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August 2012

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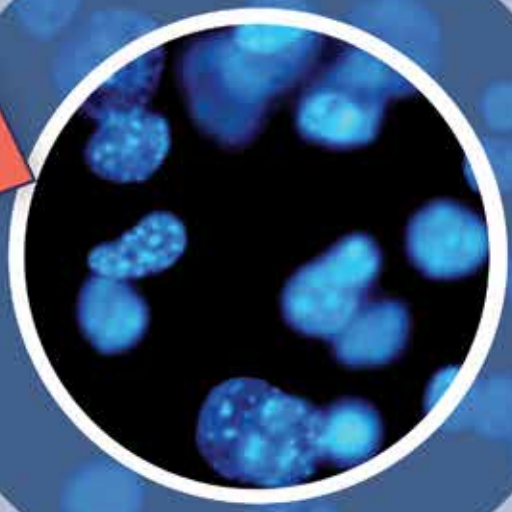

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- When scientists become parents
- Annual award winners

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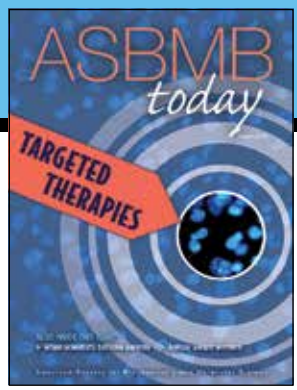

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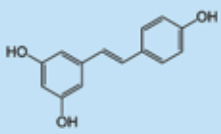

In her new series, Shannadora Hollis investigates how foods and herbs affect human health at the molecular level. **Read her column at www.asbmb.org/asbmbtoday.**

ASBMB today

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Biochemistry and Molecular Biology

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president's message

The basics of translation

BY JEREMY BERG

In many arenas, there have been attempts to distinguish between basic and translational research. In reality, basic and translational research lie along a continuum with no sharp distinctions. Furthermore, even research endeavors at the extreme ends of this continuum are critically dependent on one another. National Institutes of Health Director Francis Collins gave a presentation at the recent TEDMED conference that made this point abundantly clear. Collins devoted a considerable amount of this talk to speaking about the premature aging disorder Hutchinson–Gilford progeria. He chose this example to illustrate how drugs developed for potential use in one disease can sometimes be used to treat other diseases and that this repurposing might speed the development of new therapies.

The mutations that cause Hutchinson–Gilford progeria were first identified in 2003. These frequently occur at one particular position within the LMNA gene. This gene and its protein products, forms of lamin A varying in terms of post-translational processing, have been studied for more than two decades in the context of fundamental studies of cell biology. These studies had shown that lamin A is a key component of the nuclear lamina, the fibrillar network that lies just inside the nuclear membrane. Prelamin A is processed by farnesylation on a cysteine residue near its carboxyl terminus, proteolytic removal of three amino acids from the carboxyl terminus, methylation of the new carboxyl terminus, and a final proteolytic cleavage to produce mature lamin A, incorporated into the nuclear lamina. Mature lamin A lacks the farnesyl group since the peptide fragment that includes this group is removed by the final proteolytic cleavage. Through the use of lovastatin, a small-molecule drug that blocks the pathway leading to farnesylation, it was demonstrated that farnesylation is required for proper processing of prelamin A.

The mutation that causes Hutchinson–Gilford progeria introduces a cryptic RNA splice site that results in the production of prelamin A that is missing an internal stretch of 50 amino acids near its carboxyl terminus. The prior knowledge regarding prelamin A and its maturation pathway allowed researchers immediately to propose and then test hypotheses regarding the biochemical basis for the pathobiological mechanism of the observed mutation. The mutated protein is farnesylated but does not have this farnesyl group removed by proteolysis, and the farnesylated protein does not function properly. This observation is the basis for ongoing clinical trials that aim to block the farnesylation process through the use of drugs and drug candidates that were developed for other indications in which these biochemical pathways are important, including cancer and heart disease. In particular, farnesyltransferase inhibitors, developed as potential anticancer agents based on the fact that the frequently mutated oncogene Ras protein is also farnesylated, are being studied as components of therapy for Hutchinson–Gilford progeria. Such compounds have been shown to reverse the cellular phenotype associated with the expression of the mutated form of prelamin A, but detailed clinical trials are necessary to

determine if these compounds have desirable effects in individuals with Hutchinson–Gilford progeria.

This account illustrates how important fundamental knowledge of genes, proteins, and their associated networks and pathways are to the translational process. Because the gene and its products associated with this disease happened to have been well studied in the context of basic research, it was possible to make rapid progress in understanding the molecular basis of Hutchinson–Gilford progeria and developing potential strategies for its treatment. This is not always the case. Even with all that we have learned, in many cases molecules that are found to be associated with specific diseases are relatively uncharacterized and incompletely understood. Furthermore, almost all biomolecules are components of multiple pathways and networks, and our models of these systems undergo expansion and revision constantly as more fundamental knowledge is uncovered. These observations provide a strong impetus for continued studies of fundamental biological mechanisms. Deep exploration of the fundamental processes of life — often most effectively and efficiently obtained in the context of basic studies without any known disease connection in model organisms where the tools of biochemistry, molecular biology, genetics and cell biology can be brought forcefully to bear — pays powerful dividends and leads to unanticipated discoveries that can affect all aspects of research dramatically.

Of course, the interplay between basic and translational research is bidirectional. The characterization of molecules known to be associated with particular diseases and attempts to develop new therapeutic approaches also can reveal new fundamental information. For example, subsequent studies of the mutant form of lamin A associated with Hutchinson–Gilford progeria have revealed additional aspects of the fundamental role of this protein in affecting nuclear architecture. Tools and insights derived in this way can drive both fundamental and translational research.

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Fundamental knowledge is the underpinning of all attempts to develop new and improved therapies. Developing such therapies is tremendously challenging in large part because of holes in our fundamental knowledge of biology, particularly the biology of human populations with all of their associated genetic and environmental heterogeneity. We need the concepts and tools of biochemistry and molecular biology now more than ever to drive improvements in human health as well as other critical fields, such as energy and food production, as depicted in the recent National Research Council report on "The New Biology." Researchers who might regard themselves as sitting on one side or the other of the basic–translational spectrum will benefit from increasing their understanding of the challenges of developing a new drug or therapy from discovery through successful implementation. Successful translation is very challenging and requires considerable strategic and technical sophistication. Success also depends on having a very strong fabric of fundamental knowledge underlying the translational approach. We still have much to discover and learn!

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

Thanks, but we need more

BY BENJAMIN CORB

Last month, the National Institutes of Health Advisory Committee to the Director's Biomedical Workforce Working Group (known as the Tighlman Group) published its draft report on the state of the biomedical work force. The group was charged with developing a model for a sustainable and diverse U.S. biomedical research work force that could inform decisions about training the optimal number of people for the appropriate types of positions that will advance science and promote health — a heavy lift, to be sure! To its credit, the Tighlman Group provided hard evidence to support what many in the community have been saying for years: that the manner in which we train our work force has put the community on an unsustainable path.

While today's trainees are sold promises that their hard work in the lab will pay off with tenure-track positions in academia, the report shows only 23 percent of biomedical Ph.D.s actually reach that promised land. Nearly one in three biomedical Ph.D.s will end up with a career in the private sector, and yet our community rarely if ever provides training to Ph.D.s that will both prepare them for alternative careers and educate them on realistic employment options that will be available. This is surprising considering that the study shows that academia is quickly becoming the alternative career path.

If we are using NIH dollars to train Ph.D.s for the research and academic careers we want for them but only 23 percent of them are reaching that goal, it is time to find answers to critical questions. Are we promising young scientists a future we simply cannot deliver? Are we training too many Ph.D.s? Do we prepare our trainees for the future they will have or the future we think they should have? After asking ourselves these critical questions, we owe it to the trainees — we owe it to ourselves as the stewards of biomedical research — to restructure training experiences for the realities of today.

It is here that the Tighlman Group's report seems to fall flat. The community waited eagerly for a game-changing report with recommendations and a plan for how to build a sustainable work force, but what we got was less. The report's conclusions admit as much, saying, "The working group is aware that similar recommendations have been made in the past by other groups that studied the biomedical research workforce." Where the group had an opportunity to make strong, possibly unpopular recommendations on how to implement change for the good of the community, it seems to have punted that responsibility to others. That is unfortunate.

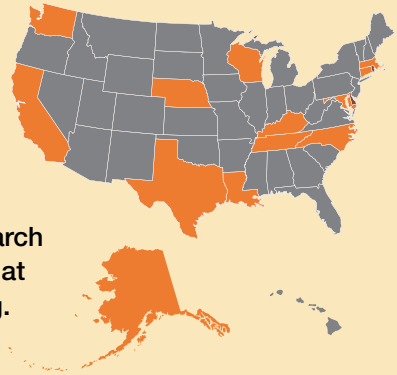
I am reminded of a quote by President Kennedy early in his administration. While talking about what he liked and disliked about the presidency, he noted that the problems that cross his desk are not easy to solve. If they were, they'd have been solved long before they reached the White House. There are difficult problems in our training system, many with unpopular solutions. It's time the leaders of our community accept the responsibility to help find the answers.

Think you have a solution? I want to hear it! Email me your recommendations to create a sustainable work force, and the American Society for Biochemistry and Molecular Biology public affairs team will deliver them to the leadership at the NIH.

Benjamin Corb (bcorb@asbmb.org) is director of public affairs at ASBMB.

THE 100–MEETINGS CHALLEGE

Members from 13 states have volunteered to join our summer challenge and meet with their U.S. senators and representatives in their home offices during the recess. To join the cause of advocating for fundamental research funds, email Corb at bcorb@asbmb.org.



asbmb member update

New chairman at Vanderbilt


YORK

John York, formerly of Duke University Medical Center, joined Vanderbilt University as chairman of its biochemistry department in July. He succeeded F. Peter Guengerich, who served as interim chairman for the past two years. York's research focuses on elucidating cellular communication networks required for cellular survival and organismal development and investigating lithium's role in the treatment of mental illness. He is a Howard Hughes Medical Institute investigator and a fellow of the American Association for the Advancement of Science.

Distinguished professorship


DUNN

Stanley Dunn of the Schulich School of Medicine and Dentistry at the University of Western Ontario won a distinguished university professorship award issued by the university this year. Dunn, who has dedicated his research career to the study of ATP synthase, won the award for his scholarly productivity and major service to the university research community. He founded in 2003 and to this day serves as the director of the London Regional Proteomics Centre, which provides faculty members and students access to key instrumentation and services through operation of a set of managed, multiuser instrument facilities. Dunn has been recognized for his work on bioenergetics and bioinformatics many times over. Upon receiving the award, he was lauded for his "unselfish nature, commonsense approach and outstanding critical judgment" by the school's dean, Michael Strong. Dunn has served on the editorial board of the Journal of Biological Chemistry and as a chairman of the Bioenergetics Gordon Research Conference.

Ohio Patent Impact Award


KOPCHICK

Ohio University's John Kopchick earlier this year won the Ohio Patent Impact Award for his co-discovery of the drug Somavert, a growth hormone receptor antagonist. Somvert is used to treat acromegaly, a syndrome that results when the anterior pituitary gland produces excess growth hormone. The patent award, issued by the Ohio Academy of Science and the Ohio State Bar Association, is reserved for inventors whose work has significantly affected an industry, the economy or medicine. Somavert was discovered in 1987 when Kopchick and his students were trying to come up with a drug to treat children with dwarfism, but instead of developing a compound that would make the patients grow Kopchick's team found Somavert inhibited growth. Today the drug is licensed by Pfizer Corp., which has yielded the university $73.5 million since the drug was approved in 2003.

Distinguished alumni award


MANN

The University of Iowa earlier this year named Kenneth Mann the winner of one of its 2012 Distinguished Alumni Awards. Mann, today a professor at the University of Vermont and one of the world's leading experts on blood coagulation, completed his graduate studies at Iowa in the 1960s under Carl Vestling. When he embarked upon his independent career in the 1970s, he fixated on the characterization of the biochemistry of coagulation – then an entirely new line of research. He went on to discover Factor V and shed light on both normal and pathogenic clot formation. Mann's work has yielded numerous improved pro- and anticoagulant drugs (he and his collaborators have had 22 patents) and promoted advances in the diagnosis, treatment and prevention of thrombotic and hemorrhagic diseases. In the past year, Mann has been named a distinguished scientist by the American Heart Association and has been presented a lifetime achievement award by the Hemostasis and Thrombosis Research Society.

An ASN fellowship


BERGEN

Werner G. Bergen, a professor at Auburn University's College of Agriculture, was named this spring one of eight new fellows of the American Society for Nutrition, an honor bestowed in recognition of his outstanding career in nutrition science and the most prestigious acknowledgment offered by the society. Bergen's lab studies the complexities of regulation of lipid and protein metabolism in agriculturally important animals at the genomic and proteomic levels. He has a particular interest in nutrient–gene interactions and the role of signal-transduction mechanisms in lipid deposition and protein synthesis and turnover. The ASN fellowship program was established in 1962, with only a handful of researchers elected each year.

Yes, indeed, our members are so accomplished that this month we had more member news items than we could print. Visit the online edition to find out who's moving up and who deserves a pat on the back. Visit www.asbmb.org/asbmbtoday.

2013 AWARD WINNERS

Avanti Award in Lipids

Susan A. Henry, Cornell University

Studies genetic regulation and signaling related to phospholipid and triacylglycerol metabolism in yeast

ASBMB Award for Exemplary Contributions to Education

James M. Ntambi, University of Wisconsin–Madison

Studies the genetic regulation of the stearoyl-CoA desaturases in metabolism and in disease states such as obesity, diabetes, atherosclerosis and cancer

ASBMB Young Investigator Award

Shu-ou Shan, California Institute of Technology

Research addresses how a novel class of nucleotide hydrolases drives the efficient and accurate delivery of newly synthesized proteins to their correct destinations

ASBMB-Merck Award

Vivek Malhotra, Centre for Genomic Regulation

Studies the mechanism of secretory cargo sorting and transport carrier biogenesis during conventional and unconventional protein secretion

Delano Award for Computational Biosciences

Helen M. Berman, Rutgers University

Focuses on the structure and interactions of biological macromolecules and the creation of computer resources to enable analysis of proteins and nucleic acids

Earl and Thressa Stadtman Distinguished Scientist Award

Brian K. Kobilka, Stanford University School of Medicine

Investigates the structural basis of G-protein–coupled receptor signal transduction

Fritz Lipmann Lectureship

Olke C. Uhlenbeck, Northwestern University

Focuses on relating RNA structure to function

Herbert Tabor Research Award

F. Ulrich Hartl, Max Planck Institute for Biochemistry

Studies of the role of molecular chaperones in protein folding and in diseases of aberrant folding

Arthur L. Horwich, Yale School of Medicine

Focuses on chaperonin-mediated protein folding

Mildred Cohn Award in Biological Chemistry

Jennifer A. Doudna, University of California, Berkeley

Studies RNA-mediated initiation of protein synthesis, RNA–protein complexes involved in targeting proteins for export out of cells and the early steps in gene regulation by RNA interference

Ruth Kirschstein Diversity in Science Award

Peter Blumberg, National Cancer Institute

Studies the regulation of protein kinase C and related mediators of diacylglycerol signaling pathways and the capsaicin receptor TRPV1 as a therapeutic target for pain

Walter A. Shaw Young Investigator in Lipid Research

Tobias Walther, Yale School of Medicine

Studies the mechanisms of lipid and membrane homeostasis

William C. Rose Award

Ivan Dikic, Goethe University School of Medicine

Studies how ubiquitin regulates cellular functions and is implicated in development of human diseases, including cancer, dermatitis and bacterial infections

Alice and C. C. Wang Award in Molecular Parasitology

Daniel E. Goldberg, Washington University in St. Louis School of Medicine

Researches metabolism of intraerythrocytic malaria parasites

2012 COMMITTEE CHANGES

council

OUTGOING

Suzanne Pfeffer – *President* – Stanford University School of Medicine

Merle Olson – *Treasurer* – University of Texas Health Science Center at San Antonio

Ruma Banerjee – University of Michigan Medical Center

Ben Cravatt – The Scripps Research Institute

John Scott – University of Washington in St. Louis School of Medicine

Joan Conaway – *Meetings Chair* – Stowers Institute for Medical Research

INCOMING

Jeremy Berg – *President* – University of Pittsburgh

Toni Antalis – *Treasurer* – University of Maryland School of Medicine

Natalie Ahn – University of Colorado at Boulder

Anjana Rao – La Jolla Institute for Allergy and Immunology

Daniel Leahy – Johns Hopkins University School of Medicine

Daniel Raben – *Meetings Chair* – Johns Hopkins University School of Medicine

publications

OUTGOING

Toni Antalis – University of Maryland School of Medicine

Kendall Blumer – Washington University in St. Louis School of Medicine

Maurine Linder – Cornell University

INCOMING

Kathleen Collins – University of California, Berkeley

Michael Yaffe – Massachusetts Institute of Technology

Enrique De La Cruz – Yale University

nominating

OUTGOING

Karen Allen – Boston University

INCOMING

Barbara Imperiali – Massachusetts Institute of Technology

Ivan Dikic – Goethe University

public affairs

OUTGOING

Thomas Baldwin – University California, Riverside

Janet Shaw – University of Utah School of Medicine

William Merrick – Case Western Reserve University

Gregory Petsko – Brandeis University

INCOMING

Craig Cameron – Pennsylvania State University

Nancy Dahms – Medical College of Wisconsin

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- Eligibility for the National Biochemistry and Molecular Biology Honor Society
- Free online and print subscription to *ASBMB Today*, the society magazine
- Free online subscriptions to:
  Journal of Biological Chemistry
  Molecular and Cellular Proteomics
  Journal of Lipid Research

ASBMB

American Society for Biochemistry and Molecular Biology

Goodbye, Columbus

BY GREGORY A. PETSKO

The throne room of the Spanish court in Madrid, some time in the late 15th century. Seated side by side are King Ferdinand and Queen Isabella. Standing before them is a tall, muscular man wearing the clothes of a sea captain, holding his hat in his hands. He speaks Spanish, but with a pronounced Italian accent.

Ferdinand: Now who's next? Oh, yes, Captain Columbus. I assume you're here to appeal the decision about your proposal.
Columbus: Yes, Your Majesties. I don't understand why my request for support was turned down.
Isabella *(leafing through some documents):* Let's see, let's see — oh, here it is. 'Finding a New Route to the Indies by Sailing West.' *(Looking up at him)* You're serious, right? I mean, this isn't some sort of joke…
Columbus: Of course it's no joke! I propose to test the hypothesis that the world is both small and round. If the hypothesis is true, I should be able to reach the Orient much faster than the current route around Africa.
Ferdinand: And if the hypothesis is wrong, you'll fall off the edge of the earth.
Columbus: Possibly. But even if it's wrong, by going where no one has gone yet, I might bump into something really interesting.
Ferdinand: What you'll bump into is the edge of the earth, and you'll fall off.
Columbus: I agree that there is risk involved, Your Majesty, but consider the impact if I'm right. In the guidelines for obtaining funding, you specify that impact is a major factor in determining if a proposal is funded.
Isabella: I know we *say* that, Captain, but we don't *mean* it. Why, if we actually judged proposals that way, many of them would fail.
Ferdinand: That's right, Liz. I mean, think of how it would look if we funded something that didn't pan out.
Columbus: But then, what criteria *do* you use?
Isabella: Oh, we don't decide these things ourselves, Captain. Your proposal was peer-reviewed. Let's see *(shuffles through more papers),* here we are. Oh, my. Your priority score was really terrible.
Columbus: Yes, I know that, but why?
Isabella: Well, the summary statement says that the Voyages of Discovery Study Section found your proposal too unlikely to succeed. For one thing, there were not enough preliminary data to indicate it was sure to work.
Columbus: But your guidelines say that a lot of preliminary data aren't required for proposals of high potential impact!
Ferdinand: And you believed that? Ha ha ha ha! What an idiot!
Isabella: Now, Ferdie. Don't be too harsh. But he's right, you know, Captain. Study Sections have to be sure a project will succeed before they recommend we fund it.
Columbus: But how can you be sure something will work unless you've already done it?
Isabella: That's exactly the point. Once you've already accomplished all your Specific Aims, people know it's safe to fund you to try to accomplish them.
Columbus *(feeling dizzy):* But where am I supposed to get the money to do that?
Ferdinand: That's not our problem. Money is so tight these days that we can't fund anything that isn't guaranteed to work. I mean, what if the Inquisition found out we were wasting money?
Columbus: But you have to have some failures if you're doing anything innovative or creative. New ideas don't always work.
Ferdinand: Well, they won't get funded, then.
Columbus: But what sort of ideas *do* you fund if you don't fund hypothesis-testing?
Isabella: Oh, big data-gathering projects that are certain to produce data, even if the data aren't very valuable. Fra Pedro de la Vega's project to count all the olive trees in Spain, for example, and put them in numerical sequence. The Olive Tree Sequencing Project.
Columbus: But what good is *that?*
Ferdinand: Beats me. But it's guaranteed to work, and besides, we already have all those trained counters from his successful Grape Vine Sequencing Project and his famous Flamenco Dancer Sequencing Project. Have to keep them working, you know.
Isabella: The other thing we fund is incremental research. Study Sections love incremental research. Nothing is as risk-free as people just doing more of

what they've already been doing.
Ferdinand: Yes, I remember now. That was another criticism of your proposal: it's way too ambitious. You shouldn't be trying to reach the Indies all at once. Now if you had proposed to sail west to, say, Portugal…
Columbus: But that's ridiculous! Everybody knows that Portugal is immediately west of Spain. Of course you can get there by sailing west. What will you learn from that?
Isabella: Not much, if anything. But it can't fail, now, can it? Besides, you've sailed to Portugal before, so the Study Section would know you can do it.
Ferdinand: Yes, your problem, you see, was in proposing to do something that no one has done before. People who hope to get funded don't do that any more. You shouldn't try to be daring and unique. Just follow what everyone else is doing.
Columbus: Then there would be no more big discoveries, no overturning false beliefs, no radical change. What sort of world would we have without them?
Isabella: A predictable one.
Columbus: I refuse to believe that a collection of my peers would think that way. May I see the list of the people who were on the review panel, Your Majesty? *(The Queen hands him a sheet of paper; he looks down at it)* But — but — I don't recognize anyone on this list! Where are the other great explorers and navigators, the ones who could appreciate what I'm trying to do?
Ferdinand: Well, we tried to get Vasco da Gama and Freddy Magellan to serve, but they claimed they were too busy with their own voyages to take the time to be on the panel.
Columbus: But this critique is unreasonable.
Isabella: Don't blame us, Captain. Blame your fellow explorers. If the science of exploration is becoming too conservative and ideas like yours can't get funded, it's not the fault of administrators like us. It's the fault of your own community. After all, you review each other's proposals. You're a victim of what the Good Book says in Matthew 10:36, *'And a man's foes shall be they of his own household.'*
Ferdinand: Liz, I'm impressed. Quoting the King James Bible, and King James won't even be born for a couple of hundred years or so.
Isabella *(blushing):* I also see here in the Summary Statement that the panel felt your budget was just too inflated. Asking for three ships! They say you should be able to manage fine with just one — the *Pinta,* say.
Columbus: Your Majesties, no one undertakes a voyage of discovery with just one ship. If anything goes wrong, you would be stranded.

Ferdinand: Well, there you go. See, that's your whole problem: you don't understand that the possibility that something could go wrong is just not acceptable anymore. Things have to be risk-free now.
Isabella *(kindly):* I'm sure this is disappointing for you, Captain, but the criticisms in this statement are very constructive, and I think after this conversation you should be able to revise your proposal so that it has a much better chance of being funded the next time.
Ferdinand: Yes, just reduce your budget to one ship, propose an easily achievable Specific Aim like discovering Lisbon, and accumulate enough preliminary data by actually going to Lisbon so the panel can be certain you know how to get there. Then there's a very good chance you will get the money you ask for, and you can use it to go even farther than you propose.
Isabella: That's right. With funding like that, you might actually reach, oh, I don't know, maybe the western suburbs of Lisbon. Wouldn't that be wonderful!
Ferdinand: You run along, now, Captain, and start working on that revised application. You just missed the next deadline, I'm sorry to say, but there will be another one in 6 months, so if you're successful the next time, you ought to be able to get started by early 1494 or so. Follow what everyone else is doing, and you'll be fine. *(Head down, Columbus slowly walks away. After he is out of the throne room, the King turns to his consort)*
Ferdinand: Well, Liz, what do you think?
Isabella: I'm not sure, Ferdie. What if he's right? What

if the world is small and round and you really can sail –
Ferdinand: Preposterous! Everybody knows that's not true. Imagine, paying good money just on the off-chance conventional wisdom might be wrong.
Isabella: But if there's even a small chance… I mean, think of the impact. Maybe we should have taken some money and let him try.
Ferdinand: What, and go against peer review? Think of the grief we'd get. It's so much safer for us, too, not to take any chances. The Inquisition is happy, you and I are happy—
Isabella: Yes, but maybe instead of everybody always following in the same direction like sheep, we ought to let some people with new ideas try to lead us somewhere else for a change.
Ferdinand: Nonsense. Look, no more talk about Captain Columbus. I guarantee you that in a few years no one will even remember his name.
Isabella *(sighing):* All right. Then let's look at this proposal for a completely new big initiative, one that we can fund ourselves. It's a proposal from Don Hernando Gonsalvo to look for very small changes in the amount of water that one finds in cisterns, accumulate as much data as possible, and attempt to connect it with something interesting.
Ferdinand: Something interesting like what?
Isabella: He doesn't say. He just says all that data will certainly tell us something.
Ferdinand: Ah yes, I remember that proposal now. The Gonsalvo Water Association Study. GWAS. Catchy. I like it. Now *that's* real science!

This article originally was published May 18, 2012, in Genome Biology and is reprinted here with permission from the author and publisher. See the original at http://genomebiology.com/2012/13/5/155.

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AN HONORABLE CAREER IN ACADEMIA

VS. AN ALTERNATIVE CAREER IN THE PRIVATE SECTOR

'There is a huge disconnect between how we currently train scientists and the actual employment opportunities available for them'

BY MARTIN ROSENBERG

The growth and biomedical promise of molecular technologies in the later part of the 20th century resulted in significant expansion of science infrastructure in government, academia and industry. More recently, fiscal pressures have reduced the availability of new independent research jobs in all sectors. Despite the fact that nonbench science jobs in the private sector remain a strong, viable option for new grads, our training systems remain focused on producing independent research scientists and do little to prepare students for science careers away from the bench. Here, I'll recount how we got into this dilemma and the obstacles to effecting real change that remain.

First, a period of expansion

National Institutes of Health funding doubled between 1998 and 2004. State governments also invested to grow their science capabilities based on potential economic returns. Between 1970 and 2000, we saw the creation and growth of the biopharmaceutical industry. The established pharmaceutical companies and other science-based industries also expanded their research to capture and exploit these promising technologies. Many new job options for trainees (and faculty) were created. As the science infrastructure expanded, so did the trainee programs needed to supply the labor force doing the work. More trainees were produced than academic or government centers could absorb as permanent faculty members. Trainees and faculty members alike moved into the industrial sector void, thereby relieving the supply and demand issues around science job opportunities.

Then, a period of stagnation

More recent trends have dramatically altered the dynamics. A number of factors have been at play, but certainly the major contributor has been the economy. NIH funding has been essentially flat for the past eight years. State economies have been stressed such that growth of state-funded science opportunities has slowed significantly. Productivity in pharma has been on the decline for a decade, and consolidation in this industry continues.

The response to these economic woes in academia and the government has been to curb new faculty growth. Though the faculty ranks are aging, its members remain reluctant to retire and move on. Due to their power, savvy and experience, older faculty continue to compete for and utilize major resources that perhaps should be used to support new investigators. This stagnation, in part, has led to the extension of the training period. Ph.D. training is now generally six to eight years instead of four, and the norm has become two postdoctoral experiences of three to four years each prior to securing a first permanent job. This is a predictable result when job opportunities become scarcer while the need for the trainee work force remains.

Radical response from private sector, but hope remains

In the past few years, tens of thousands of science-based jobs have been eliminated from industry, especially at the large pharmaceutical companies. Biotech investments have been reduced and shifted away from research-stage initiatives to focus on nearer-term product development.

Pharma companies also have altered their strategic focus in response to internal cost constraints and productivity issues. They have shifted large portions of resources into a variety of outsourcing models, thereby creating new opportunities for scientists in new business models.

There remain a number of employment bright spots in the private sector. Pharma outsourcing has led to the creation of new contract research organizations, partnerships with academic centers, government-sponsored consortia and various nonprofit public–private alliances in the hope that these approaches will provide the much-needed cost controls and innovation engine to create new drugs. Importantly, this strategic shift by pharma provides alternative funding sources for academia, has stimulated job growth in various support functions and aligns well with the NIH translational research focus promoting academic drug discovery. In addition, the medical devices and diagnostics industries continue to flourish, fueled by the economic pressure on health care and the promise of personalized medicine. Other science-based industries, including tool and reagent providers, food and environmental monitoring, nonprofit organizations, forensics, biofuels, science journalism, and even nutraceuticals and cosmetics also offer employment opportunities.

Roadblocks to repositioning training programs

What may well be underappreciated is that the majority of the science jobs in the private sector are not bench-research based. Rather, most of the jobs available (Table 1) have little to do with the focus of our entire academic training system. There is a huge disconnect between how we currently train scientists and the actual employment opportunities available for them.

Several factors impede the ability to recognize and adapt to the trainees' needs. The academic mentoring system lacks information and knowledge about private-sector science vocations. Faculty members teach what they know, and the result is that basically they produce clones of themselves – teachers and research professors. The faculty members have little experience with industry and, in particular, with most of the job categories shown in Table 1. The science-education system would have to seek expertise proactively from the private sector to convey these employment opportunities to their trainees. There appears to be a reluctance to do so.

Then there is the perception that positions other than independent research or teaching faculty are lesser choices. A recent description of career paths provided by a research professor exemplifies the problem. The implication was that students could follow an honorable career in academia or an alternative career in the private sector. Sadly, this arrogance and Ivory Tower attitude not only impede educational transition but, more importantly, lead many faculty members to avoid the issue by ignoring its existence.

Systemic change is needed

Perhaps the greatest hurdle to effecting change and better preparing trainees for positions that do exist is the nature of the highly competitive research-funding system itself. The research infrastructure requires trainees to carry out its basic functions: experimentation and publication. Trainees are the major labor force used by established faculty, and thus training is focused on driving independent bench research for faculty to achieve their funding, status and advancement. It matters not what future employment opportunities look like for the trainees; the training is intimately linked to the survival of the funding infrastructure that advances basic science knowledge.

This is the reality of our current system, but we must find ways of broadening our trainees' experiences to prepare them to compete and perform at science-based jobs away from the bench. There is no doubt that bench experience is a necessary part of training, but it no longer suffices to prepare students for today's job opportunities.

Table 1

Private-sector jobs other than research

- Preclinical analysis
- Safety assessment
- Regulatory affairs
- Clinical science
- Contract research organization management
- Project management
- Program management
- Alliance management
- Business development
- Technology transfer
- Venture funding
- Marketing
- Operations/ manufacturing
- Sales
- Science and patent law
- Information sciences

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RIGHT ON TARGET

BY RAJENDRANI MUKHOPADHYAY

Finding therapies that take down only one biological molecule remains a challenge

Since 1990, Richard W. Hanson at the Case Western Reserve University School of Medicine has been living with cancer. An expert in metabolism and an opera aficionado with a weakness for Mozart, 77-year-old Hanson has chronic lymphocytic leukemia, the most common form of leukemia in adults. Over the past 12 years, Hanson has endured six rounds of chemotherapy, taking purine analogs, antibodies and other drugs to stop his mutant B-cells from multiplying indiscriminately. Each round of chemotherapy has come faster and harder on the heels of the last. "If you have a disease like CLL, it becomes more than just an abstraction," says Hanson. "It becomes a critical part of your life."

But Hanson is a scientist to the core, so he has turned himself into an experiment. Over the past year and a half, he has participated in a clinical trial for a drug that specifically targets a tyrosine kinase in B-cells. With the new drug, Hanson sees the promise of targeted therapies: "I can truthfully say that without this drug I would be in that big lab in the sky."

Targeted therapies are drugs designed with the knowledge of the target's mechanism of action and biochemical role. In

contrast, traditional drug discovery is more happenstance. Compounds, such as natural products, are screened against a number of targets or cells; the ones that show an effect are then studied to understand why selectivity exists.

Targeted therapies are considered to be a relatively new paradigm in drug discovery. The sequencing of the human genome and the following genomic revolution have dramatically increased the number of possible biological targets. As Vern Schramm at the Albert Einstein College of Medicine of Yeshiva University points out, drugs used to be found by screening combinatorial chemical or natural product libraries. This now means that medications in the U.S. Food and Drug Administration's current approved list hit perhaps just 1 percent of the biological molecules that can be targets. "We've really only scratched the surface," says Schramm.

Much of the excitement about targeted therapies is seen in the cancer world. Historically, a number of chemotherapeutic drugs, like the purine analogs that Hanson took, were little more than poisons that attacked rapidly dividing cells, both healthy and cancerous.

Therapies for other diseases, such as autoimmune, psychiatric and cardiovascular conditions, fared better. "You knew there was a molecule that was involved in a particular pathology, and you targeted it," says John Kyriakis of Mercury Pharma. In-depth molecular knowledge was missing for many kinds of cancers for a long time.

But the notion of targeted therapies for cancer is a long-standing one. As Siddartha Mukherjee explained in his Pulitzer prize-winning book "The Emperor of All Maladies," Paul Ehrlich, who won the 1908 Nobel Prize in medicine, dreamed of finding a magic bullet that could distinguish between malignant and normal cells. Stanley Farber and dozens of other physicians and scientists followed him, hunting for chemicals that could specifically seek out cancer cells.

Indeed, some experts note that "targeted therapies" can be a buzz term. Every drug is targeted in some sense. Furthermore, a number of targeted therapies, despite their name, inadvertently hit other molecules, much like traditional chemotherapeutic drugs.

HOW GLEEVEC SHOOK UP CANCER THERAPY

Targeted therapeutics took the cancer world by storm more than a decade ago. In 1998, trastuzumab, better known by its trade name Herceptin, came out of Genentech. It was an antibody that bound to HER2/neu receptor on breast cancer cells. But in 2001 a molecule came along that made scientists and oncologists take note. It targeted a kinase.

"Ever since the discovery of kinases and signaling phosphorylation in the 1960s, the consensus was you'd never be able to make a specific kinase inhibitor because they all bind ATP in exactly the same way," says David Stokoe of Genentech. Kinases are involved in signaling pathways that control critical functions, such as the cell cycle, protein expression and genome stability. As the first kinase structures appeared in the early 1990s and the Human Genome Project eventually showed that there were at least 500 of them, many scientists doubted if it would be possible to get an inhibitor specific enough to hit just one or two.

Imatinib, best known by its U.S. tradename Gleevec and marketed by Novartis, washed those doubts away. Developed in the late 1990s by Nicholas Lydon, formerly at Novartis and now at Blueprint Medicines, Brian Druker of Oregon Health and Science University, Janet Rowley at the University of Chicago, and others, imatinib was the first drug to inhibit specifically the Bcr-Abl receptor tyrosine kinase that is the root cause of chronic myelogenous leukemia. The constitutively active Bcr-Abl kinase is produced by a reciprocal translocation between chromosomes 9 and 22. Ninety-five percent of CML patients have this mutation, which also shows up in several other cancers.

Unlike conventional chemotherapeutic drugs, imatinib targeted only the cancerous cells expressing the mutant kinase and left alone the cells lacking it. The FDA approved the drug in May 2001, and Time magazine put the drug on the cover as the magic bullet to cure cancer.

Although designed as an inhibitor of Bcr-Abl, the compound also inhibits the platelet-derived growth factor receptor, a cell-surface tyrosine kinase and c-kit, a cytokine receptor on hematopoetic stem cells that is a tyrosine kinase. Mutant PDGF receptors are involved in chronic myelomonocytic leukemia, and c-kit mutations are found in stomach

cancers. For these reasons, the FDA expanded its approval for imatinib to treat 10 different cancers by 2011. In January, Lydon, Druker and Rowley were awarded the Japan Prize for their work.

Imatinib drove home the point that, although all kinases use ATP, "every enzyme is mechanistically different in atomic detail," says Schramm. The drug changed the treatment of CML. Prior to imatinib, CML chemotherapies eventually forced patients to get bone-marrow transplants. Now more than 90 percent of CML patients are treated with a pill. Very few go on to have transplants, and the number of deaths caused directly by CML per year is less than 100 in the U.S., says John Byrd of Ohio State University. "The therapy has completely changed how the disease is managed."

DESIGNING TARGETED THERAPIES

Imatinib set off the hunt for more targets in cancer. Targets can be defined in several ways. They can be genetic mutations, such as the one that produces Bcr-Abl. Another way to define a target is to pinpoint molecules that are essential in metabolic and signaling pathways. Once a target is identified, scientists also have to make sure that it's accessible to drugs.

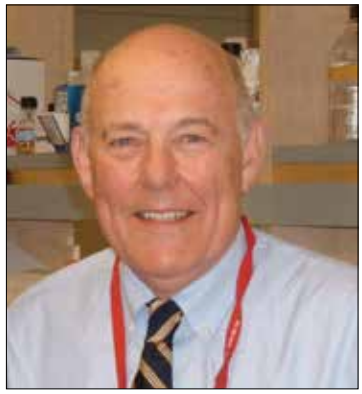
But as Stokoe explains, it's often difficult to find genetic changes that are responsible for the cancer. Most cancers, especially solid tumors, "are just genomic carnage. All hell has broken loose," he says. "I think the hard part is to try and find the genetic alterations that have actually benefited the tumor cell over all of the noise that has come along for the ride."

The drug that has kept Hanson out of the "big lab in the sky" illustrates the principles of targeted therapy design. Before he took the drug, Hanson's B-cells were crowding out red blood cells and platelets and enlarging his lymph nodes to the point that his blood circulation was affected. Walking down a hallway became hard work. He sweated at night. With a weakened immune system, he was always worried about getting infections. After the sixth round of chemotherapy, Hanson's lymphocyte level was 30 times higher than normal.

Because cancerous cells continue to mutate, "the clone you started with is not the clone that kills you," says Hanson. He eventually experienced the common CLL mutation in which the short arm of chromosome 17, where the gene for p53 resides, was deleted. His B-cells were free of the tumor suppressor. "That's a true death sentence," he says. The life expectancy for patients with that mutation is, on average, up to a year.

That's when Hanson heard of a clinical trial at the Arthur G. James Cancer Hospital at the Ohio State University Comprehensive Cancer Center that was being run by John Byrd and his colleagues. The trial was testing a drug developed by Pharmacyclics that binds to a molecule called Bruton's tyrosine kinase, or Btk for short. Hanson was allowed to enroll in the trial during its early phases.

Joseph Buggy at Pharmacyclics describes how the company knew to go after Btk. There was 10 years of scientific literature supporting the importance of the B-cell receptor signaling pathway in B-cell proliferation. Btk is an essential kinase in the signaling pathway downstream of the B-cell receptor. The pathway in which Btk is involved leads to the phosphorylation of several proteins that are antiapoptotic. When phosphorylated, these proteins prevent apoptosis.



HANSON

But the most critical piece of information about Btk was genetic. There is a disease called X-linked agammaglobulinemia in which patients lack mature B cells. "That told us that if we could come up with a molecule that was selective enough for Btk, it shouldn't affect other organs or tissues," says Buggy.

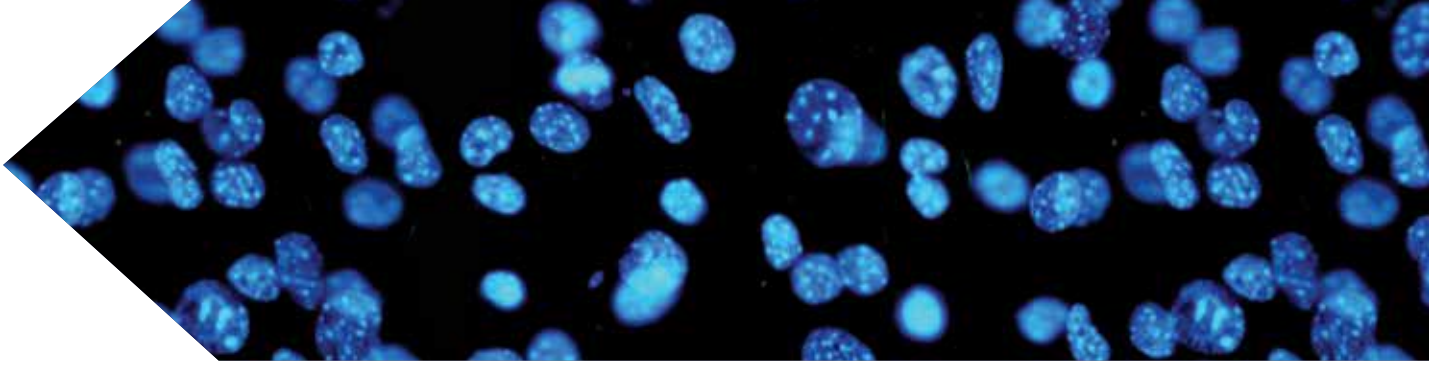
Every expert interviewed for this article emphasized that genetic validation is the key to finding proper targets. Genetic validation "takes guesswork and the need to understand the biology almost out of it," says Kevan Shokat at the University of California, San Francisco. "For every degree you get separated from the mutated human oncogene, the more biology is incumbent on you to figure out in order to be sure it's going to be a satisfactory target."

Pharmacyclics developed ibrutinib, an irreversible Btk inhibitor that binds to a cysteine found in only 10 or so kinases. When this drug blocks Btk, it induces apoptosis in cells that otherwise refuse to die (1). The irreversible binding of ibrutinib to the kinase meant that "you can durably inhibit the target, even if the drug is eliminated quickly" from the body when it's not bound to the enzyme, says Buggy. Once bound, ibrutinib molecules cling onto Btk for as long as 24 hours. The drug is now going onto phase III clinical trials.

Hanson now pops a 420-mg pill of ibrutinib every day. He says the daily dose "has made me feel like I have a future. I am amazed by it. I should be dead."

CHALLENGES

But it's not a completely rosy picture with targeted therapies, and a number of challenges dog the hunt for targets. For instance, earlier this summer, a group of researchers, which included Bert Vogelstein of Johns Hopkins University and Kelly Oliner of Amgen, demonstrated why colorectal cancer patients



eventually develop resistance to a targeted therapy called panitumumab after several months of treatment (2). They showed that well before these cancer patients started on the drug treatment they had a number of tumor cells with randomly mutated genes that evolved into providing resistance to the drug.

Side effects remain a concern, despite these drugs being so-called "targeted therapies." "We are seeing toxicities," says Thomas Force of Temple University, citing two examples – sunitinib, sold by Pfizer as Sutent to treat gastrointestinal stromal tumors, and dasatinib, marketed as Sprycel by Bristol-Myers-Squibb to treat certain adult leukemias.

As Force explains, one organ that is inadvertently affected by drugs that target kinases is the heart. The heart is an enormous consumer of energy. Any perturbations to the energy production system, either from dialing down or up kinase activity, could cause cardiac dysfunction. Other organs may be affected, but the heart, says Force, is "the first thing to go." With more therapies targeted against kinases in the pipeline, Force anticipates that researchers will see cardiac abnormalities crop up in some patients taking some of the drugs over the long term.

Another challenge is knowing when the therapy will work. Vemurafenib is a drug developed by Plexxicon and Hoffmann–La Roche that received FDA approval for the treatment of late-stage melanoma last summer. It is an inhibitor of B-Raf oncogene, which is mutated in about 60 percent of malignant melanomas. Patients with a particular mutation, the V600E mutation in which the valine at position number 600 in the kinase is replaced with glutamic acid, respond well to vemurafenib. But if the drug is given to patients who don't have the mutation, they develop a secondary cancer.

"It's the prototype right now for a drug that can be given safely to only patients with a mutation" in B-Raf, says Shokat. "If you give it to a patient who does not have the mutation and may have a Ras mutation, they are going to get another cancer induced. It's not life-threatening like the first one, but it's not going to benefit them."

Other stumbling blocks are emerging. For instance, researchers are beginning to appreciate that kinases are dynamic entities that can easily change their conformations. Vemurafenib causes secondary cancers in patients missing the V600E mutation because it causes B-Raf to dimerize. The dimerized kinase stimulates more signal transduction. "Now that we know that happens, we can screen for molecules that don't disrupt the kinase conformation and don't allow dimerization," says Shokat. "But just until a few years ago we didn't think that was all that important."

Targets can be two-faced. One kinase that drug companies are pursuing hotly is TOR. Shokat and colleagues recently demonstrated that TOR can either help or hinder therapy. They showed that inhibition of the TOR kinase could inadvertently cause acceleration of the very signaling pathway the inhibitor was supposed to stall, because TOR is involved in both positive and negative regulation of the Raf/ERK pathway. Depending on whether it's dialing the pathway up or down, TOR can be either a target or an antitarget (3). "The difficulty is TOR is not a target in every cancer setting, but that's because cancer is not one disease," says Shokat.

Another challenge is that the number of feasible kinase targets is limited. "We're running out of good kinase targets," says Stokoe. "There are probably five to 10 really well-validated kinases that are known to drive tumorigenesis in a significant number of tumors." The restricted number of known good kinase targets also limits the ways in which signaling pathways can be disrupted, narrowing down possibilities for therapies.

But it's important to note that kinases aren't the only molecules that lend themselves to the endeavor of targeted therapies in cancer and other diseases. Molecules such as nuclear receptors, histone modifiers, poly ADP ribose polymerase and proteins involved in ubiquitination are all candidate targets.

Despite the obstacles, the optimism for targeted therapies is unabated. Experts urge continued support for fundamental research in molecular biology and biochemistry so that findings can be translated into the clinic in the form of targeted therapies. Byrd, who does both fundamental research and patient care, sees the bridge from bench to bedside every day. "When what you're doing in the lab is touching patients like Dr. Hanson to put their disease into remission, that's just very special," he says.

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Balancing act

Early-career scientists discuss the challenges of juggling work and family life

BY CRISTY GELLING

Academic science does not have a reputation for being family friendly. The competition for jobs and grants and the clash of biological and tenure clocks seem to be fueling a pervasive fear that a career in science and a satisfying family life are mutually exclusive.

This has consequences for science. A study published last year found that nearly half of female faculty and a quarter of male faculty felt their careers in science had prevented them from having as many children as they would like (1). Having fewer children than desired was even more common among postdoctoral fellows, and such feelings were the only significant predictor of whether they were planning to seek careers outside of science.

Whatever the causes and consequences of this fear, I think we need to hear more from those at the center of the issue: early-career scientists with young children. So on behalf of all those friends who are standing at the brink of parenthood and professional success, I asked 25 postdocs and untenured faculty, both men and women, to share their perspectives and advice on being scientist-parents. What are the challenges? What strategies do they use to cope? And, most importantly, what advice do they have for all those fearful would-be parents?

> **"Often I wonder if I am really being a good enough mother [...] alternatively, I wonder if I am doing good enough research to come across as a serious researcher."**
>
> – Assistant professor

CHALLENGES

There were many different kinds of challenges that the respondents described, but recurring themes were sleep deprivation, unpredictable schedules, guilt and negative judgment from colleagues. Some were worried about the instability of academic jobs. Some struggled with finances, and one had relied on food stamps.

But overwhelmingly, the biggest challenge was a shortage of time.

Welkin Pope, a research assistant professor at the University of Pittsburgh with one child and one on the way, likened becoming a parent to getting a second, time-consuming job on top of an existing, equally time-consuming job.

Josh Anzinger, a lecturer at the University of the West Indies, became a parent during postdoctoral training at the National Institutes of Health. He pointed out that even though all his time is spent either working or being a parent, there is still no way to get everything done, saying, "Unfortunately, this puts you at a disadvantage if you're pursuing an academic career. Academics is not a family-friendly job."

In addition to time management, many respondents were concerned about inequitable access to benefits, such as leave and day care, for postdocs and graduate students, especially for those who lacked employee status at their institutions (2). In such cases, legislation that is designed to protect employees may not apply, consistent benefits policies may not exist, and access to employee resources like on-site day care, employee parking and dependent health-care coverage may be limited.

Even when the rules are clear, they are often inadequate. Only 23 percent of institutions in the Association of American Universities provide postdocs with a policy of six weeks of paid maternity leave (3). Graduate students, who often don't have the financial resources to go without pay, fare even worse. Only 13 percent of institutions provide six weeks of paid maternity leave, and 3 percent provide one week of paid parental leave to fathers.

These kinds of problems are typically handled by negotiation

between the student or fellow and his or her mentor. Like most of the respondents, Pope was grateful for her mentor's generous support. "But not everyone is so lucky," she warned. "We need institution-level support."

STRATEGIES

Strategies for dealing with the challenges of parenthood were incredibly diverse. Some of the respondents arranged for family day care, shared a nanny, used on-site day care, or relied on nonworking or flexible spouses. They created their own support networks by seeking out other parents on campus. They negotiated help at work from lab mates and passed projects along to collaborators. They managed their time with the help of meticulous planning and task prioritization. They never worked at home or often worked at home; they kept very strict working hours or very flexible ones; they went to work very early or late.

The only strategy that was universally popular was taking advantage of the flexibility of academia.

Faculty members have more control over their work tasks and hours than many other professionals. Flexibility is also the positive flipside to the informal work status of postdocs and graduate students. For example, many respondents mentioned negotiating flexible working arrangements with their mentors. Pope gradually transitioned her focus toward bioinformatic work, which improved the predictability of her schedule and allowed her to work from home one day a week. Even though she still worked full time, she said, it made a big difference just to have one morning when she didn't have to get her family ready or have to "lug the breast pump around."

Access to this kind of flexibility is not just a luxury. A large body of research across many kinds of workplaces consistently indicates the importance of workplace flexibility, and workers with access to flexible work practices have both greater job satisfaction and fewer mental-health issues (4).

ADVICE

Finally, I asked the scientist-parents what advice they would give to early-stage scientists thinking about becoming parents. Despite the inevitable differences of opinion and idiosyncrasies of personal advice, three tips were offered repeatedly.

The first was that parents should have realistic expectations. Bridgette Hagerty, an assistant professor at York College of Pennsylvania, cautioned that "you need to recognize that everything will take longer than it used to, and you may need to make small sacrifices in terms of how much you accomplish."

The benefit of realistic expectations is also supported by the results of a study presented last year that found that working mothers who held the attitude that they would be able to balance their work and family lives with ease were at more risk for depression than those who anticipated difficulties (5).

Accepting that the balance of work and family commitments is different every day and is different for different people is also a crucial step in letting go of the idea that there is some perfect balance that every parent must strive for. Hagerty had to train herself not to feel guilty about making time for her daughter. "Recognizing the fact I can still be a good professor despite choosing to not work during every free moment of my day has been the best strategy to maintain sanity," she said.

Another common recommendation for postdocs and graduate students was to choose potential mentors very carefully. One respondent, who chose to remain anonymous, recounted her approach to interviewing for postdoctoral positions. "I looked for good science, of course, but I also looked for PIs with kids and for labs where other postdocs and students had kids. I figured if several people in the lab had children, then it was a family-friendly lab."

However, Michael O'Donnell, a postdoc at the University of Washington, pointed out that, even though his three mentors during his time as a parent-researcher have each had very different family lives, they were all incredibly supportive of his own. "The important point is to never assume that someone will behave in a certain way just because of who you think they are," he said.

The final piece of advice was strikingly popular, with almost the same words used by each person who gave it: There is never a "good" time to start a family.

Emily Holt, an assistant professor at Utah Valley University, explained what this means.

"I know many academicians that waited to have kids until after they got their faculty position or even after earning tenure. Clearly risk of complications with pregnancy, and even conception, increases with age, so this can be a risky proposition. Alternatively, if you have your children early, you can feel tugged at all ends with no end in sight."

"Just go for it," is what Anzinger would tell those thinking of starting a family. "It's going to be very rough, but it is well worth it."

Compared with the practical challenges, the rewards of parenthood are much harder to describe in a brief survey, but all the respondents emphasized that they had made the right decision.

Hagerty wrote to me, "I would make the same choices if given the chance to go back in time. Being a mother and a biologist are both essential parts of who I am, and I am so very fortunate to have the chance to fulfill both those roles."

Here is a sampling of the respondents' perspectives, edited for style and clarity.

LIFE NEVER STOPS

"My oldest daughter was born while I was working on my Ph.D. Since my wife was also a graduate student, neither of us qualified for maternity or paternity leave, and we only were allowed 10 sick days. We had to be creative with our schedules. I took the morning work shift, and my wife the afternoon. Many times I would be getting into the lab at 4 a.m. This brought about challenges when I needed to meet with others, coordinate schedules with other people, or appear at work without spit-up all over my shirt. It also brought about extreme tiredness and disorientation. My second daughter was born while I was writing my dissertation. Again, my wife and I did not qualify for leave since we were graduate students, so again we would take shifts. However, this time I would take my daughter with me to work. I would strap her to my chest in one of those baby carriers, write while she slept, feed and change her, and repeat. It worked out pretty well.

I think the best advice I could give to someone thinking of starting a family is: It is never a good time. Life never stops, and if you are one of those people who want to wait for a good time before you have kids, you are going to be waiting a long time, because a good time won't happen. Or, if it does, I wouldn't bet on your reproductive parts still functioning at their optimum."

- Philip Morton is a postdoc at the University of Oklahoma Biological Station and the father of two daughters.

TALK TO YOUR ADVISER

"The most difficult thing was finding good affordable day care, which is true no matter what profession you are in. In Seattle, there is a shortage of day-care facilities with wait lists as long as a few years. This is not hyperbole. We couldn't find a day care with openings, so we decided to team up with another family and start a nanny share, where one nanny watches the two kids at the same time. But nannies are expensive, so we invented an arrangement. The nanny watched the kids three days per week. I watched them one day per week, and the other mom watched them one day per week. That way we could afford the nanny, and I got to spend an extra day with my son. It worked because I have a very understanding adviser who didn't mind if I didn't come into lab on Thursdays for 1.5 years. His attitude is, 'You are on a salary. Just get your work done.' My lab mates were also pretty great with starting cultures for me so that I could be ready to go the next day.

Talk to your adviser ahead of time to see what his or her attitude is toward flexibility. When I interviewed for my postdoc, I didn't come out and ask him, but I did talk to members of the lab with kids and ask them how they worked out their work–life balance. Also, work out the details of maternity or paternity leave and subsequent child-care flexibility early in your pregnancy, so if there are any issues they can get worked out ahead of time. If your adviser isn't being reasonable in your eyes, perhaps there is someone else you can talk to — the head of the department or another professor."

- Catherine Konopka is a postdoc at the University of Washington, has one son and is expecting a second child.

LET GO OF THE GUILT

"I first become pregnant during my last year of grad school, and many of my student peers wondered if I was sabotaging all that I had worked for. This line of thinking is grossly unfortunate in that it perpetuates the stereotype that you cannot have children and be a scientific researcher. Also, most grad and postdoc programs are not fully prepared to support women who decide to start a family while in training, and I would like to see that change!

The hardest part for me was realizing and accepting that work–life balance is highly fickle and quite often unpredictable (you can't do anything about a puking kid on the morning of your big meeting or experiment) and to let go of the guilt involved with doing one over the other. But once someone told me that I need not apologize for doing what I had to do — that goes for work and family — I felt better about my decisions. My advice would be never to let anyone else dictate what is and what is not best for you. If you do let someone tell you how you should live your life, you are basically being bullied. And no one likes a bully."

- Jeanne Garbarino is a postdoc at the Rockefeller University and the mother of two daughters.

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Author's note: I would like to thank all the scientists who took time out of their busy lives to respond to my questions. I would particularly like to acknowledge my fellow scholars in the Faculty Institutes for Reforming Science Teaching IV program.

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THE JOURNAL OF BIOLOGICAL CHEMISTRY

Epigenetic state and fatty-acid synthesis connect

BY RAJENDRANI MUKHOPADHYAY

The influence of metabolic pathways on epigenetic states is an important area of research, because it will help us to understand connections between the environment, nutritional levels and epigenetic status. In a recent Paper of the Week in the Journal of Biological Chemistry, Luciano Galdieri and Ales Vancura at St. John's University showed that there is competition inside cells for the pool of a key metabolite and acetyl group donor, acetyl-CoA (1). The tug-of-war is played between fatty-acid synthesis in the cytoplasm and histone acetylation in the nucleus. The rate-limiting step in fatty-acid synthesis is the enzyme acetyl-CoA carboxylase, which uses acetyl-CoA to make malonyl-CoA. As Vancura explains, the fact that no one had explored the mechanism by which altered fatty-acid synthesis affects gene transcription "prompted us to study how acetyl-CoA carboxylase activity affects histone acetylation." The investigators hypothesized that reduced expression or activity of acetyl-CoA carboxylase would result in a bigger pool of acetyl-CoA in the cell and increase histone acetylation. Galdieri and Vancura tested out their hypothesis in yeast and, just as they suspected, found that the reduced expression of acetyl-CoA carboxylase boosted acetylation of histones and changed transcriptional regulation. Their data showed that, in the case of their model system of yeast, fatty-acid biosynthesis competed for acetyl-CoA with histone acetylation, affecting transcription control. Vancura says next they would like to explore how acetyl-CoA carboxylase is regulated in mammalian cells, including ones that are cancerous and involve higher levels of lipid synthesis.

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THE JOURNAL OF LIPID RESEARCH

The heartbreak of psoriasis: It's more than merely skin deep

BY MARY L. CHANG

Psoriasis is an autoimmune disease in which the rate of growth of skin cells increases as a result of the body's mistaken immune response to skin cells as a pathogen. In the 1960s, the advertising campaign for Tegrin, a medicated shampoo containing coal tar, boasted that the product relieved eczema, seborrhea and "the heartbreak of psoriasis." The cheeky phrase even reappeared in popular culture when it was referenced in the 1978 film "Grease."

Some 50 years later, it might come as a surprise to the marketing team behind the oft-quoted advertisement that psoriasis has been linked in more recent years to systemic inflammation and systemic metabolic disorders, including cardiovascular ones that affect the heart. The increased risk of cardiovascular disease was first reported in the 1970s. Epidemiological studies that followed bolstered this notion, even when the studies controlled for usual CVD risk factors such as age, sex, diabetes, hypertension, hyperlipidemia, smoking and obesity, suggesting that psoriasis independently increases the risk for CVD. Additionally, studies indicate the more severe the

A key observation in this paper is that even with modest inflammation attributed to psoriasis significant changes in HDL structure occur.

manifestation of psoriasis, the greater the risk one has of developing CVD.

While psoriasis is known to the lay community more as a problematic and disfiguring skin disease, the systemic inflammation inside the body that accompanies the disease should not be overlooked, emphasize Journal of Lipid Research Associate Editor Kenneth R. Feingold and editorial board member Carl Grunfeld, who wrote the commentary "Psoriasis: it's more than just the skin" that appears in the August issue of the JLR. It is now well documented that an increased risk of atherosclerosis occurs in other chronic inflammatory disorders, such as HIV infection and rheumatoid arthritis; these disorders cause increases in serum triglyceride levels and HDL levels that also are observed in psoriasis, which Feingold and Grunfeld point out as reasons psoriasis should be considered a model relevant to the wide array of diseases that can cause systemic inflammation that can lead to CVD.

The commentary was written in response to "Psoriasis alters HDL composition and cholesterol efflux capacity," a paper authored by Michael Holzer of the Medical University of Graz in Austria and colleagues; that article also appears in the August issue. In it, Holzer et al. explore the structure and function of HDL in patients with psoriasis. Using quantitative shotgun proteomic profiling, they determined that the composition of HDL of psoriasis patients is very different compared with healthy people.

A key observation in this paper is that even with modest inflammation attributed to psoriasis significant changes in HDL structure occur. Another notable finding is the discovery that HDL from psoriasis patients is less efficient at sending cholesterol out of macrophages, the critical first step in the reverse cholesterol transport pathway, noted for its potential importance in preventing atherosclerosis. The results of the study demonstrate that psoriasis, while widely viewed as a skin ailment whose physical manifestations often are challenging to treat, has real consequences on a molecular level, altering the structure of HDL and contributing to an increased risk for developing atherosclerosis and other CVD.

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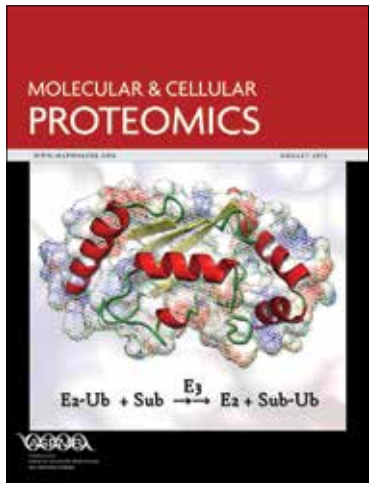
MCP **MOLECULAR & CELLULAR PROTEOMICS**

Morphine at the molecular level

BY RAJENDRANI MUKHOPADHYAY

Morphine, a potent opiate, is the gold standard in clinical medicine for relieving agonizing pain. But it is highly addictive and, outside of the clinic, plays a role in the transmission of the human immunodeficiency virus through needle sharing. Researchers have known that morphine suppresses the immune system but haven't understood how the drug causes changes at the molecular level. A team led by Joseph M. McCune at the University of California at San Francisco and Richard D. Smith at the Pacific Northwest National Laboratory addressed this question in a recent paper in Molecular & Cellular Proteomics (1). They studied three African green monkeys and three pigtailed macaques, chosen because they differ in their susceptibility to simian immunodeficiency virus, the primate version of HIV. The investigators quantified differences in the proteomes and immune responses at the organ, individual and species levels in both groups in response to morphine. As expected, both primate species showed decreased immune responses. "However, at the proteome level, we were surprised at the magnitude, in terms of numbers, of proteins that significantly changed in abundance across all tissues and fluids," says Smith. This observation suggested that there were different mechanisms at play to give the same immunosuppressive response to morphine. Because their systems-biology approach generated a detailed map of the molecular changes when a SIV-infected host ingests morphine, Smith says, the investigators can start exploring how the suppressed immune system affects other infections.



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jbc THE JOURNAL OF BIOLOGICAL CHEMISTRY

Friends and lipids

BY RAJENDRANI MUKHOPADHYAY

Friendships bring good conversation and laughter. In the case of Michael S. Brown and Joseph L. Goldstein at the University of Texas Southwestern Medical Center at Dallas, a friendship also brings scientific breakthroughs and a Nobel Prize. In a recent Journal of Biological Chemistry Reflections article, Brown and Goldstein described the genesis of their 46-year friendship as well as their research endeavors.

Brown and Goldstein first met in 1966 in Boston as medical interns at the Massachusetts General Hospital. Brown was from Philadelphia. Goldstein was from a small town in South Carolina. Despite their different backgrounds, "we were drawn together by a shared fascination with clinical medicine and medical science and a desire to one day make discoveries of significance to both," they write in the article.

After several years of research training at the National Institutes of Health, Brown and Goldstein moved in the early 1970s to UT-Southwestern. They began to study homozygous familial hypercholesterolemia, a rare disease of high cholesterol levels that causes devastating cardiovascular problems in children with the condition.

Between 1972 and 1985, Brown and Goldstein established the disease's underlying molecular mechanisms, leading to the discovery of the low-density lipoprotein receptor, its role in receptor-mediated endocytosis and how it controls blood cholesterol levels. In 1985, they were jointly awarded the Nobel Prize in medicine or physiology "for their discoveries concerning the regulation of cholesterol metabolism."

In their Reflections article, Brown and Goldstein opted not to focus on their famous work but instead discussed six projects they have pursued over the years. One project involved the study of macrophages that have receptors that scavenge abnormal macromolecules, including ones in atherosclerotic plaques. Other researchers have gone on to show that these scavenger receptors play roles in innate immunity, microbial pathogenesis and various pathologic processes, such as atherosclerosis. Another project led to the finding that blindness in little boys with an X-linked retinal disease called choroideremia involved Rab proteins. These proteins, which regulate vesicle fusion reactions, could not be modified with geranylgeranyl groups in the boys with the disease.

Another project tackled Niemann–Pick C disease, a lysosomal storage disease. The project revealed that the membrane protein NPC1 has a cholesterol binding site in its soluble NH2-terminal extension, not in its membrane domain. The finding now gives a mechanistic explanation for the disorder.

A project with ghrelin resulted in the identification of the enzyme that covalently attaches an octanoyl chain to ghrelin, which is essential for ghrelin's biological activity, and the demonstration that octanoyl-ghrelin maintains blood sugar during chronic starvation.

The two remaining projects involved the identification of monocarboxylate transporters and the possibility of the first effective treatment for a disease of the adipose tissue called lipodystrophy.

Mike Brown (right) and Joe Goldstein have a friendship that has stood the test of time.

For their voluminous scientific output, Brown and Goldstein credit their students and postdoctoral fellows, their institute and philanthropic support from members of the Dallas community, including Ross Perot. The support has been critical. "When we embarked on each of our six excursions, we had no preliminary data of the type required by review committees of the National Institutes of Health," Brown and Goldstein note in their article. All they had, they say, were "outrageous hypotheses."

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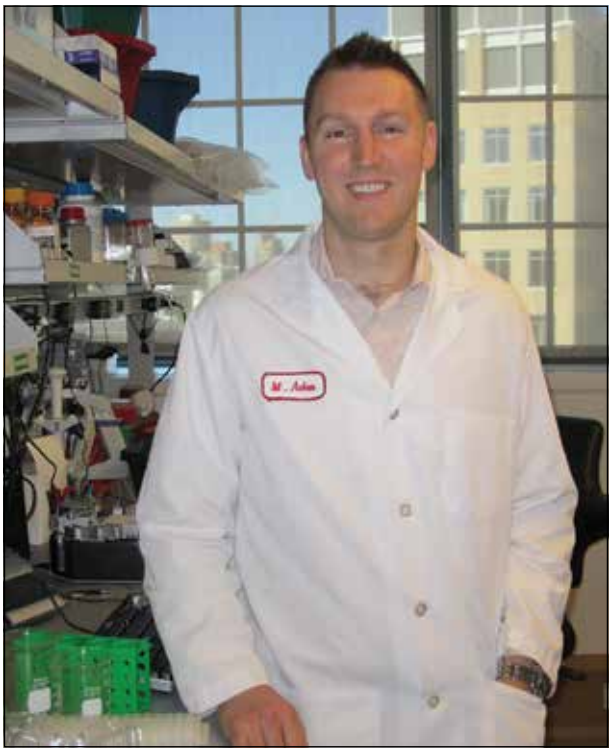
Good outcomes

BY JON LORSCH

As professors in graduate institutions, our ideas on mentoring usually began with our own experiences as students and postdocs, and by definition our experiences revolved around how to become professors at graduate institutions. In other words, we begin our mentoring careers fairly clueless about mentoring, at least beyond our narrow view of what the outcome of successful mentoring should be. But from cluelessness can spring enlightenment.

Don't we owe it both to our students and to society to help guide our trainees toward the careers that suit them best regardless of whether they fit our mold?

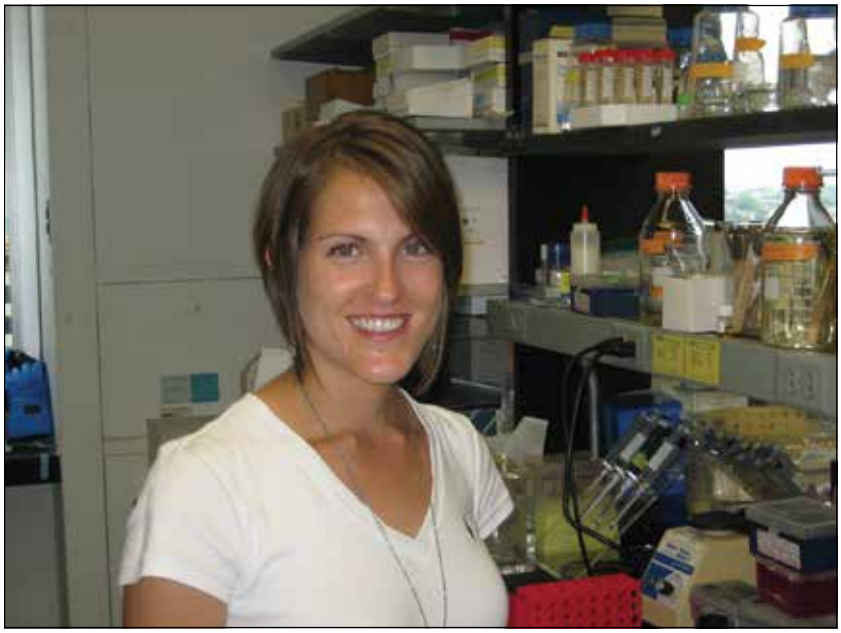
I had a mentoring epiphany recently. It sprang from the career paths of two Ph.D. students who graduated from my lab one year apart. Mike Acker was a student in our umbrella biological sciences program. As he was entering the final phase of his studies, I called him into my office and told him it was time for him to start looking for a postdoctoral position. Note that "postdoctoral position" could technically mean any job after graduating, but in this case I did mean a postdoctoral research fellow position; that's what I considered the natural path after a Ph.D. Mike was quite happy about this and did the requisite background reading and thinking, wrote some letters, went on a few interviews and landed a spot in a top-flight lab in a top-tier school. After a very successful stay there, he was hired as a senior scientist by a major pharmaceutical company. That certainly seemed like a successful outcome of a graduate education.



MIKE ACKER

Julie Takacs was a student in the same graduate program. A year after Mike graduated, I asked Julie, whose studies were then also nearing completion, to come and meet with me to discuss her postdoctoral plans. I expected her to be happy about this request, but instead I thought I detected a distinct note of anxiety in her "OK." And she did not come to see me. A week later, I again asked her to stop by. Again, no visit. It wasn't until the fourth request that Julie finally came by. When I asked her what she wanted to do next, she sheepishly said that she was "pretty sure" she didn't want to do a research fellowship and that what she was really excited about was the possibility of teaching science in a high school. It took me a second to take this in. It's not that I thought it was a bad idea; it's just that I had never really thought about it before. In retrospect, I should have thought about it, because Julie had spent much of her spare time in graduate school mentoring high school and college students, and she clearly excelled at it and took great pleasure in it. But all my training and expectations were geared toward my own experiences and goals – running a research group at a university. I was, to put it mildly, clueless.

But as the gears slowly turned, I realized that Julie, with her scientific knowledge and research training, could have a profound, positive impact as an educa-



JULIE TAKACS

tor. In fact, if you consider how many students she and others like her could turn on to science and the positive effect an influx of science-literate young people could have on our country, it is hard to argue against her chosen career path. Julie is now a Teach for America corps member teaching chemistry at an inner-city high school in Baltimore. I consider this as great an outcome of graduate education in the life sciences as Mike's position as a researcher.

The problem is that although more and more of us are having this epiphany, not everyone has yet been converted from the research-is-the-only-positive-outcome dogma to the idea that society will reap significant benefits by having well-trained scientists in a wide variety of fields, such as secondary school education, law, business, public policy, politics and journalism. Luckily, you don't have to take my word for it, because more important and famous people than me are saying the same thing. Bruce Alberts, editor-in-chief of Science magazine and former president of the National Academy of Sciences, recently called for the creation of a profession of "science adapters": Ph.D. scientists who will work in school districts across the country to develop new science curricula and better methods for teaching science in K–12 classrooms (1). Jeremy Berg, former director of the National Institute of General Medical Sciences and president of the American Society for Biochemistry and Molecular Biology, in summarizing a recent NIGMS report that concluded that society would benefit from scientists entering a wide variety of careers, was quoted in Science as saying, "We need to remove the pejorative aspect of the term alternative careers" (2). A more recent National Institutes of Health report on the scientific work force comes to the same conclusion (3).

Even without the wisdom of luminaries such as Alberts and Berg, the numbers speak for themselves: Only 15 percent of students who obtained Ph.D.s in the life sciences between 2000 and 2001 were in tenure-track faculty positions in 2006 (4). Even if it takes some students seeking academic jobs longer than six years after graduation to find them, it has become clear that the majority of Ph.D. scientists we are training today ultimately will follow alternative career paths. And our students themselves have figured out that they can have a positive impact on society using their scientific training in a variety of ways; two recent studies showed that a majority of life sciences graduate students are considering careers outside of the traditional academic research path (5, 6). Don't we owe it both to our students and to society to help guide our trainees toward the careers that suit them best regardless of whether they fit our mold? And shouldn't we consider any career path that benefits from a student's scientific training as a good outcome?

One of the goals of the ASBMB mentoring committee is to spur us to think more deeply about our roles as mentors. I hope that this column and the ones that follow will encourage you to think about what you consider to be a positive outcome for your trainees and to reflect upon what you can do to help them achieve their career goals.

Jon Lorsch is a professor in the biophysics and biophysical chemistry department at the Johns Hopkins School of Medicine and a member of the ASBMB Mentoring Committee.

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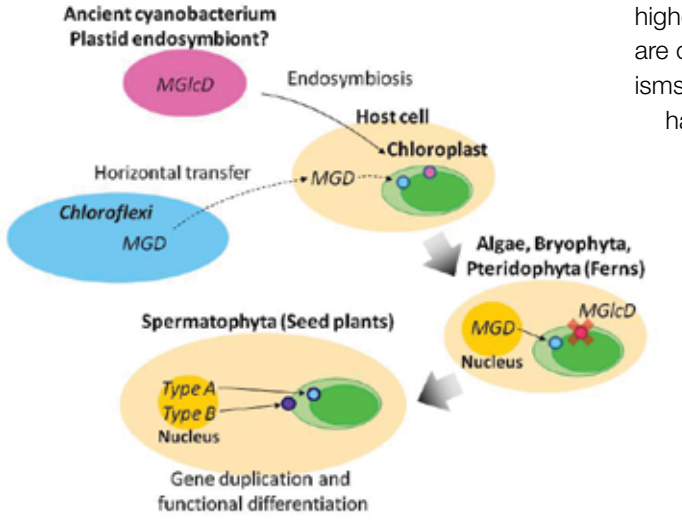
Galactoglycerolipids

Why are these lipids so commonly abundant in photosynthetic organisms?

BY HIROYUKI OHTA, YUICHI YUZAWA AND MIE SHIMOJIMA

Galactoglycerolipids, namely monogalactosyldiacylglycerol (MGDG) and digalactosyldiacylglycerol (DGDG), are commonly abundant in photosynthetic organisms, particularly in oxygen-evolving photosynthetic organisms such as cyanobacteria, algae and higher plants (1). Because these lipids are major components in their photosynthetic membranes, they have long been regarded to have important functions in their cells. Indeed, their necessity in photosynthesis, chloroplast development and embryogenesis has been shown in model plant Arabidopsis (2). Higher plant chloroplasts are thought to be acquired by endosymbiosis of an ancient cyanobacterium. In fact, membrane lipid compositions of cyanobacteria and chloroplasts greatly resemble each other. One could easily imagine that biosynthetic machineries of these membrane lipids in chloroplasts also have been derived from the endosymbiont cyanobacterium. But unexpectedly, the plant type of MGDG synthase gene has never been found in cyanobacterial genomes determined so far (3). Unlike plant cells, MGDG is synthesized by a two-step pathway in cyanobacteria. More specifically, monoglucosyldiacylglycerol (MGlcDG) is primarily synthesized by MGlcDG synthase, and then the glucolipid is further epimerized to MGDG by an unknown epimerase (4, 5). This MGlcDG synthase belongs to glycosyltransferase gene family GT2, whereas higher plant MGDG synthase is GT28 (5).



A model for evolution of higher plant galactolipid synthase

We recently revealed that higher plant MGDG synthase has rather been derived from filamentous anoxygenic phototroph Chloroflexi independently of the early endosymbiotic event of chloroplasts (3, see figure). MGDG was suggested to have an important role in a large light-harvesting complex chlorosome in some anoxygenic photosynthetic bacteria. Chlorosomes are self-assembled supramolecular bacteriochlorophyll aggregates covered with a single-layer membrane (6). The requirement of the MGDG for another anoxygenic phototroph recently was proved in the green sulfur bacterium Chlorobaculum tepidum (7). MgdA was identified as a MGDG synthase gene in that bacterium. However, only the heterozygous mutants of the gene could be isolated. The mutant analysis revealed that MGDG has an important role in the chlorosome assembly. Interestingly, the C. tepidum MgdA encodes a galactolipid synthase belonging to the GT1 family, which is largely distinct from those in Chloroflexi and higher plants. These findings indicate that galactolipids are commonly important in all photosynthetic organisms, but nevertheless their biosynthetic machineries have been established independently in each photosynthetic organism.

Galactolipids not only provide building blocks of photosynthetic membranes but also function as essential components in the photosynthetic reaction center complexes (8). Another interesting feature of galactolipids is their role in membrane lipid remodeling, in which galactolipids replace phospholipids under phosphate-starved circumstances (1). Upon phosphate shortage, higher plants globally degrade phospholipids in both plastidic and extraplastidic membranes, including plasma and mitochondrial mem-

branes. Nonspecific phospholipase C (9) and soluble phosphatases (10) are known to be involved in the phospholipid degradation and to provide phosphates sufficient for plant survival. Instead, a galactolipid DGDG is supplied as a substitute of the membrane phospholipids (11).

Higher plants acquired this type of galactolipid synthesis on the surface of the outer envelope almost 320 million years ago (in the Carboniferous period), just after Spermatophyta (seed plants) emerged (3, figure). The outer-envelope MGDG synthase (Type B) mainly supplies MGDG as a precursor for the DGDG synthesis, particularly under phosphate-starved conditions (12). This function is different from inner envelope MGDG synthase (Type A), which is crucial for the synthesis of bulk membrane galactolipids in chloroplasts (2).

We hypothesize that the acquisition of another galactolipid synthetic pathway in the outer envelope may have been one of the critical developments for the current prosperity of seed plants, because nutrient shortages might have become more common after the landing of plants. As described above, photosynthetic membranes are mainly composed of glycolipids except for about 10 percent of phosphatidylglycerol. This may have saved excess usage of phosphorus-containing lipids in the ancient ocean before the landing of plants and brought about an explosive increase in photosynthetic organisms on Earth. Seed plants have acquired another advantage to become larger in size by using galactolipids even outside the chloroplasts, because phosphorus is one of the major minerals in cell components.

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Advancing women of color in academia

Efforts are needed across the board to instill confidence and commitment to careers in STEM fields

BY MARION B. SEWER

Although all women in academia are challenged with maintaining a balance between career and family, women of color (that is, black, Hispanic, and Native American women) face additional demands that make advancement up the academic ladder even more arduous. These challenges stem from a diverse array of factors, including inherent bias, cultural differences related to the role of women as primary caretakers and excessive institutional responsibilities. Minority females not only are expected to serve on institutional committees but also to champion diversity initiatives actively. Collectively, these challenges can impair advancement.

Several studies over the past decades have demonstrated significant losses in the numbers of women of color with increased rank. These losses are particularly evident at transition points (for example, the transition from postdoctoral scientist to assistant professor, assistant professor to associate professor, and associate professor to full professor). This reduction is exacerbated by the already low percentage of women of color in science, technology, engineering and math fields and by the high percentage of women of color who hold nontenure-track positions. For example, in 2008 women of color held only 1 percent of tenured positions at non-underrepresented minority universities (1). Meanwhile, women of color represent 7.5 percent of tenured faculty at URM[1] institutions. Although the number of women who obtain STEM doctoral degrees continues to increase, the number of women of color who obtain STEM doctoral degrees is disproportionately low compared with the percentage of women of color in the U.S. population.

While these data can seem discouraging, they do point to specific targets for policy intervention. For example, mentoring programs can have positive effects and stem the losses of women of color at critical transition points. To that end, several professional societies, universities and funding agencies have implemented mentoring programs to facilitate the ascension of women of color. For example, the National Science Foundation's Increasing the Participation and Advancement of Women in Academic Science and Engineering Careers program, known as ADVANCE, is charged with implementing strategies at universities that increase the number of women who consider academic careers in the STEM disciplines. Programs supported by ADVANCE include ones aimed at developing a national networking forum for women of color at colleges and universities and providing leadership-development training for female faculty members at URM institutions.

Establishing programs to foster the advancement of women of color in academia also positively affects female students from populations underrepresented in the sciences. A 2010 study revealed that exposure to same-sex experts in academic environments engendered in female students both confidence and a commitment to pursue STEM careers (2). This exposure to female role models is particularly important given that the greatest losses in underrepresented minorities from the biomedical pipeline occur during the transitions between high school and college and between undergraduate and graduate school.

More recently, the National Academy of Sciences held a conference in June called "Seeking Solutions: Maximizing American Talent by Advancing Women of Color in Academia" to define further the problems women of color face in academia and to formulate strategies to increase their numbers. In addition to presenting data on career paths taken by minority women

Continued on page 36

A 2010 study revealed that exposure to same-sex experts in academic environments engendered in female students both confidence and a commitment to pursue STEM careers.

Rise and shine for science

Saturday Morning Science at the University of Missouri is showing that science is for everyone

BY MELODY KROLL

Experts say it won't work: a series of public science talks on Saturday mornings. How many people would give up their Saturday mornings to go listen to academics talk science?

In Columbia, Mo., more than 27,000 people, and counting.

Saturday Morning Science is a popular science lecture series held every Saturday morning on the Columbia campus of the University of Missouri. The public outreach program, which has been running continuously since 2003, has featured more than 200 talks and boasts an average weekly attendance of 150 people, the vast majority of whom are drawn from the community.

"I've been in national-level meetings where I've heard 'experts' explicitly say outreach programs like this don't work," said Bruce McClure, MU professor of biochemistry and one of the program's organizers. "The presumptions are that scientists are poor communicators and that audiences demand the kind of experience they get in science museums."

Not so, say McClure and his fellow organizers, Dawn Cornelison, associate professor of biological sciences, and Marc Johnson, associate professor of molecular microbiology and immunology.

"We all love science. We love talking about science. We love telling people about how science is cool and neat and fun and applicable," said Cornelison. "Saturday Morning Science is an opportunity to talk about the cool stuff, the stuff that excites us."

Some of the cool stuff discussed in recent talks includes microbial life at ocean vents, how frogs locate and choose mates, life as a NASA astronaut, tissue regeneration and cold fusion.

The organizers assume this enthusiasm for science and the diversity of topics are what bring people back every Saturday. According to several regular attendees, they are correct.

"I go because it is a great way to learn cool science. The scientists come across as real people who are motivated and funny and full of human foibles but who are driven and passionate," said Joseph Polacco, a retired professor of biochemistry who has been attending the talks regularly since 2008.

ALL PHOTOS COURTESY OF THE UNIVERSITY OF MISSOURI

During his talk on superconductivity, MU physics professor Paul Miceli demonstrates the temperature-dependent electrical conductivity of metals cooled by liquid nitrogen.

Similar reasons motivate retiree Raymond E. Plue's regular attendance for the past five years. "Science is so interesting and fun, and the speakers present their information in that manner. I also appreciate the wide range of science disciplines covered in the talks," he said. Plue, who compared the talks to being "not unlike the Smithsonian magazine," also has invited several of the scientists to give follow-up talks at his local Rotary meetings.

Dawn Cornelison, Bruce McClure and Marc Johnson work together to organize Saturday Morning Science at the University of Missouri in Columbia, Mo.

"If someone is contemplating starting something like this, you should not stop if you have only half a dozen or a dozen people attend. As long as the audience is engaged, that's all that is important."

– Bruce McClure, Saturday Morning Science co-organizer

If you build it, they will come

Saturday Morning Science is the brainchild of Wouter Montfrooij, an MU associate professor of physics. He adapted it from a similar program in Ann Arbor, Mich., called Saturday Morning Physics, which he attended with his father-in-law while a postdoctoral fellow at the University of Michigan. Montfrooij was attracted by the format but was interested in learning about other fields of science.

"The best way for me to do that was to get speakers to tell me about them, and I thought other people would like to listen as well," recollected Montfrooij.

He was right. McClure attended the first series of talks and was hooked immediately. McClure volunteered to help Montfrooij organize the next round of talks and also pitched in to buy donuts for the audience, which at the time numbered about a couple dozen at most.

Thinking back to those first talks, McClure reflected on how the audience has grown. "If someone is contemplating starting something like this, you should not stop if you have only half a dozen or a dozen people attend. As long as the audience is engaged, that's all that is important. We started with a handful of people

The program's budget comes from three on-campus sponsorships as well as one-time monetary gifts from local donors and from Monsanto Corp.

in the room, and now we're often packing a 250-seat auditorium. We got there by consistently having talks that people want to come hear."

Johnson, who joined the program as an organizer in 2006, echoed the importance of good talks. "I would venture to guess that 50 percent of our audience now come out of routine. They have faith the talk will be good and that they'll learn something."

Local high school physics teacher Matt Zeitz agrees, which is why he often can be seen on Saturday mornings filling up a row of auditorium seats with anywhere between 10 to 15 of his students. "I love having my students attend Saturday Morning Science. It exposes them to the myriad topics that are available for them to pursue as careers and to the spectacularly brilliant professors who present," said Zeitz.

Although Lee Elementary School teacher Sally Bloom initially was motivated to attend to receive in-service credit, "the varied and interesting talks" have kept her coming back with her husband and teenage son for the past four years. She shared that, although some talks have been "out of my knowledge base, I can honestly say I learned something new at every Saturday Morning Science I attended."

In response to enthusiastic teachers like Zeitz and Bloom, the organizers in 2009 began videotaping the talks, which they make available on the program's website (satscience.missouri.edu) and the university's iTunesU site.

Fostering an informal atmosphere

"It is simply not true that scientists are poor communicators," said McClure. "But it's important to embrace the differences between a professional talk or a teaching lecture and a public-engagement opportunity."

Some tips McClure offers speakers include staying away from jargon, starting from the basics, setting a modest goal of getting across one or two big ideas, and using a lot of visuals and ordinary language. Most importantly, however, speakers are strongly encouraged to interact with the audience through an open question format, demonstrations or activities, and by sharing items from their research. Items brought in by speakers have ranged from bear skulls and live bats to DNA and compost. Previous speakers also have arranged visits to facilities, including Columbia's research reactor and a research farm.

Such interactions help foster an informal atmosphere, which, according to McClure, has been an essential element of the program's continuing success. "There are few opportunities for that kind of person-to-person engagement between scientists and an interested audience. People cherish the time to engage scientists one on one and vice versa," said McClure.

Refreshments also help. The vast majority of the program's budget goes toward providing simple refreshments, such as donuts, bagels, juice and coffee. The program's budget comes from three on-campus sponsorships as well as one-time monetary gifts from local donors and from Monsanto Corp.

The organizers do not claim running the weekly program is easy. "It's a labor of love," said Johnson, who mentions giving up 24 Saturday mornings a year as one of many responsibilities involved in running the program.

Thus, it is perhaps the organizers' shared commitment to science and science outreach that is at the heart of the program's success.

"It is our responsibility as scientists to communicate what we do to the public," remarked Johnson. "The divide between what scientists do and what the public understands seems to be increasing. I like to think we're giving the public the tools to think about what we do as scientists and its applicability to all our lives."

"Plus," he added, "I enjoy the talks myself."

Melody Kroll (krollmm@missouri.edu) is executive staff assistant for the division of biological sciences at the University of Missouri. She also regularly attends Saturday Morning Science.

Saturday Morning Science website: http://satscience.missouri.edu

Those who want more information about the program or tips for starting a similar program in their own towns can contact Bruce McClure at mcclureb@missouri.edu

Exposing students to various career options early in graduate training

BY CAROLYN MACHAMER

When should Ph.D. students begin to think about what they want to do when they graduate? What is the best mechanism for exposing them to diverse career paths? How can faculty members at research institutions advise their students on careers they know little about? And how do we prevent students from prolonging their training because they are not sure what they want to do next? These are questions graduate program faculty members and administrators across the country are trying to answer. Here, I describe a recent experiment at the Johns Hopkins University School of Medicine that we conducted to address these issues.

The impetus

Only a fraction of biomedical Ph.D. trainees eventually obtain academic faculty positions, and the National Institutes of Health now recognizes that society can benefit from well-trained scientists working in different careers (1, 2). The Biochemistry, Cellular and Molecular Biology Graduate Program at Hopkins, of which I am director, has a long history of training successful biomedical researchers. But we never have offered opportunities to our students to explore careers outside of academia. Our institution has an excellent professional development office that sponsors workshops on preparing curricula vitae and résumés and interviewing for jobs and occasional career seminars. However, our students are not taking full advantage of these opportunities.

The experiment

We instituted what we're calling career-exploration workshops. We tapped into our extensive program alumni network to find participants who could hold informal discussions with current students. The goal was to get students to start thinking about the variety of career paths early in their training, to help them become competitive in a career that interested them the most and to foster networking with professionals outside of academia.

Third-year students were required to attend at least one of four workshops held in May. The topics were chosen based on student interests: undergraduate teaching, science writing and editing, the biotechnology and pharmaceutical industries, science policy, government and technology transfer. Each workshop included a recent graduate as well as one or two more seasoned graduates to offer different perspectives. The workshops were not career fairs but rather informal discussions with lots of time for questions.

An advanced student who attended all the workshops said her desire to strive for an academic position at a research-intensive institution was solidified after hearing about other careers.

The outcomes

Many third-year students attended at least two of the workshops, and some attended all four. Because this was the first time we held the workshops, students beyond their third year also were invited; they made up half of the audience at each session. The discussions were lively and included a broad set of questions for discussion leaders. Several common themes emerged, including the importance of networking, developing good communication skills and obtaining relevant experience in the career of interest.

Students reported that they found the workshops helpful, and some already have contacted one or more discussion leaders. Most third-year students said they felt it was not too early to begin thinking about how they want to use their degrees. Many said it was useful to meet alumni at both early and later career stages. An advanced student who attended all the workshops said her desire to strive for an academic position at a research-intensive institution was solidified after hearing about other careers. Another excellent outcome was that a student interested in science writing later

Continued on page 36

Reader comments

Demand is high for ASBMB-sponsored career symposia

This is such a great idea. Career planning is very big in many trainees' minds at the moment. We've seen an upsurge in demand for similar events at Yale. A Women in Science at Yale alumni career panel of three young alumna drew 90 students and postdocs, and a new student organization, Career Network for Yale Science Ph.D.s, has helped coordinate a number of well-attended events, such as a panel, networking session and dinner with speakers from defense careers.
— KRISTY LAMB, PH.D. CANDIDATE AT YALE UNIVERSITY

Five years of giving rural students second chances

The Aspirnaut Program will probably be something I can hold on to for the rest of my life in whatever I do. By working in the laboratory at Vanderbilt as part of this program, I have gained unprecedented knowledge that I wouldn't receive at my high school -- probably not till college. Dr. Billy Hudson … was always supportive and reminded me I was special. Every day, I walked into the lab with a new goal, a new responsibility and a new set of skills that will always be with me. From this program, I received an awesome amount of experience in a top laboratory in the country, but most importantly I gained new access to what I could become. … I don't know what I want to be -- between an engineer, doctor, researcher and a businessman. As a Junior at Omaha High School in Omaha, Ark., I can only say, "Thank you, Dr. Hudson, for everything!" — BRENNAN BOONE

The Aspirnaut program changed my perspective about everything I knew about college. It gave me the confidence within to believe that I can achieve the dreams I had but thought would not come true. I know now that I am capable of anything I put my mind to. I owe a huge thanks to Drs. Billy and Julie Hudson. They are wonderful people who know just how to get involved with young people and give them an opportunity to become more knowledgeable. This was one of the best experiences of my entire life, and I would not have as much knowledge as I do had I not gone. I really cannot thank you more for making it possible to come to Vanderbilt and do research. It's really amazing that this had been made possible for all these kids. I am proud to be called an Aspirnaut student and hope to stay one for life. Thank you for giving perspective and confidence this summer. I had a really great mentor, and the time spent at Vanderbilt this summer was amazing. Thank you once again! — HALEY HARRINGTON

Send your letters to asbmbtoday@asbmb.org.

The buzz on the blog

Mucus, flatworms and us:

In a recent paper in Molecular and Cellular Proteomics, researchers showed that the freshwater planarium Schmidtea mediterranea has proteins in its mucous coating that are strikingly similar to ones in human mucus and other secretions, such as tear fluid. Some of the matches made sense. Others, well, not so much.

Rodent meals affect drug tests:

Researchers at the University of New Hampshire analyzed 54 studies and concluded that, in rodents, having free access to food is likely to affect the results of tests for the toxicity and cancer-causing effects of new drugs and other substances.

Visit wildtypes.wordpress.com.

Continued from page 30

in academia, the speakers addressed differences in gender biases across races and ethnicities, the role of federal funding agencies in effecting change, initiatives developed by professional societies and new strategies for implementation.

While it is clear that large-scale, global initiatives are warranted to increase the number of minority women in academia, individual minority and non-minority faculty members nationwide also can take steps to foster the development of minority female trainees at all levels.

[1]URM institutions are historically black colleges and universities, tribal universities, and universities that are more than 50 percent minority serving.

Marion B. Sewer (msewer@ucsd.edu) is an associate professor at the Skaggs School of Pharmacy and Pharmaceutical Sciences at the University of California, San Diego, and a member of the ASBMB Minority Affairs Committee.

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Continued from page 34

initiated a student-produced newsletter, which will be distributed electronically to current and former students as well as faculty members.

The future

From my perspective, putting together these workshops was gratifying. The response from our students was positive. I was concerned that it would be difficult to recruit discussion leaders, but, amazingly, all 11 alumni whom I invited agreed enthusiastically. Clearly, this experiment was successful and will become a regular feature of our program. The next step will be to determine the best mechanism for instituting optional internships that will further promote career exploration.

Carolyn Machamer (machamer@jhmi.edu) is a professor in the department of cell biology and the director of the biochemistry, cellular and molecular biology graduate training program at the Johns Hopkins University School of Medicine.

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Short-Chain Phospholipids as Detergents

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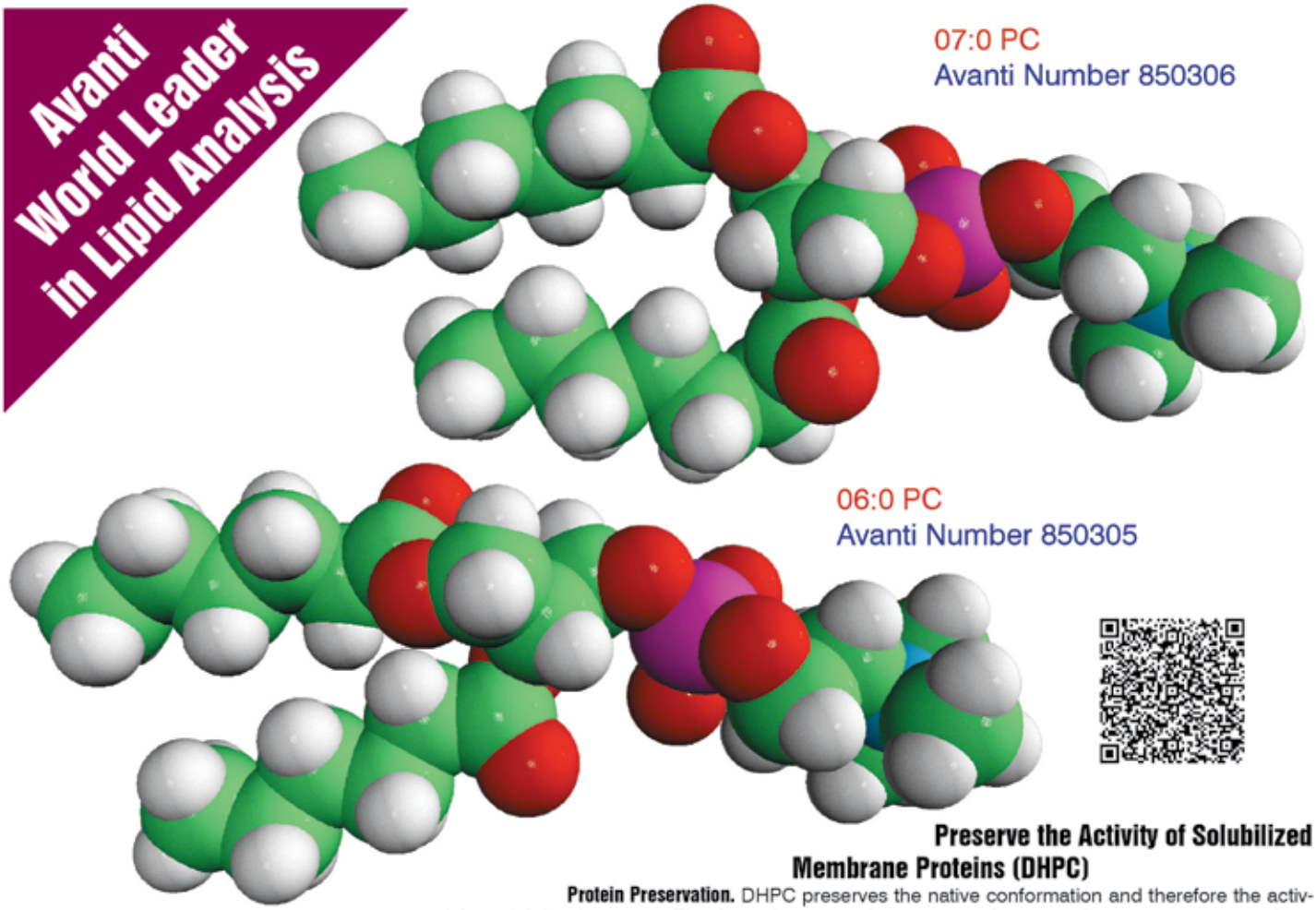

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Solubilization Mechanism. DHPC is thought to exert a wedge-like effect on the neighboring lipids, mainly due to its bulky polar group and short hydrocarbon chains. This produces membrane destabilization at relatively low DHPC concentrations. All membranes investigated are solubilized at an identical DHPC/lipid ratio. This finding is taken as evidence that DHPC primarily interacts with the lipid bilayer and not with the membrane proteins. The principle underlying the preservation of the native protein structure is the inability of DHPC to displace intrinsic membrane lipids from integral membrane proteins.

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Lyso PG	14:0, 16:0, 18:0 & 18:1 Lyso PG
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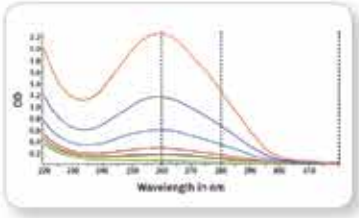

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