol accumulation.

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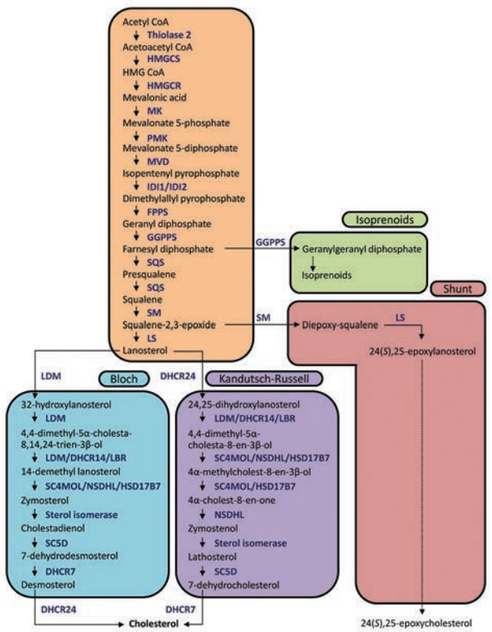
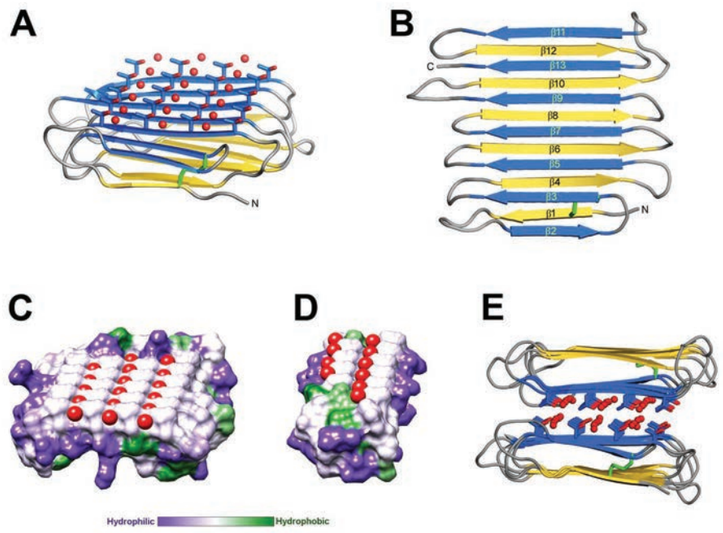


Cholesterol synthesis pathway. The mevalonate pathway leads to lanosterol, which can then be diverted into either the Bloch pathway, producing cholesterol via desmosterol, or the Kandutsch-Russell pathway, via 7-dehydrocholesterol. Two other branches also diverge from the mevalonate pathway. Isoprenoids are produced by geranylgeranyl-diphosphate synthase (GGPPS) acting twice to convert farnesyl diphosphate to geranylgeranyl diphosphate, and flux through the shunt pathway occurs when SM acts twice to convert squalene 2,3-epoxide into diepoxysqualene, eventually leading to the production of 24(S),25-epoxycholesterol. Intermediates and enzymes in this shunt pathway are not yet fully elucidated but are presumed to follow the Kandutsch-Russell pathway. *MK, mevalonate kinase; PMK, phosphomevalonate kinase; MVD, diphosphomevalonate decarboxylase; FPPS, farnesyl-pyrophosphate synthase; SQS, squalene synthase; LDM, lanosterol 14α-demethylase; SC5D, sterol C5-desaturase.*



Crystal structure of RiAFP. A, overall fold of RiAFP. β-strands are shown in blue and yellow. The threonine side chains and coordinated water molecules (red) on the IBS are shown in ball-and-stick representation. The disulfide bond is indicated in green. B, secondary structure diagram with sequentially numbered ice-binding β-strands in blue, hydrophilic β-strands in yellow. N and C represent the protein termini. C and D, flat ice-binding surface of RiAFP (C) and TmAFP (D), represented by a hydrophobic surface diagram produced in chimera, which relies on the Kyte-Doolittle scale to rank amino acid hydrophobicity. Water molecules coordinated by the threonine hydroxyls on the IBS are shown in red. E, RiAFP dimers in the crystallographic asymmetric unit, with the ice-binding surfaces packed face to face.

Potent antifreeze protein's structure determined

BY NATALIE OSAYANDE

Creatures that manage to survive extremely cold conditions do so by employing a number of clever behavioral and biological strategies. Some vertebrates, plants, fungi and bacteria produce antifreeze proteins, which bind to and prohibit the growth of intracellular ice crystals that otherwise would lead to the organisms' demise.

In a recent paper in The Journal of Biological Chemistry, researchers at Yale University and Queen's University reported the crystal structure of the most potent antifreeze protein known — RiAFP, found in a longhorned beetle. Though Rhagium inquisitor isn't exactly a pretty insect, it is pretty tough: It can survive temperatures as low as –25°C in Siberia by synthesizing RiAFP.

Using X-ray crystallography, the research team determined the RiAFP structure contains 1,914 non-hydrogen protein atoms, with no atoms heavier than sulfur by ab initio direct methods, revealing a β-solenoid structure with polypeptide chains that contain capping structures that reverse the handness (from left to right or vice versa) of the strands at the end terminus. These structures prevent end-to-end interactions that lower the solubility of RiAFP and lead to oligomerization and aggregation.

RiAFP is the first antifreeze protein isolated that can be produced in large amounts (up to 50 milligrams/liter of cell culture). The authors say that the "hyperactivity and efficient recombinant production" makes it a good candidate for future experiments that will explore the protein's freeze resistance, control of ice growth, and form and structure.

Antifreeze proteins of different, unrelated species have been explored for many years. They illustrate the concept of convergent evolution — when unrelated species develop similar traits to adapt to their environments. Knowing more about how antifreeze proteins work could improve our ability to engineer freeze-tolerant crops and raise more hardy fish. Some makers of consumer products have even dreamed up nature-inspired, if not necessarily cheap, goods like Crème de la Mer's Lip Balm ($50 at department stores), which is said to be infused with a marine antifreeze protein to protect your pout from even the harshest weather.

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James E. Darnell's 'Reflections'

A brief history of the discovery of RNA and its role in transcription – peppered with career advice

BY JOSEPH P. TIANO

James Darnell begins his Journal of Biological Chemistry "Reflections" article by saying, "graduate students these days have to swim in a sea virtually turgid with the daily avalanche of new information and may be momentarily too overwhelmed to listen to the aging. I firmly believe how we learned what we know can provide useful guidance for how and what a newcomer will learn." Considering his remarkable and groundbreaking discoveries in RNA processing and eukaryotic transcriptional regulation spanning 60 years of research, the "aging" Darnell's advice should be cherished.

When Darnell started medical school at Washington University School of Medicine in St. Louis, there were two local Major League Baseball teams. (The Browns left for Baltimore three years later in 1954.) It was during his second year at medical school, while studying streptococcal disease in Robert J. Glaser's laboratory, that Darnell realized he "loved doing the experiments" and had his first "career advancement event." He and technician Barbara Pesch discovered that in vivo penicillin treatment killed streptococci only in the exponential growth phase and not in the stationary phase. These results were published in the Journal of Clinical Investigation and earned Darnell an interview with Harry Eagle at the National Institutes of Health.

Darnell arrived at the NIH in 1956, shortly after Eagle had shifted his research interest to culturing animal cells in vitro. His culture medium, Eagle's minimal essential medium, is still used by millions of scientists worldwide. Since Eagle was at that point focused on cell metabolism, he suggested that Darnell take up a side project on poliovirus replication in mammalian cells in collaboration with Robert I. DeMars. It turned out that DeMars' Ph.D. adviser was also the adviser of James Watson (of double-helix fame), so Darnell met Watson, who invited him to give a talk at Harvard University. Darnell subsequently was offered a job as an assistant professor at the Massachusetts Institute of Technology by Salvador Luria (Watson and DeMars' adviser). A take-home message is to embrace side projects, because you never know where they may lead: In Darnell's case, such a project helped to shape the rest of his career.

Darnell arrived in Boston in 1961. Following the discovery of DNA's structure in 1953, the world of molecular biology was turning to RNA in an effort to understand how proteins are made. Darnell's background in virology (it was discovered in 1960 that viruses used short-lived RNA to replicate) was ideal for the aim of his first independent lab: exploring mRNA in animal cells grown in culture. While at MIT, he developed a new technique for purifying RNA along with making other observations suggesting that nonribosomal cytoplasmic RNA may be involved in protein synthesis.

In 1964, Darnell moved to Albert Einstein College of Medicine for full professorship and a generous 250-percent salary increase. (He notes that by this time he had a wife and three sons.) By this time it was hypothesized that heterogenous nuclear RNA was a precursor to mRNA, but the experiments to demonstrate this were encountering difficulties. At Einstein, Darnell discovered RNA processing of pre-tRNAs and demonstrated for the first time that a specific nuclear RNA could represent a possible specific mRNA precursor.

In 1967 Darnell took a position at Columbia University, and it was there that he discovered (simultaneously with two other labs) that mRNA contained a polyadenosine tail. The three groups all published their results together in the Proceedings of the National Academy of Sciences in 1971. Shortly afterward, Darnell made his final career move four short miles down the street to Rockefeller University in 1974.

Over the next 35-plus years at Rockefeller, Darnell never strayed from his original research question: How do mammalian cells make and control the making of different mRNAs? His work was instrumental in the collaborative discovery of splicing in the late 1970s and in identifying and cloning many transcriptional activators. Perhaps his greatest contribution during this time, with the help of Ernest Knight, was the discovery and cloning of the signal transducers and activators of transcription (STAT) proteins. And with George Stark, Andy Wilks and John Krowlewski, he described cytokine signaling via the JAK-STAT pathway. Darnell closes his "Reflections" with perhaps his best advice: Do not get too wrapped up in your own work, because "we are all needed and we are all in this together."

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Recent findings on presenilins and signal peptide peptidase

BY DINU-VALENTIN BĂLĂNESCU

GxGD proteases are a family of intramembranous enzymes capable of hydrolyzing the transmembrane domain of some integral membrane proteins. The GxGD family is one of the three families of intramembrane-cleaving proteases discovered so far (along with the rhomboid and site-2 protease) and includes the γ-secretase and the signal peptide peptidase.

Although only recently discovered, a number of functions in human pathology and in numerous other biological processes have been attributed to γ-secretase and SPP. Taisuke Tomita and Takeshi Iwatsubo of the University of Tokyo highlighted the latest findings on the structure and function of γ-secretase and SPP in a recent minireview in The Journal of Biological Chemistry.

γ-secretase is involved in cleaving the amyloid-β precursor protein, thus producing amyloid-β peptide, the main component of senile plaques in Alzheimer's disease patients' brains. The complete structure of mammalian γ-secretase is not yet known; however, Tomita and Iwatsubo note that biochemical analyses have revealed it to be a multisubunit protein complex. Its catalytic subunit is presenilin, an aspartyl protease.

In vitro and in vivo functional and chemical biology analyses have revealed that presenilin is a modulator and mandatory component of the γ-secretase–mediated cleavage of APP. Genetic studies have identified three other components required for γ-secretase activity: nicastrin, anterior pharynx defective 1 and presenilin enhancer 2.

By coexpression of presenilin with the other three components, the authors managed to reconstitute γ-secretase activity. Using the substituted cysteine accessibility method, Tomita and Iwatsubo refined of topological analyses, which suggested the catalytic aspartates are located at the center of the nine transmembrane domains of presenilin, by revealing the exact location of the enzyme's catalytic site. The minireview also describes in detail the formerly enigmatic mechanism of γ-secretase mediated cleavage.

SPP, an enzyme that cleaves remnant signal peptides in the membrane during the biogenesis of membrane proteins and signal peptides from major histocompatibility complex type I, also is involved in the maturation of proteins of the hepatitis C virus and GB virus B. Bioinformatics methods have revealed in fruit flies and mammals four SPP-like proteins, two of which are involved in immunological processes. By using γ-secretase inhibitors and modulators, it has been confirmed that SPP shares a similar GxGD active site and proteolytic activity with γ-secretase. Upon purification of the human SPP protein with the baculovirus/Sf9 cell system, single-particle analysis revealed further structural and functional details.

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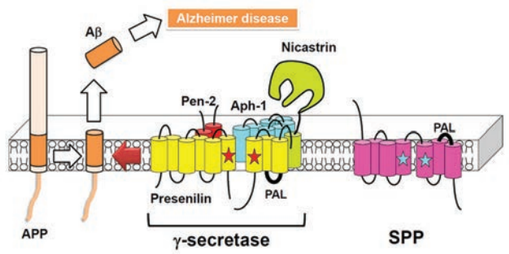

FIGURE 1. Schematic depiction of γ-secretase and SPP. Gamma-secretase executes the intramembrane proteolysis of several single membrane-spanning proteins, including APP. The core complex of gamma-secretase is composed of PS, Nct, Aph-1, and Pen-2. SPP forms a homotetramer in its enzymatically active state. The topologies of PS and SPP are completely different. However, both PS and SPP harbor conserved catalytic motifs (aspartates are shown by stars) and the PAL motif (bold lines).

THE JOURNAL OF LIPID RESEARCH

Thematic series on fat-soluble vitamins begins

BY MARY L. CHANG

Vitamins A, D, E and K are the four fat-soluble vitamins required to maintain good health in higher organisms. The July issue of the Journal of Lipid Research marks the beginning of a thematic series on these vitamins coordinated by editorial board member William S. Blaner of Columbia University. The special section in the July issue includes an introductory editorial by Blaner and four reviews from experts on vitamin A. Subsequent issues this year will explore vitamins D, E and K.

In developing countries, vitamin A deficiency remains a major public health concern, and much research is focused on identifying populations most at risk. Coordinated efforts in molecular research to develop vitamin-A-fortified plant sources could help eradicate this public health problem. Epidemiologic studies are being conducted to understand how dietary intake of the vitamin might be related to development or incidence of certain diseases. The four thematic reviews in July's JLR focus on vitamin A's molecular actions and its metabolism.

In one review, Abdulkerim Eroglu and Earl H. Harrison of Ohio State of University explore the research insights on carotenoid conversion to vitamin A, carotenoid metabolism to create apo-carotenoids, and the actions and metabolism of carotenoids in higher animals.

Columbia University's Sheila M. O'Byrne and William S. Blaner's contribution to the series examines how vitamin A is stored in the body as retinyl esters, how they evolved, and how mobilization of these stores is achieved through the actions of specific vitamin-A-binding proteins and enzymes.

Natalia Y. Kedishvili of University of Alabama at Birmingham reviews what is known of the formation of retinoic acid and how it is broken down and eliminated from cells and tissues.

In the fourth and final review, Ziad Al Tanoury, Aleksandr Piskunov and Cecile Rochette-Egly of France's Institut de Génétique et de Biologie Moléculaire et Cellulaire discuss what is known about the retinoic acid receptors, how retinoic acid can affect genomic expression and the nongenomic effects of vitamin A.

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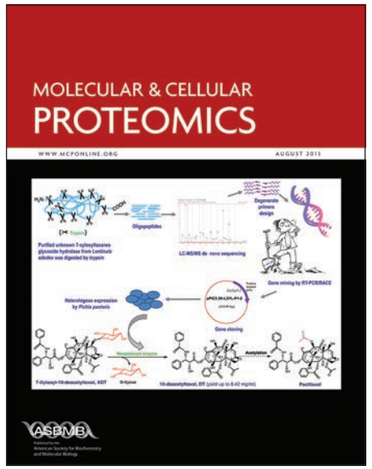
MCP **MOLECULAR & CELLULAR PROTEOMICS**

Protein quantification: by mass spectrometry or Western blotting?

BY RAJENDRANI MUKHOPADHYAY

In the past several years, a mass spectrometric method known as selected reaction monitoring or multiple reaction monitoring increasingly has proved to be adept at quantifying a targeted set of proteins in a complex sample. In a recent editorial in the journal Molecular & Cellular Proteomics, associate editor Ruedi Aebersold at the Swiss Federal Institute of Technology Zurich and co-editors Ralph A. Bradshaw and Alma Burlingame at the University of California, San Francisco, say that the time has come to let the protein-quantification data generated by SRM or MRM stand on their own and that they don't need to be supported by data from the protein-quantification workhorse used in most molecular biology and biochemistry laboratories, Western blotting.



In Western blotting, a method that was developed more than three decades ago, proteins from a sample are separated on a gel and transferred onto a membrane. The presence of a certain protein is then determined by highlighting the band that contains it using putatively specific antibodies. The density of the highlighted band reflects the relative abundance of the protein in the sample.

SRM also was developed decades ago for the quantification of small molecules in complex samples. More recently, the method has been adapted for use in targeted quantitative proteomics. Much like Western blotting, the method detects and measures the amounts of known proteins in complex samples. Peptides derived by proteolysis of a protein sample are ionized in an electrospray ion source; the peptide ions uniquely associated with the targeted protein or proteins are isolated and fragmented. The signal intensity of fragment ions uniquely associated with the targeted peptide then is recorded over time, indicating the abundance of the peptide in the sample.

In their editorial, Aebersold, Burlingame and Bradshaw explain, "Authors who submit papers containing quantitative protein data generated by MS are frequently asked by reviewers to validate some of the values by Western blotting. We believe with the advances that have occurred that this request is now outdated, causing the unnecessary use of scarce resources and not achieving the main intent: objective cross-validation of results."

The authors say they support the use of independent techniques to verify results, but in this case the quality of SRM data outstrips that of Western blotting. For example, the mass spectrometric method measures several peptides per quantified protein, thus generating several independent measurements, whereas in Western blotting only a single signal, the intensity of the detected band, is available.

However, the authors add that their argument against using Western blotting to validate protein-quantification data obtained by SRM "should not be construed as meaning the Western blots have no value and that the technique should be dropped from the arsenal of useful biological methods." Rather, they say, the notion of Western blotting as the gold standard "for quantifying proteins in complex samples has to be seriously questioned, now that SRM assays for proteins can be developed and used with comparative ease."

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Lessons learned

Notes on becoming an educator outside of academia

BY CARL PETERS

I am an applications scientist with BMG LABTECH. The role of applications scientist varies depending on the company. At BMG, I perform a primarily educational role. This suits me well and fulfills my long-standing desire to teach.

Academic background

I followed a fairly traditional path within academia. After receiving my degree in biology at Hastings College in Nebraska, I moved into a Ph.D. program at Northwestern University. I was a member of one of the first cohorts to enroll in the Integrated Graduate Program in Life Sciences at Northwestern University's Medical School campus in downtown Chicago. This program is now called the Driskill Graduate Program.

Because I was at a graduate-school campus, I did not have the required teaching load that many graduate students have. However, I believed at the time that teaching was going to be important for my future, so I volunteered to serve as a teaching assistant beyond what was required, initially assisting with a medical histology class and subsequently with a graduate-level cell signaling course.

This is the first lesson I learned: Don't be passive. You are responsible for your education. If you feel that there is an aspect your program lacks, don't just accept it. Be proactive and seek out opportunities that will fulfill your needs.

Learning to teach

Because I enjoyed teaching so much, it remained a priority during my first postdoc at the University of California, San Francisco.

UCSF had a joint program with San Francisco State University called the Postdoctoral Teaching Fellowship Program. Through this, I learned more about learning theory and the variety of teaching and learning styles.

When I moved back to Chicago for a second postdoc, I seized the opportunity to teach at Roosevelt University.

Finally, when the lab I was working in moved to Washington State University, I was able to capitalize on the opportunity to teach part time, which eventually turned into a full-time teaching position.

Whenever a new opportunity arose, I did not hesitate to offer to help. In this way, I was not only involved in teaching standard lecture and lab courses but also became involved in the burgeoning online opportunities at WSU. Again, this exemplifies the need to be proactive. The chair of my department said it well: "Get involved in as many projects as possible. Make yourself indispensable."

Finding the right fit

Throughout my time as a student, postdoc and teaching faculty member, I developed many great relationships with both faculty members and students. To this day, I am in contact with many talented people who are using their Ph.D.s in different ways.

Within industry, the variety of occupations these colleagues were performing was quite impressive and showed me that, if I wanted to, I could follow this path. So when I decided to move away from WSU for personal reasons, I cast the net wide and sought opportunities in both the academic and private sectors.

The ability to work from home on several different online teaching projects allowed me to apply for a wide variety of jobs, and I leaned on my network to get me in the door. With several near misses at job opportunities behind me, I was told about the job at BMG by two colleagues from my time at Northwestern.

This time the fit was right on both sides of the table, and I was happy to make a final relocation to North Carolina to pursue the opportunity. The job search experience was longer than I had hoped but showed me the importance of having a good network. Without it, you are making the process harder on yourself than it needs to be. It is vital to develop and foster your network; you never know if it will be the difference that

gets you that coveted interview so you can shine.

On the job

As I said before, I view my role as an application scientist as one in which I am continuing to serve as an educator. The main difference is that my audience is made up of consumers of a product that I am endorsing. Therefore, it is great for me that BMG LABTECH is such a well-respected company with a track record of excellence. It is easy to speak well of a company whose product performance speaks for itself.

One major part of my job is producing notes that describe how our microplate readers have been used to perform various assays. Many of these assays use commercially available technologies or kits. Therefore, it is important that I have a relationship with the various reagent companies. With these companies, we decide whether or not I will perform tests in my lab space at BMG or at the labs of the reagent companies. I then compile the data generated into short application notes that provide some background and describe the assay principle and setup. The final step of the process involves me presenting the data and discussing its significance to consumers.

Another way I generate application notes is by connecting with our customers. I keep an eye out for reports of novel approaches that have been performed using BMG microplate readers. These can be in the form of journal articles or presentations at scientific conferences. I then contact the authors and work with them to produce an application note. I also develop presentations for meetings, webinars and sales demonstrations.

So as you can see, I am truly using all the skills I developed during my time in academia. I am still very much connected to current literature, I still employ the skills I learned while working in the lab, and I write and create presentations based on data from the experiments I or other scientists within BMG or our collaborators have created.

I also am still learning, which is very important to me. I have a much better appreciation for how instrumentation can help the performance of an assay.

I am not where I, as a graduate student, predicted I would be, but I am very happy that I kept an open mind. Which leads me to the final lesson I have learned: Keep your options open. There are many different avenues to a career that will make you happy.

Carl Peters (carl.peters@bmglabtech.com) is an applications scientist at BMG LABTECH, a developer and manufacturer of microplate reader instrumentation.

Taking a holistic view

Using social network analysis to better understand student support structures and facilitate success in biomedical education and training

BY SUZANNE BARBOUR AND VICTORIA A. SHIVY

Many students lack confidence or feel anxious when they are first thrown into big science – with the attendant needs to navigate complex research protocols, fit in and function with teams of seasoned students and postdocs, and locate and establish working relationships with new research mentors.

For students unacquainted with this traditional academic-training model, these tasks may seem burdensome on top of the expectations of earning good grades and completing demanding coursework.

The pressure to fit in can be especially challenging for first-generation and underrepresented minority students, who may have limited exposure to the social norms and expectations of a laboratory or other research environment. Additionally, first-generation and URM students may arrive at universities with different sets of familial and cultural experiences.

For more than a generation, formal, federally supported programs have been in place to identify and recruit underrepresented students to biomedical-research training programs. Students in these programs typically are offered support addressing their economic needs and educational preparation.

However, interventions designed to help these students have shown mixed success, and we argue that this is largely because efforts to date have failed to take a holistic view, including both the academic and social needs of students and trainees.

The standard model

Considerable research and intervention-related attention has focused on the dyadic mentor-protégé relationship. That body of work assumed students seek and obtain all necessary support from individuals who serve in defined mentoring roles.

Solid mentoring relationships certainly can facilitate training experiences in the biomedical sciences, offering students access to tangible, informational and emotional support. Mentored research experiences have been shown to enhance undergraduate students' motivation, interest and readiness for careers in biomedical research (1 – 4).

As scientists and educators, some of us may have leaned hard on our mentors for professional and perhaps also personal support. Yet not all students find suitable or supportive mentors.

Underrepresented and minority students in the sciences are at risk for inadequate mentoring relationships (5). Students can and do persist and succeed in the absence of strong mentoring relationships, but these students are at higher risk for attrition. Additionally, years of effort to improve mentoring in science have yielded only limited results with respect to retention and success of underrepresented students. Some scientist-educators simply may lack interest or skill in providing substantive emotional support, especially in a competitive funding environment where research must come first.

As scientists and educators, some of us may have leaned hard on our mentors for professional and perhaps also personal support. Yet not all students find suitable or supportive mentors.

A growing body of evidence suggests that it is critical to look beyond dyadic mentoring relationships to support students effectively, especially URMs, in the biomedical sciences pipeline, and here we briefly present an innovative way for doing so.

Looking beyond mentors

Social network analysis (SNA), as a theory and data analytic method, allows for investigation of larger and more comprehensive social networks, going well beyond examination of dyadic relationships.

SNA emerged in the 1970s, and network theory, the related study of the processes and mechanisms interacting with network structures that yield individual- or group-based outcomes, is developing rapidly as a field of study (6).

This cross-disciplinary research area is now of interest not only to social scientists but also to epidemiologists, biologists and physicists. Network theory, commonly associated with big data, has been applied to such disparate topics as the prediction of flu pandemics, the assessment of individuals' voting behavior and understanding marriages between Florentine families in the 15th century.

The methodology also can be adapted to help us understand and intervene with networks of students in the biomedical sciences pipeline. By better understanding the structure and characteristics of students' social networks and associating network structure with student characteristics (e.g., gender, ethnicity, grade point average, publications and presentations), it may be possible to help the students to support themselves.

In brief, a social network is defined as a set of actors or nodes (for example, a group of students) that are interconnected by a set of defined ties (for example, amount of lab time spent together or interpersonal support). Ties interconnect these actors to form paths, and within a network, the pattern of ties represents structure. These structures can be represented mathematically. Hence, the position of actors has meaning, as do the characteristics of the network structure.

Examples of network structure characteristics include actor centrality – how prominent an actor is within the network. Actors who are prominent are extensively involved in network relationships. SNA researchers have derived numerous measures of actor centrality. In contrast, actors may be isolates and remain relatively unconnected to other actors within the network. Typically this would be seen as a liability.

Using SNA to see ties among those in a science department

A network of students and faculty mentors working within a biochemistry department can be studied with regard to, say, interpersonal support.

The researcher selects students, perhaps first-year students, and faculty members who define the network to be studied. The researcher also identifies the type of tie (support) or relationship to be studied.

At the outset of the academic semester, students and faculty members have little familiarity with one another, and hence no one individual supports any other. The network, in effect, is unconnected with regard to support. However, as individuals begin spending time together and interacting, they begin exchanging support. In other words, at some second measurement point, all individuals in the network can respond to the question "Who here provides you with support?" By the end of the first semester of students' first year, all individuals in the network (actors or nodes) can be connected, and the network can be examined for structural features.

Such a study would employ a full-network, or whole-network, research design that examines the supportive ties among first-year students and their faculty members. If the study is conducted longitudinally, the investigator can study how supportive relationships among students and faculty members evolve over time.

At the outset of the academic semester, students and faculty members have little familiarity with one another, and hence no one individual supports any other. The network, in effect, is unconnected with regard to support. However, as individuals begin spending time together and interacting, they begin exchanging support.

Alternatively, investigators might elect to study an egocentric, or personal, network, which can be considered a subset of the full network and either extracted from the whole or studied in the main. Egocentric networks can be created in a more streamlined manner – that is, simply by asking the students, "Among people in the biochemistry department, who are the three of four people who provide you with support?" In this case, the full network is not used; hence, the structural features of the full network cannot be analyzed thoroughly.

SNA in action

Some researchers who study students in the biomedical sciences pipeline are beginning to use network analysis. For example, Cecilia Rios-Aguilar of Claremont Graduate University is studying URM community college students' success as it relates to their virtual communities, the supportive online relationships that students create and use to help one another achieve success.

Rios-Aguilar argues that successful students are more connected both academically and socially. In this sense, students' virtual communities augment, or perhaps supplant, mentoring relationships.

In community-college settings, students have more limited face-to-face access to mentors and peers. By contrast, biomedical science students at four-year institutions frequently interact with mentors and peers in person, and those interactions have the potential to provide different kinds of support or assistance – tangible, informational and emotional. Those interactions, such as team-oriented lab work, in-class presentations and one-on-one coaching sessions, also make demands upon students' interpersonal skills.

Teaming up with social scientists

Supportive social networks are critical to all students, especially those just entering competitive, research-oriented fields such as those in the biomedical sciences. For underrepresented minority students, a supportive social network may be a critical adjunctive factor to their academic success.

Social network analysis offers many opportunities to investigate and intervene with the aim of first understanding and then strategically strengthening students' networks. It also allows investigators to determine whether the impact of the emergent social milieu exceeds the impact of the mentor-protégé relationship. If so, then support for students in the biomedical sciences pipeline should become more holistic and perhaps less focused on mentoring. Students in these programs still may need assistance with their economic or educational readiness, but additional focus could be placed on strengthening students' abilities to support one another.

Application of methods derived from network theory will allow us to understand and then perhaps bolster students' confidence, increase their retention and success in the laboratory, and thereby increase their interest in careers in research. Meaningful collaborations between biomedical scientists and educators and social scientists trained in SNA are needed to assess and refine our training paradigms in ways that promote the supportive social networks necessary for student success.

Social network analysis

- The methods and theory first were studied quantitatively by social and behavioral scientists.
- The tradition extends to the 1920s.
- Network science, as a discipline, now extends well beyond the social context, seeing contributions from applied mathematical and statistical sciences and applications to the natural sciences, social and organizational sciences, economics and political science, and information science.

Biomedical science trainees

- Students arrive at biomedical training programs with a set of existing social ties and social connections that offer support and buffer them from stress.
- We invite and implore students to expand their existing social networks to include fellow students, faculty mentors, fellow lab members and others.
- The success of our students depends on their ability to navigate toward the larger social network of biomedical students and biomedical scientists.

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Coenzyme A: when small is mighty

BY ROBERTA LEONARDI AND SUZANNE JACKOWSKI

Coenzyme A is an essential, universally distributed, thiol-containing cofactor that works as the major acyl group carrier in all cells. This molecule is involved in hundreds of reactions and is required for the metabolism of fatty acids, carbohydrates, amino acids and ketone bodies.

CoA is a major regulator of energy metabolism, although it often is overlooked. Acetyl-CoA in particular is strategically positioned at the crossroads of energy metabolism. Just like all the roads lead to Rome, both anabolic and catabolic pathways converge at the formation of this small molecule, yet acetyl-CoA maintains order by reinforcing the partition of pyruvate between synthesis and degradation through its differential regulation of pyruvate dehydrogenase and carboxylase. Traffic control beyond this metabolic junction is exerted by acetyl- and other acyl-CoAs through both allosteric and post-translational regulation.

Several acyl-CoAs produced as metabolic intermediates are potent allosteric modulators of key enzymes, such as carnitine palmitoyltransferase I and acetyl-CoA carboxylase, and transcription factors, such as HNF4-α (1) and PPARα (2). Acetyl-CoA is used to modify enzymes, transcription factors and chromatin covalently and reversibly to govern their activities (3 – 5). Covalent acylation by long-chain acyl-CoAs directs proteins to membranes where substrates are activated and stimulate cell growth and proliferation in cancer (6).

These ingenious mechanisms coordinate the expression and activity of a multitude of enzymes and processes with the energy state of the cell. Thus, CoA and a few other small molecules like NAD+ and ATP can act as global regulators of cellular metabolism both together with and independent from the action of key transcription factors.

Consistent with these key functions, CoA levels are flexible in cells so that the available supply is sufficiently adaptive to metabolic challenge. But at the same time, CoA levels are maintained at threshold amounts, suggesting that an oversupply could be detrimental to function. Decades of studies have established that regulation of the CoA biosynthetic pathway occurs at the initial step catalyzed by pantothenate kinase (PanK) in bacteria and eukaryotes (7, 8).

Mammals possess four closely related PanK isoforms, PanK1α, 1β, 2 and 3, and these enzymes are regulated through feedback inhibition by CoA species and through activation by long-chain acylcarnitines and acylethanolamides. Not all the PanK isoforms are equally responsive to this allosteric regulation, and PanK2 and 3 are significantly more sensitive than PanK1α and 1β. The localization of the PanK isoforms in different subcellular compartments and their tissue-selective distribution profiles are additional features that provide combinatorial control over CoA levels in distinct cell types.

But why is there so much redundancy, and why are there so many variations on the same theme? We recently have started to get some answers from the generation of mice that lack one or more PanKs.

The single Pank1, Pank2 and Pank3 knockout mice are viable and overtly normal, with the exception of the Pank1 knockout mice that exhibit a clear metabolic phenotype. Deletion of any two Pank genes leads to either embryonic lethality (Pank1/3 and Pank2/3) or death before weaning age (Pank1/2), indicating that the isoforms can compensate for each other and that redundancy is necessary for life. The combination of isoform abundance and regulatory properties roughly correlates with the total amount of CoA in tissues and organs, so that tissues where PanK1α or 1β are most abundant (liver, heart, kidney) have higher CoA levels than tissues where PanK2 or 3 predominate (brain, skeletal muscle).

Finally, the particular localization of each PanK isoform in the cytosol, mitochondrion or nucleus may enable the response to ligands that govern activity and flux through the CoA biosynthetic pathway. The PanKs may be sensors in situ that respond to fluctuations in the local concentration of acetyl-CoA, acyl-carnitine or acylethanolamide and adjust the rate of CoA biosynthesis.

The recent characterization of mice with complete chemical inhibition of all the PanKs (9) and of mice lacking Pank1 alone or in combination with Pank2 (10, 11) has established clearly the connection between PanK expression → CoA levels → metabolism. This represents an important starting point to try and understand the complex pathology of PKAN (pantothenate kinase-associated neurodegeneration), a severe neurological disorder caused by mutations in the human PANK2 gene. The majority of these mutations are expected to decrease significantly or abolish PanK2 activity, thus suggesting that lower CoA could be the underlying cause of reduced neuronal metabolism and function in PKAN patients.

Unfortunately, Pank2 knockout mice do not reproduce the human disease, and an important future challenge will be to generate a mouse model to investigate the connection between CoA levels and neurodegeneration and, above all, to accelerate the identification of a treatment for the disease.

Given the central role of CoA in the regulation of metabolism, another important question to address will be whether metabolic diseases like diabetes are associated with dysregulated tissue CoA levels and what the importance of CoA-degrading enzymes is in the regulation of this cofactor. Clearly, research thus far has shown that cofactors such as CoA, ATP and NAD+ can limit the output of a pathway in a manner similar to reduced enzyme levels.

Perhaps CoA is regulated to prevent overactivity within a pathway, and the future research challenge will be to establish the hierarchy among those biological processes that require CoA. CoA is required for hundreds of reactions and regulates metabolism at several different levels that include 1) substrate delivery for enzymatic reactions, 2) allosteric and post-translational regulation of enzymatic activity, and 3) regulation of gene expression through reversible acetylation of histones and transcription factors.

So keep CoA in mind next time you see a metabolic phenotype: It might just happen that a pharmacological organic acid is activated by this cofactor, thereby reducing the effective concentration of CoA for normal cellular and biochemical functions.

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