ASBMB today

June 2012

SPORTS DOPING

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- Profile of George Stark

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This conference will bring together a diverse group of scientists who seek to define how the conformations of cellular proteins are achieved and maintained, and what happens in the cell when aberrant protein conformations arise. By definition, the scientific presentations at this meeting emphasize the use of cutting-edge techniques in biochemistry, biophysics, and computational science, and in genetics, cell biology, and imaging technologies. Because a growing number of diseases are linked to alterations in protein folding and structure, there is a strong emphasis on the impact of specific proteins in human health, aging, and disease. In addition to talks from known leaders in this field, ample time is set-aside for formal and informal scientific discussions and for highly interactive poster sessions.

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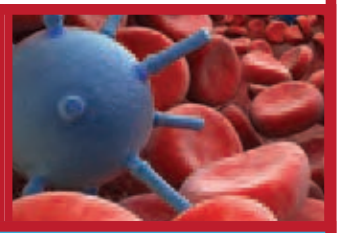

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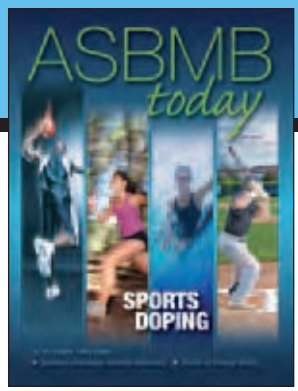

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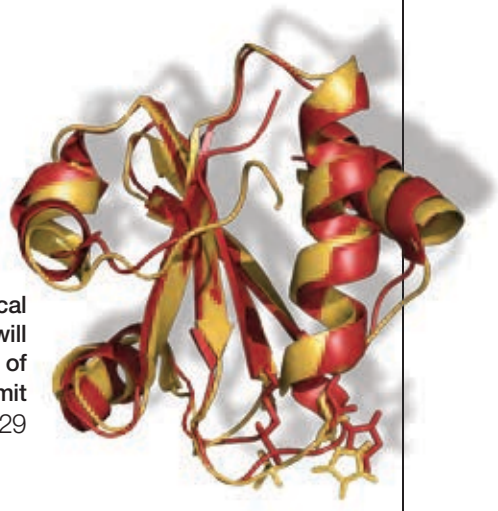

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Complementary skills: *communicating*

Last month, ASBMB Today contributor Aruni S. Arachchige Don launched her online-only series about the skills that young scientists should acquire to advance their careers— both inside and outside of the lab. It seems her message resonated with readers, as her introductory column was consistently one of the most-read articles on the site. Don't miss her column this month about written and oral communication.

The making of a science policy fellow

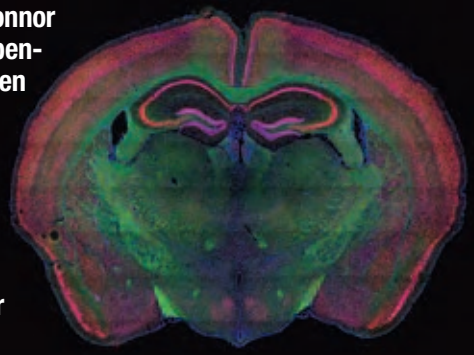
If you've ever met ASBMB science policy fellow Julie McClure— say at the annual meeting tweetup or on Capitol Hill— you probably wouldn't describe her as shy. In the online issue, ASBMB Today contributor Pumtiwitt McCarthy profiles McClure to let us know how the gutsy woman went from the lab to the halls where laws are made and what kind of advice she has for scientists in a variety of scenarios. A sneak peak: "Stop referring to careers outside of academia as 'alternative.' If only one out of 10 biology Ph.D.s becomes tenured faculty at an R1 university, then academia is the exception— not the rule."

MORE MEMBER NEWS

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.

Big bucks for brain research

ASBMB Today contributor Connor Bamford reports on the happenings at the Seattle-based Allen Institute for Brain Science, which just got an infusion of $300 million from Microsoft co-founder Paul G. Allen, bringing his total financial investment in the independent research center to a reported $500 million.



Thank you, ASBMB

BY SUZANNE PFEFFER

It is hard to believe that my two-year stint as president of the American Society for Biochemistry and Molecular Biology will end in a few weeks' time. Without reservation, service to this society has been a rich and rewarding experience. I have had a chance to meet and work with some wonderful people, I have learned many lessons, and I feel energized to continue to do what I can in support of the community of scientists at large.

I owe a special thanks to ASBMB staff members, who are outstanding and do so much behind the scenes to enable our society to operate smoothly. Our executive director, Barbara Gordon, has assembled a terrific team that works together to produce our journals (overseen by Nancy Rodnan), organize our meetings and workshops (overseen by Joan Geiling, Jlynn Frazier and Weiyi Zhao), and oversee our finances (Steve Miller). Thanks to every member of the ASBMB staff for all you do on our behalf.

Joan Geiling has been ASBMB's meetings manager since 2004. We have her to thank for all the behind-the-scenes work on our annual meetings.

Geoff Hunt, formerly an ASBMB science policy fellow, now is the society's outreach coordinator. Next month, look for his new outreach column in ASBMB Today.

I am proud to have helped recruit new editors-in-chief — for the Journal of Biological Chemistry (Martha Fedor) and ASBMB Today (Angela Hopp) — and also to have recruited a new director of public affairs, Ben Corb. We have created a new Public Outreach Committee led by Geoff Hunt, our former public policy fellow, and Lee Gehrke and established a new mentorship committee led by Fred Maxfield. We initiated ASBMB-sponsored career symposia around the country, at which students and postdoctoral fellows meet with alumni of their own institutions to learn about the breadth of career choices that await biochemistry and molecular biology Ph.D.s.

I had the pleasure of supporting the creation of new awards, including the Alice and C.C. Wang Award for Excellence in Molecular Parasitology, the new Mildred Cohn Award for contributions to biochemistry using physical approaches, and an enhanced award to honor Herb Tabor for his lifelong service to ASBMB and the JBC. Tabor is a truly remarkable man — it has been a special treat for me to get to know him a little better during my term.

Under Ben Corb's direction, ASBMB has had more than 250 visits with lawmakers since September 2010.

A great deal of the work accomplished by the ASBMB is done by volunteers who contribute their ideas, energy and time to make the world of science a better place for all of us. To our council members, committee chairs and committee members, thank you for your good work and willingness to give back. No one has enough time these days, yet these ASBMB members find time to contribute. I enjoy participating in ASBMB committees because it gives me a chance to meet new people and interact with colleagues whom I would not normally

have the opportunity to work with. The projects undertaken require creative problem solving — a process that most scientists enjoy. Teaming up with my counterparts from different institutions helps me to feel that I am part of a much larger family of biochemists and molecular biologists. We share a common language, culture and lifestyle and share joys and challenges alike. I hope each of you will consider volunteering some of your time to participate in the larger family of science.

Merle Olson of the University of Texas Health Science Center began his term as treasurer in 2009 and will complete it this month.

Two ASBMB leaders deserve special recognition. Merle Olson has served as the ASBMB's treasurer for the past several years and has done an outstanding job of overseeing our finances and investments. As he completes his term at the end of this month, know that our investments have fully recovered from the economic downturn and are performing well at this time. Toni Antalis will assume the role of treasurer in July, and she has worked closely with Merle this year to learn how society finances operate.

Joan Conaway will step down as chair of the Meetings Committee. A former councilor, Joan has a long record of service to the ASBMB and has been a wonderful mentor to all the program chairs who worked with the committee to develop our annual meeting programming. Heartfelt thanks to Joan for all her efforts. Dan Raben will become chair of the Meetings Committee at the end of this month.

PHOTO: JAY CASILLAS, STOWERS

Many thanks to Joan Conaway of the Stowers Institute for Medical Research for her leadership of the society's Meetings Committee.

Another highlight of my term was the opportunity, earlier this year, to testify in support of science funding before the Labor, Health and Human Services, Education, and Related Agencies Subcommittee of the U.S. House of Representatives' Committee on Appropriations. This committee sets budgetary priorities for the U.S. Department of Health and Human Services, which includes the National Institutes of Health. Corb has been nurturing relationships with staff members of this committee to help the ASBMB continue to be a valued contact when science-funding issues arise. Since Corb joined the ASBMB in September 2010, we have had more than 250 visits to more than 100 member of Congress. Julie McClure, the ASBMB's science policy fellow, has worked closely with Corb to train our members how to talk with their congressional representatives and explain the importance of science and science funding.

Jeremy Berg of the University of Pittsburgh will take over as ASBMB's president in July.

I am extremely pleased that my successor, Jeremy Berg, is so well qualified to lead the ASBMB over the next several years. Last month's President's Message included a number of lab credos for the practice of science. At a recent dinner to honor our ASBMB annual award winners, each awardee was asked to share his or her favorite credo. Jeremy contributed one of the best: "When a student complains that nothing is working, I tell that student to get a large beaker, fill it with water and heat it to 100°C. Water always boils." Know that the ASBMB is in very good hands. It has been an honor to work with Jeremy in his capacity as president-elect this year, and I will continue to support him in my role this coming year as past president of the ASBMB.

Thanks to each of you for the privilege of serving. XOXO

ASBMB President Suzanne Pfeffer (pfeffer@stanford.edu) is the Emma Pfeiffer Merner professor of medical sciences and a biochemistry professor at the Stanford University School of Medicine.

100 meetings: It starts with you

BY BENJAMIN CORB

If you are a regular reader of this column — or even if this is your first time — you are without doubt aware of the dire situation science funding faces in this country. The bottom line is that federally funded research, which many feel is the key to improving our nation's financial situation and the solution to many of the world's challenges, is limited by financial constraints as our nation's leaders grapple with a sluggish economy and crippling debt crisis.

Members of Congress across the political spectrum see value in investing in research and development and in agencies like the National Institutes of Health and the National Science Foundation. These agencies are easy to support, considering the public good that comes out of that research combined with the substantial positive economic effects that come from funding basic research. However, what was once a slam dunk for advocacy lately has been a tougher sell. "I'd love to increase the NIH budget… if we had more money to spend" is a line I hear often.

If you are a regular reader of this column, you've seen advice on how to talk to your elected representatives and reports on the American Society for Biochemistry and Molecular Biology's efforts to change attitudes toward funding research. You've read quotes from students and faculty who have come to Washington, D.C., to advocate for NIH funding. Maybe you yourself have thought about participating, if only you could afford to leave the classroom, lab or office for a three-day trip to Washington.

This summer, the Public Affairs Advisory Committee, the advocacy arm of the ASBMB, is challenging members nationwide to get involved. This being an election year, members of Congress will be spending much of August and October in their home districts meeting constituents and campaigning for votes. The time is right for members of the scientific community to meet with their representatives and talk about all the wonderful research that is going on in laboratories in members of Congress' own backyards. Members of Congress focus on the issues their constituents consider important. The ASBMB wants to show Congress that there are literally thousands of researchers who think science funding is a vitally important issue for both the health and the economic future of our nation. However, we can only do that if our members are the ones doing the talking.

So here's the challenge. Can we find 100 volunteers from the ASBMB membership who will meet with their representatives in their home district offices? ASBMB public affairs staff will set up the meeting, provide you with background information and talking points, train you to communicate your science to a nonscientific audience, and even go with you to the meeting if that's what you'd like. The ASBMB public affairs staff will do as much (or as little) as you request to make your meeting a resounding success and to find converts among policymakers — converts who will come back to Washington energized and supportive of the scientific endeavor.

The question is this: Who will be the first volunteer? XXXX

Benjamin Corb (bcorb@asbmb.org) is director of public affairs at the ASBMB. Follow him on Twitter at www.twitter.com/bwcorb.

asbmb member update


DARNELL


ROEDER


LEVY


VARSHAVSKY

Darnell, Roeder win nation's largest prize in medicine

James E. Darnell Jr. and Robert G. Roeder, both of The Rockefeller University and pioneers in the field of gene regulation and expression, won the Albany Medical Center Prize in Medicine and Biomedical Research, the nation's largest prize in medicine. Darnell leads the Laboratory of Molecular Cell Biology at Rockefeller, and Roeder leads the Laboratory of Biochemistry and Molecular Biology. They will share the $500,000 prize. Medical center officials said they recognized the pair for giving medical professionals and researchers tools to improve health and combat diseases. "Jim Darnell and Bob Roeder have been at the forefront of our understanding of gene expression since their first groundbreaking discoveries in (eukaryotic) RNA (synthesis and) processing more than 40 years ago," Rockefeller's president, Marc Tessier-Lavigne, emphasized. "Their contributions to this field have provided indispensable support to scientists and physicians in the fight to understand and combat diseases like cancer, heart disease and autoimmune disorders."

Levy is recognized with a lifetime achievement award

Stuart B. Levy, a distinguished professor of molecular biology and microbiology and of medicine at Tufts University School of Medicine, won the American Society for Microbiology's top award for his sustained contributions. Levy "has dedicated most of his life to antibiotic resistance," his nominator, Hiroshi Nikaido of the University of California, Berkeley, said. "Throughout his career, he has not only elucidated the genetics and biochemistry of one of the most important mechanisms for drug resistance but also strived to minimize the selection and spreading of resistant bacteria." Levy is credited with discovering the inner membrane Tet protein, which pumps tetracyclines out of the cell. He also discovered regulatory operon mar RAB, which regulates the expression of multidrug resistance and virulence, and coined the term "societal drugs" to describe antimicrobials. He is also known for a landmark paper demonstrating the effects of antibiotics found in animal feed on the environment and the transfer of resistant bacteria from animals to farm workers.

The Otto Warburg medal for Varshavsky

The German Society for Biochemistry and Molecular Biology has named Alexander Varshavsky of the California Institute of Technology the winner of the Otto Warburg Medal, the highest German award for biochemists and molecular biologists. Varshavsky's group discovered the first and major biological functions of the ubiquitin system and the first degradation signals in short-lived proteins. It also cloned the first ubiquitin ligases. The Otto Warburg Medal has been awarded by the society since 1963 to honor pioneering achievements in fundamental biochemical and molecular biological research. Thus far, seven of the winners have gone on to receive the Nobel prize. The award includes a prize of 25,000 euros.

Congrats are in order!

Ten members of the society were named new members of the National Academy of Sciences:

Nancy Bonini
Gideon Dreyfuss
Paul Englund
Rachael Green
Tina Henkin
Sabeeha Merchant
Roy Parker
Gisela Storz
Richard Young
Louise Chow

The following have been elected into the American Academy of Arts and Sciences:

James M. Berger
Thomas Curran
Sarah Carlisle Roberts Elgin
Danny F. Reinberg
Brenda A. Schulman

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SPORTS DOPING:
an extreme game of biology

Cheating athletes manipulate various aspects of molecular biology and medicine to improve their performance.

BY RAJENDRANI MUKHOPADHYAY

As London gears up for the 2012 Summer Olympic Games, cheating athletes and antidoping officials continue their game of hide-and-seek. Doping is as old as sports itself, but the past few decades have seen the phenomenon grow more sophisticated. As our understanding of molecular biology, biochemistry, pharmacology and medicine improves, athletes become even more cunning in their exploitation of advances in these fields.

Enhancing sporting prowess goes back to the ancient Greeks, who used special diets and concoctions to improve their athletic abilities. In the 19th century, cyclists and other endurance athletes dabbled in molecules like strychnine, caffeine and cocaine. But doping exploded in the 20th century with advances in molecular biology and pharmacology. The Danish cyclist Knud Enemark Jensen died during competition at the 1960 Rome Olympic Games after taking amphetamines. With the introduction of synthetic anabolic steroids for increasing muscle mass in the 1960s, sporting authorities knew they had to take action. Testing for stimulants began in 1967; in the 1970s, the International Olympics Committee started to test for anabolic steroids.

These days, testing for performance-enhancing substances and techniques is routine and has a unified front. The World Anti-Doping Agency, established in 1999, is an independent foundation of the IOC. It works with intergovernmental organizations, governments, public authorities, and other public and private entities to stay at the forefront of the fight against sports doping. WADA has research programs to support investigations into ways molecular biology, biochemistry, analytical chemistry and pharmacology can be applied to fight doping. It also maintains an extensive list of prohibited substances and methods for performance enhancement.

ABUSE OF BIOLOGICAL MOLECULES AND DRUGS

Medicines, designer drugs and biological molecules are popular in the doping world despite the fact that authorities have safeguards in place for most of them. A classic example is erythropoietin, known as EPO. It's a glycosylated protein hormone that stimulates bone marrow to produce red blood cell precursors. In the 1980s, the biotechnology company Amgen introduced the first synthetic version of EPO, called Epogen (1). The drug was designed to treat anemia in patients suffering from chronic kidney disease and other illnesses that cause a drop in red blood cell count.

But cheating athletes immediately saw the drug's potential to increase their blood's oxygen-carrying capacity during competition. Twenty-six years after the introduction of Epogen, synthetic variants of EPO still dominate the list of preferred doping agents. "EPO continues to be a problem because it's so potent and works so well," says sports doping expert Don Catlin at Anti-Doping Research. So many cyclists were caught doping with EPO and other drugs during the 1998 Tour de

France that the media dubbed that year's competition the "Tour de Shame."

A detection method for EPO based on isoelectric focusing exists (2). But as Catlin notes, "There is a variety of ways to hide [EPO] and stay underneath the radar." The method looks for the differences in glycosylation that make endogenous and synthetic versions of EPO migrate slightly differently on the gel. The biggest limitation of the test is that it can detect a synthetic EPO only if the drug is taken within two to five days of testing. The testing is also time and labor intensive, for it takes 48 hours to complete and is finicky. "In that context, it's not the greatest test in the world," says Catlin. "But it keeps nailing a small percent of those who are using EPO."

"If an athlete were ever to be in a position to add an extra gene of EPO or growth factor, they can gain a significant advantage."

Testosterone, an anabolic steroid, is another popular drug for abuse. Catlin's group developed a carbon isotope ratio mass-spectrometric analytical approach in the 1990s to catch it (see sidebar). The test snagged U.S. sprinter Justin Gatlin, who won gold medals in the 2004 Games, and 2006 Tour de France winner Floyd Landis. Major League Baseball player Ryan Braun was accused of testosterone doping earlier this year but had his positive test result overturned in court when his legal team argued that his urine sample had not been handled according to protocol.

Other abused biological molecules include synthetic versions of human growth hormone and luteinizing hormone, which is involved in testosterone production. These hormones present challenges in detection to antidoping researchers. "Our job is always to differentiate between the naturally circulating substance from the doping agent. Whatever is identical to the human body is very difficult for us to identify and to prove that this substance was a misuse of a drug rather than a natural variation," says biochemist Mario Thevis at the German Sport University. Most of the methods for detecting doping rely on chromatography and mass spectrometry.

Drugs available on the market aren't the only headaches for antidoping authorities. A major component of the antidoping efforts is developing detection methods for pharmaceuticals not yet on the market. Thevis gives the example of selective androgen receptor modulators, which are a new type of anabolic agents in phase III clinical trials. They stimulate growth of muscle and bone. The potential drugs already are being abused, says Thevis, pointing to the case of Jamaican 400-meter runner Bobby-Gaye Wilkins, who was banned from the world championships in Doha in 2010 after she tested positive for a selective androgen receptor modulator called Andarine. That case, says Thevis, "demonstrated we are not chasing ghosts. We are going after drugs that are not yet approved for the market but are definitely being misused by elite athletes."

The BALCO scandal of 2003 illustrated that some athletes were willing to take drugs that federal agencies and antidoping authorities didn't even know existed. BALCO was a company that illicitly provided athletes with a substance known as "the clear" that was later identified by Catlin's group to be the molecule tetrahydrogestrinone. THG is an anabolic steroid that binds to the androgen receptor to boost muscle mass. Federal law-enforcement authorities eventually caught a number of athletes who used it, including British 100-meter sprinter Dwain Chambers, American sprinter Marion Jones and MLB player Barry Bonds.

BLOOD AND GENETIC TRICKS

Blood doping is another matter: Cheating athletes get clinicians in their entourages to dupe the hemoglobin count test by adjusting their red blood cell counts before and after competition. In some cases, authorities track the volume percentage of red blood cells. In a tricky manipulation, cheaters increase their red blood cell counts by taking drugs like EPO during the off-season. They withdraw the hemoglobin-rich blood and refrigerate it. When competition season starts, once the antidoping inspector leaves with blood samples from the athletes for testing, the

cheaters transfuse the stored blood back into their bodies and head out to compete loaded with extra hemoglobin. After the competition, they quickly withdraw some blood to bring their red blood cell count back to normal and wait for the antidoping inspector to do the post-competition test. Just as with some synthetic hormones, there isn't a good way to tell apart stored red blood cells from ones that are currently circulating in the bloodstream to catch blood doping.

Genetic manipulations have been on WADA's radar screen for a decade, although no athlete has yet been caught using them. Gene doping is essentially the flip side of gene therapy. Gene therapy has made recent gains in treating illnesses like genetic-based severe combined immunodeficiency disease and Leber congenital amaurosis, a retinal disease that progresses to total blindness by adulthood.

Because of gene doping's growing potential, WADA's science director, Olivier Rabin, says the agency has been proactive against its exploitation. "If an athlete were ever to be in a position to add an extra gene of EPO or growth factor, they can gain a significant advantage," he says. "We believe that this technology one day will be an option for some athletes who will not hesitate to consider it."

Gene doping is certainly attractive to manipulate muscle, blood and pain-perception systems — "anything that enhances the ability to train and to deliver blood to exercising tissues and to increase endurance or explosive muscle function," says Theodore Friedmann at the University of California, San Diego, a gene therapy expert who helped to establish the organization's research program in the area.

He says while gene doping isn't yet reality, "there have been some high-profile instances of very prominent athletic trainers making attempts to obtain genetic tools, like the viral vectors that express transgenes." Friedmann cites the 2006 case of a German trainer, Thomas Springsteen, who was arrested and brought to trial for making attempts to obtain Repoxygen, a drug that was in preclinical trials to put an erythropoietin gene into patients suffering from bone marrow failure from chronic kidney disease or cancer.

ALWAYS SEEKING NEW ANTIDOPING TOOLS

Detecting gene and other forms of doping is complicated for authorities, because they are limited in the types of samples they can take from athletes. They can't do anything as invasive as muscle biopsies,

so they have to rely on techniques that can detect doping in blood and urine. The experts cite the relatively new -omics methods as potential ways to better catch doping. "We believe they are going to be an important component of our arsenal," says Rabin. "We have different projects looking at all the different levels of -omics."

Rabin says WADA researchers have some interesting concepts in the works, such as looking for the molecular signatures of doping. "When an athlete dopes with a substance or a cocktail of substances, she or he is looking for a physiological impact. It's to enhance transfer of oxygen, muscle mass and other different physiological capabilities," says Rabin. "These create an imbalance in the body's homeostasis that we believe will be reflected at different -omics levels." He says a challenge researchers are facing is distinguishing between signatures caused by physical exertion, which elite athletes do intensely, and those signatures caused by doping.

For now, the thinking is that -omics technologies are not quite there yet for antidoping enforcement. Molecular geneticist James Rupert at the University of British Columbia in Canada received WADA funding to explore the possibility of using RNA transcripts to tell if an athlete has doped with EPO. "The test I was proposing would work for any source of erythropoietin, including gene doping," he says.

But he says his group concluded after preliminary work in mice that there wasn't sufficiently robust differential gene expression to be detected reliably in urine or blood. Rupert says there probably are differential gene expression patterns at the tissue level, but that doesn't help antidoping authorities, because they cannot sample tissues. He adds that also compounding the problem is that the genetic variation and background frequencies of people cover a wide range. This is an impediment because "we really wouldn't have any specificity for our test," says Rupert. "It's very important with a doping control test that you have high sensitivity and specificity, because you don't want to falsely accuse people."

To better track athletes and understand their individual physiologies, WADA implemented the Athlete Biological Passport program in 2009. The program tracks athletes throughout the year — not just at competitions — to make sure that they are not using performance-enhancing substances or methods. Antidoping authorities take measurements for blood, endocrine and steroid parameters to know what an athlete's normal physiological range is and to find deviations.

The beauty of the biological passport, says

Molecular quirks in sports

Molecular biology presents interesting riddles to the antidoping world. An example is the story of Finnish cross-country skier Eero Mäntyranta. Mäntyranta won three gold medals in the Winter Olympics of 1964 and was suspected of doping. Tests showed that he had 15 percent more red blood cells than normal, but he didn't have signs of blood doping.

In 1993, the group of Albert de la Chapelle at the University of Helskini in Finland demonstrated that a genetic mutation produced a truncated erythropoietin receptor (3). Mäntyranta carried the mutation. In 1995, Harvey Lodish's group at the Whitehead Institute showed this truncated receptor was insensitive to a feedback loop that would turn it off. The receptor's malfunction meant that the bone marrow produced more red blood cells than normal (4).

Don Catlin at Anti-Doping Research gives another example of molecular biology complicating doping detection. For the testosterone-detection technique developed by Catlin's group, the test looks at the ratio between testosterone and epitestosterone, a version of testosterone that has no known function. In normal men, the ratio is 1:1. But in an athlete doping with testosterone, the ratio goes up. WADA sets a T/E ratio of 4:1 or higher as the possible sign of doping.

In developing the test criteria, Catlin noticed that the testosterone levels in some of the Asian male study participants never fluctuated, even though he knew he was injecting them with synthetic testosterone. In terms of doping, this would give certain athletes "a license to steal," says Catlin.

For testosterone to be excreted in urine, it has to be first turned into a glucuronide conjugate by uridine diphosphoglucuronosyl transferases. Catlin began to suspect these Asian men had deletions in one of these enzymes.

In 2006, the group of Anders Rane at the Karolinska University Hospital in Sweden published findings that explained Catlin's observations. Rane's group described how double deletions in the gene for UGT2B17, the enzyme that does most of the glucoronide conjugation to testosterone, led to differences in testosterone excretion between Korean and Swedish men. The Asian men had very low T/E ratios (5). The polymorphism is almost seven times more common among Koreans than Swedish Caucasians.

Rupert, is that "you're serving as your own control… Every time I measure your parameters, I reinforce what I know about you, so it makes my baseline values get better." The moment an athlete deviates from his or her normal range, it's a reason to be suspicious. Deviations can occur either because of doping or illnesses. Rupert suggests the biological passport should be expanded to use genetic information, which can help in some cases, such as the Eero Mäntyranta case (see sidebar), to tell genetic outliers from cheating athletes.

REAL OR FAKE ABILITY?

With the high stakes of money and fame in sports, doping will remain a fact in years to come. Athletes are desperate enough to try anything. They have scientists and clinicians in their support groups constantly mine the scientific literature, searching for clues about any substance that will improve performance and fly under the radar of the authorities. Even if a compound is shown to change properties of cells in a petri dish in a way that could be interpreted as better performance, some athletes are willing to give it a shot despite the lack of safety data.

"What is scary to us scientists is that some people are ready to take substances without proper clinical trials," says Rabin. "I worked in the pharmaceutical industry [before]. We took all these precautions to go from animal models to first administrations in humans and then to patients. But then we realized some athletes didn't even bother to wait. The drug went straight from the test tube to their bodies!"

Catching doping athletes is not just about bringing cheaters to courts of justice. Doping is dangerous and can be lethal. And performance enhancement doesn't only affect the athletes involved: It cheats the fans. As Friedmann sums it up, "Are you watching an army of molecular biologists and chemists at work, or are you watching truly beautiful human effort?"

Rajendrani Mukhopadhyay (rmukhopadhyay@asbmb.org) is the senior science writer for ASBMB Today and the technical editor for the Journal of Biological Chemistry. Follow her on Twitter at www.twitter/rajmukhop.

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Meet Ruma V. Banerjee

Ruma V. Banerjee, a professor of biological chemistry at the University of Michigan, joined the ranks of the Journal of Biological Chemistry associate editors earlier this year. In December, along with colleague and JBC Associate Editor William Smith, Banerjee oversaw a JBC minireview series on redox sensing and regulation. Here she offers some insights on her work at her home institution and with the journal.

Q: ***Would you briefly explain what your research group is studying?***

My research focuses on deciphering the molecular traffic lights that regulate the flow of sulfur. Sulfur metabolism furnishes cells with their favorite methyl donor SAM, or S-adenosylmethionine, as well as the antioxidant glutathione, the gaseous signaling molecule H_2S, and taurine, an abundant amino acid. We are particularly interested in how key traffic junctions are policed by enzymes that use B vitamins — B_{12}, B_6, folate — as cofactors and the metabolic diseases that result from their impairment. These enzymes in turn play critical roles in regulating cellular methylation and redox homeostasis. We are also interested in how an intracellular relay system traffics B_{12}, a rare but essential cofactor, using proteins that work as enzymes and as escorts, dressing up the vitamin into its biologically active forms and delivering it to its target enzymes.

Q: ***Tell us about your academic background and research training.***

I grew up in India as an army brat, changing 10 schools before graduating at the age of 14. Although I was very interested in physics as a high school student, I chose biology in college and obtained my bachelor's and master's degrees in botany from Delhi University. I moved to the U.S. for graduate school and studied with Jim Coward, a medicinal chemist, then at Rensselaer Polytechnic Institute in New York. In my first week at RPI in Jim's class, I had my first encounter of the biocatalysis kind and was hooked! My formal training is in mechanistic enzymology with an emphasis on enzymes that use coenzymes — B_{12}, B_6, folates and heme — to broaden their catalytic and regulatory repertoires. My program has broadened to include cell and animal studies

to interrogate cell–cell redox communication in the adaptive immune system.

Q: ***With whom did you train as a postdoc, and what was your work like there?***

I trained at the University of Michigan with Rowena Matthews. It was in her laboratory that I moved from synthetic chemistry to molecular biology and biophysical studies on proteins. Michigan has always been a haven for enzymology, and the late '80s were a very stimulating time with the labs of Vince Massey, Charles Williams, Martha Ludwig, Dave Ballou and Rowena Matthews converging at weekly meetings over beer to discuss speedy enzymes!

Q: ***Did anything occur — in a milestone sort of way — that made you choose science as a career?***

I think I never lost the curiosity that children are naturally born with about nature and knew at an early age that I would be a scientist — but not the particular flavor. I remember meeting an aunt at the age of 12 on winter break in India from her graduate program in Boston, where she was training with Lynn Margulis. I found her enthusiasm for science to be infectious and thought it would cool to live the excitement that she felt about her work.

Q: ***During grad school or postdoc, did something especially impress you to choose the path you've blazed in research?***

I trained with very smart and successful people who seemed to have found the secret to work–life balance. So the ability to have one's cake and eat it too, as embodied by my mentors, was an important early lesson in navigation for me. In terms of science, I was enticed by the interface between molecular and clinical research, and ever since my graduate student days I have belonged to a community where the conversation is between clinicians and basic scientists. For me, this interface has the headiness of fundamental discovery balanced by the sobriety of knowing of lives affected by disease. Over the years, I have been contacted by parents and relatives of individuals affected by inborn errors of metabolism affecting enzymes that I study. I am eager to help with providing information and samples in an effort to accelerate the pace of finding cures. That this community even follows my work is always a surprise to me.

Q: ***What does it mean to you, on a personal level, to be an associate editor for the JBC? What was your reaction when you were asked to be an associate editor?***

I was surprised to be asked since I had no previous association with the editorial board of JBC. I am almost a month into the job now and really enjoy it. It provides early glimpses into developing stories and allows one to help shape them into stories well told. So it's a chance to learn from and to contribute to the community.

Q: ***What do you do outside of the lab? Hobbies?***

The start of my independent career coincided with having my first child and then, three years later and still as an assistant professor, my second one. So over the years, my hobbies have been relegated to various degrees of backburner status. I enjoy theatre, reading (Murakami is my favorite author), yoga/meditation, writing and painting (watercolors).

Q: ***For scientists in training, do you have any words of wisdom or a favorite motto?***

I like Churchill's saying: "We make a living by what we get; we make a life by what we give."

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Fanning the fire

Young member is blazing a trail to become a pediatric endocrinologist and helping others along the way.

BY KENNETH J. MOORE

Growing up in the rural town of Edwards, Miss., Angel S. Byrd harbored a love of math and science. When she was 5 years old, her father died. Her mother moved her and her two older brothers to Jackson, and Byrd eased her heart by focusing on school to make her family proud. "I put all of my energy into school — all my troubles, all my worries," she says. "I just went hard in school, and I'm so thankful that I did." That focus and dedication to studies has paid off for her.

Byrd is nearing the end of the Ph.D. portion of her dual M.D./Ph.D. program at Brown University; she will defend her thesis next March. But Byrd has goals beyond her medical research career trajectory — she is passionate about helping others achieve their dreams. She is a repeat ASBMB Hill Day participant, having attended in both 2009 and 2011, and last month she helped a group of students realize their potential by sharing her educational journey with them at California State University, Dominguez Hill.

From a young age, Byrd challenged herself to gain direct experience in her scientific and social interests. She joined her mother, a social worker, in visits to the local homeless shelter, where many

From left: United Negro College Fund President and Chief Executive Officer Michael Lomax, Merck Research Labs President Peter S. Kim, and Merck CEO and President Kenneth C. Frazier congratulate Byrd on her Merck Graduate Science Research Dissertation Fellowship during the 2011 United Negro College Fund/Merck Fellows Day reception at Normandy Farms in Blue Bell, Pa. PHOTO: MERCK & CO. © 2011

people were sick. Interacting with these people made Byrd want to know more about the nature of their illnesses.

"I liked math and sciences, and I'm passionate about helping people," she says. To Byrd, the middle point between those two passions was to become a doctor. She shadowed physicians during high school, getting an appreciation for the medical practice and strengthening her commitment to practicing medicine.

Byrd had a detailed attack plan: She knew she wanted to go to medical school at Brown, so she applied to Tougaloo College in Mississippi because the college partners with Brown. In the summer before Byrd started her chemistry studies at Tougaloo, she attended its six-week program that helps prepare students interested in medical or science-related programs. "The program played a vital role in solidifying my decision to pursue a career in science and medicine," Byrd says. "You have to see if you like things before you do them. You can look at it from the outside, but until you immerse yourself in something, you just don't know."

A NEW LOVE

Because Tougaloo encourages students to gain research experience, Byrd found another love: scientific inquiry. In the summer of 2002, she took an internship at Beijing University, where she studied the expression of the insulin-producing PDX-1 gene in prokaryotes.

This experience exposed Byrd to a new path of fundamental research. When Byrd returned to Tougaloo, she participated in the Jackson Heart Study, conducting research on the molecular basis of cardiovascular disease and health disparities among the black population in Jackson. The next summer, Byrd conducted research at the Weight Control & Diabetes Research Center at Brown University's Miriam Hospital through the Leadership Alliance, an organization that helps underrepresented students become leaders. She interacted with patients while studying genes that might play a role in diabetes. Watching how people changed their behaviors and lifestyles to counter diabetes inspired Byrd and gave her the desire to increase awareness about the disease in her region.

"I found that I really loved research," she says of her work in China, at Tougaloo and at Brown. "But I wasn't going to stop the dream of going to medical school — so I combined both." In the midst of her summer research program at Brown, Byrd applied to the school's dual M.D./Ph.D. program, which she now almost has completed.

STUDYING IMMUNE RESPONSE

With most of her Ph.D. research under her belt, Byrd has only the final two years of medical training left. Her Ph.D. research focuses on primary human neutrophils — white blood cells — and how they act within the body.

Recently, Byrd identified neutrophil extracellular traps — when the cells sacrifice themselves and expel their DNA like a net to capture invading bacteria or viruses. "These traps are such a new phenomenon. They're so fragile that we didn't have the tools to identify them," she says. "Now, we have so many innovative ways to analyze cells, we're actually able to see what's really going on." She is looking at the traps to determine how much of a good thing is too much: when the system becomes perturbed with excess inflammation or when blood vessels become clogged.

Angel Byrd (second from left) celebrates her achievements at the 2011 UNCF An Evening of Stars television event in Pasadena, Calif. With her are fellow awardee Eric Marks Jr. (from left), United Negro College Fund President and Chief Executive Officer Michael Lomax, Black Entertainment Television CEO Debra Lee and other awardees Delrisha White, Raavin Evans and Fatima Bodrick. PHOTO: BET/UNCF

Byrd says she ultimately wants to become a pediatric endocrinologist, taking advantage of translational medicine to understand Type 2 diabetes on an individual basis and to help inform patients so that they can make appropriate lifestyle changes to improve their health. But she isn't waiting until she has the degree to start giving back to her community.

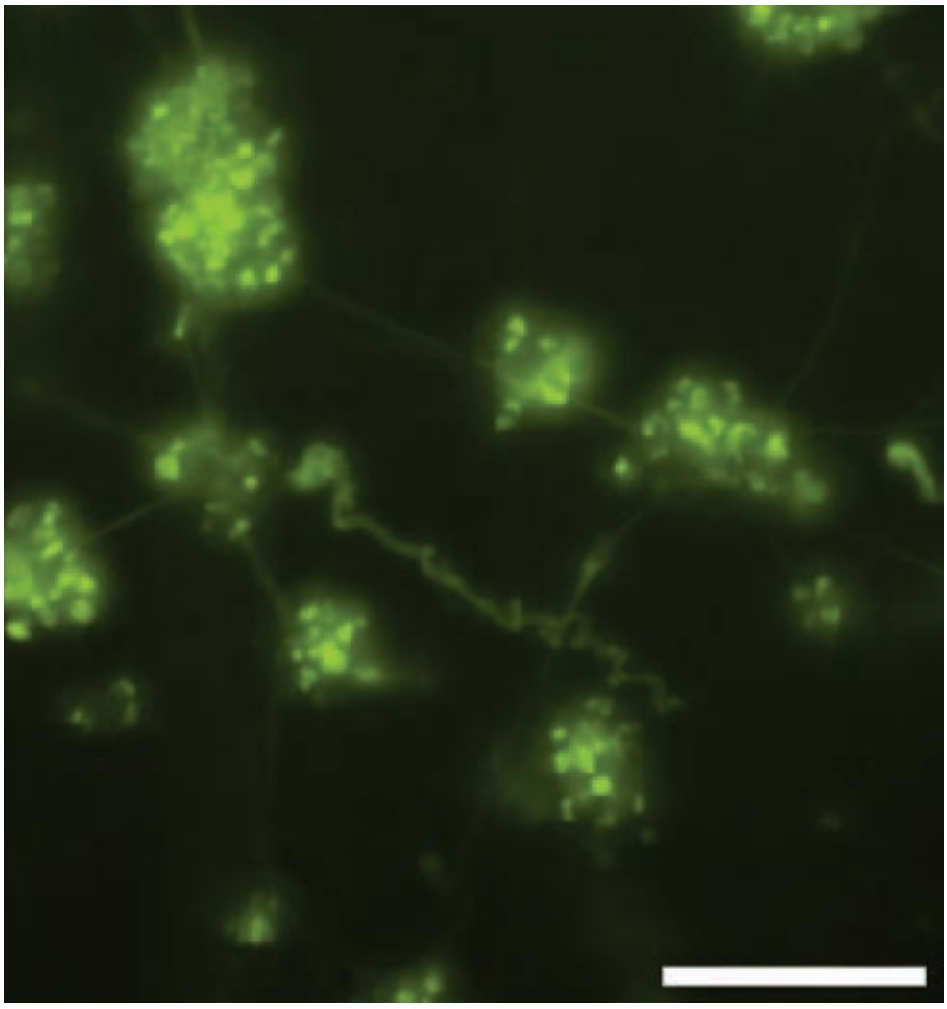
COMMUNITY VALUES AND GIVING BACK

The first years of her dual program were "strictly the research — work, work, work," Byrd says. She focused on her own goal to make sure she would achieve it before she started focusing on helping others reach their goals. "I knew there was a point that I had to decide when to reach back and help somebody else," she says. Now that she sees the light at the end of the tunnel for her Ph.D., Byrd can contribute to her community in new ways.

"Going back to help those who are along the way in their own academic paths also is very high on my priority list," Byrd says. She participates in the annual Leadership Alliance symposium, moderating sessions and oral presentations and working directly with undergraduates. "I try to reach back and make sure that I'm keeping that pathway open for the next generations that are coming through," she says.

Byrd's Christian faith is also important to her, and her involvement in the faith community is one of the driving forces behind her passion to contribute. Recently, Byrd helped organize a cotillion and beautillion — a coming out celebration at which youth show their commitment to improving society while becoming young adults.

Still, Byrd says, "I don't do nearly as much as I want to do and as much as I hope one day I will be able to do when I'm established in my career. I do as much as I can with different organizations where I can fit in and do something that has an impact."



Using the fluorescent, intercallating dye Sytox Green, Byrd is able to detect the neutrophil extracellular traps — when white blood cells throw their DNA to capture invading microbes. Scale bar is 100 µm. PHOTO: ANGEL BYRD

Because of Byrd's academic and research achievements, she has been awarded a Gates Millennium Scholarship and a Merck Graduate Science Research Dissertation Fellowship, both through the United Negro College Fund. Last fall, Black Entertainment Television profiled her in its program "An Evening of Stars of Educating our Future." That honor "validates all the hard work," Byrd says.

Kenneth J. Moore (kennethjamesmoore@yahoo.com) is a Washington, D.C.-based freelance writer covering biochemistry, microbiology, and food and crop sciences.

A conversation with NSF's Parag Chitnis

BY ANGELA HOPP AND JULIE McCLURE

Parag Chitnis, director of the Division of Molecular and Cellular Biosciences at the National Science Foundation, first arrived at the agency in 2002 on loan from his university for what he thought would be a relatively brief stint as a program director. But, as often happens, life had other plans. Instead of heading back to Iowa State University to continue his research on plant biochemistry, he was promoted to deputy director and then director of the division. Chitnis, who once was a member of the American Society for Biochemistry and Molecular Biology and who served on its Education and Professional Development Committee for several years, talked with ASBMB Today Editor Angela Hopp and the society's science policy fellow, Julie McClure, about what kinds of research projects the NSF is looking to fund.

Q: ***Why is it important for our readers to know what's going on at the MCB division?***

Most of the NSF funding for the ASBMB membership comes from my division, followed by the Division of Chemistry and Division of Physics, because some of the biophysical and chemical biology work is supported by those other divisions.

Q: ***What are the main differences between the NSF and the National Institutes of Health in terms of projects sought?***

The first thing is that the division itself tries to give higher priority to quantitative, predictive and theory-driven science. So a combination of computation and experiment is preferred over just experimental research using traditional approaches… The other area that I think the NSF really takes pride in is exploring the frontiers at the intersections of biology with other disci-

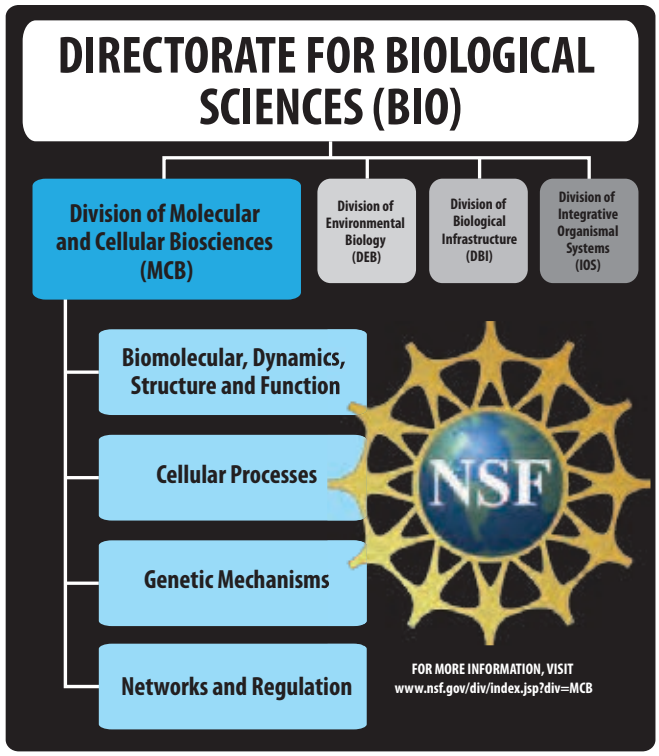
plines — chemistry, physics, math, computer science, also engineering. Because all of those disciplines are supported by NSF and those divisions are here under the same roof, we make an extra effort to encourage research at these interfaces.

Q: ***Are there specific funding mechanisms at the NSF that support projects that span the disciplines?***

There are some new mechanisms, but the regular grants that are submitted to NSF are reviewed (for that crossover). In the case of MCB, 10 percent of our awards are co-funded with other directorates. What program directors do, if there is something that crosses the discipline, is go and talk to the program directors in that discipline and co-review those proposals. And, if the proposals do well in the review process, program directors in different divisions co-fund them.

I think readers probably want to be aware of this so they don't try to limit their project just because they think, "Oh, this is too physical, and I don't want to send it to a division in the Biology Directorate." Because they need to realize that, even though some aims are more physical or very much chemistry, we have a mechanism to review those things. I think we want (principal investigators) to consider their projects without thinking about disciplinary boundaries.

There is a new mechanism called CREATIV (for Creative Research Awards for Transformative Interdisciplinary Ventures) that's for interdisciplinary science that is really high-risk and high-impact. Up to a million dollars can be given without external review if program directors in two or more disciplines agree to fund one. Again, this program was created to address the same issue: Are there projects that don't fit in one or more disciplines, and are we losing those?



Q: ***What kinds of projects really aren't in line with the NSF's goals and strategies?***

The projects that are funded by the Biology Directorate are for basic science purposes and not for their health relatedness. What we look at is the impact of the project on the advancement of science in general — basic principles — and not because it's important for finding a drug for a disease. In enzymology, for example, if it's just another enzyme with the same kind of mechanism that is already known, we would be less interested in funding that type of project, but it may be perfectly fine to be funded at the NIH, because that enzyme is involved in a metabolism important for a disease.The other major difference is we want applicants to address how a project integrates education and research. And that's what we call the "broader impacts" criteria. It's in addition to the intellectual merit, and we take it very seriously.

Q: ***What are examples of broader impacts?***

For example, Hazel Holden (of the University of Wisconsin-Madison) has a project where she took crystallography to middle schools. A typical broader impact is involving and mentoring undergraduates in your research. Another one is taking examples from your research to your classroom.

Q: ***Are there differences in size or duration of grants compared with the NIH?***

We can fund up to five years, and I think we'd emphasize that the award duration should be in proportion to the scope of the project. It should be something the PI decides. Unless the review says that there isn't enough work to do for five years, we do not adjust duration. But otherwise, what the PI asks for we give them. Our current median size is $200,000 a year, and that includes indirect costs. But, of course, the range is from $100,000 to $1 million a year. Last year's funding rate of MCB was about 16 percent.

Q: ***The deadline structure at the MCB division has changed. Can you tell us about those adjustments?***

About a year ago, the division changed its practices based on the advice of an external committee, which comes and evaluates us every three years. We had deadlines every six months, and they told us that wasn't enough time for meaningful revision if the grant gets declined, because once the PI found out there were only a few weeks left before the next deadline. That's not enough time to revise the proposal meaningfully. So we shifted the cycle length to eight months. Now we have at least two months for the PI to revise. Also, instead of four cycles every two years, now we have three cycles every two years. Some of the other divisions in the BIO directorate have moved to one cycle a year, but most of those divisions may not be relevant to ASBMB members. Now we are evaluating the impact of this change on the PIs and the review process.

Q: ***How do you see these deadline changes affecting those seeking tenure?***

For the beginning investigator, they have five chances in two years. They can also send us CAREER proposals separately. Deadlines for those CAREER proposals are in July. The funds for CAREER and regular proposals come from the same pot, so the funding rate is about the same. These (CAREER awards) are five-year grants for untenured assistant professors where they talk about their research as well as their educational activities to start off their career. The size is about the same in MCB at $200,000 a year for five years for a CAREER grant.

Q: ***Are there other differences between the NSF and the NIH you want to emphasize?***

At NSF, the program directors make funding decisions, while the panels, the equivalent of study sections at NIH, are advisory to program directors. The panels put the proposals into categories instead of numerical scores, and then the program directors look at all those highly rated proposals and prepare a list of projects that will complement and advance the portfolio of projects that are already funded. That would mean balancing the demographics, diversity, types of projects, areas of science. NSF's responsibility is, even though we are not a mission agency, to have the top scientific infrastructure in the country, so that's why we look at the geographical distribution or different areas of science or different types of institutions.

Q: ***Who are the NSF program directors?***

About half of our program directors come from a university on loan, and they go back to the university. They come here for one to two years. So we have a direct connection to the community that we serve. The remaining program directors are permanent. And when they get hired, they are typically tenured, full professors at universities, and we hire them because they have had strong records of publication, grantsmanship, vision for the future directions in science, and they can represent the community well.

Q: ***Is there anything you want to emphasize for those ready to submit to the NSF?***

I think what we are really looking for is high-risk, high-impact ideas that will advance the field substantially, because those have a better chance for us to make a bigger impact on the progress of science. Some of the projects we funded, even though the peer review didn't rate them highly, ended up starting new fields or the PI won NIH Director's Pioneer Awards.

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STARK RAVING MAD FOR SCIENCE

George Stark's enthusiasm for understanding signaling pathways and developing biochemical methods is infectious.

BY RAJENDRANI MUKHOPADHYAY

George Stark of the Cleveland Clinic is as comfortable in a kitchen as he is in a laboratory. The son of a restaurant owner, Stark says, "learning how to handle myself in a restaurant was good training for how to be a good chemist." In fact, an extremely good biochemist. Stark's scientific accomplishments, such as the development of Northern blotting for detecting RNA and the discovery of the JAK-STAT signaling pathway, have garnered him many accolades, including the 2011 Herbert Tabor/Journal of Biological Chemistry Lectureship, awarded by the American Society for Biochemistry and Molecular Biology each year for excellence in biological chemistry and molecular biology (1).

As a boy in the 1940s, Stark spent hours working in his father's eatery, Stark's Beef and Beans, in Washington, D.C. Watching his father's struggles made Stark decide at a young age that the restaurant business was not for him. His father agreed. His father, whom Stark describes as "a dominant personality… a go-out-and-get-'em business man," had grand plans for his only son (Stark has two older sisters). "It was the typical 'My son should be a doctor!'" says Stark with a laugh.

Stark's mother was a quiet woman who worked as a bookkeeper to hold the family steady through the highs and lows of the restaurant business. His parents didn't know much about science, Stark says, but, based on what they were aware of, they encouraged him to pursue medicine. To get the boy started, the family moved to New York City so Stark could attend the Bronx High School of Science for his senior year.

He went on to Columbia College for his undergraduate degree, but as he got more into his premedical school studies, Stark says, he realized he really wanted to do research, not medicine. A

Stark with his wife, Mary Beck; son, Robert; and daughter, Janna. PHOTO COURTESTY OF GEORGE STARK

comparative anatomy class cemented the decision. "Looking at a bunch of pins stuck in a dissected frog and trying to remember the names of what was underneath each pin was daunting for me," he says. "I can remember things very well if I can link them in a logical chain, but the names of all these nerves and so forth in the frog were not linkable in a logical chain for me!"

In what he calls an act of self-defense to avoid medical school, Stark stayed on at Columbia for graduate school in the laboratory of his undergraduate adviser, Charles Dawson, to study ascorbate oxidase from yellow crook-necked squash. In a Reflections article for the Journal of Biological Chemistry, Stark recalls spending happy hours in the cold room peeling mounds of the vegetable because the enzyme was concentrated in its skin (2).

Stark followed his graduate studies with a stint at The Rockefeller University as a postdoctoral fellow with soon-to-be Nobel laureates Stanford Moore and William Stein, who had invented the amino acid analyzer and sequenced bovine pancreatic ribonuclease. It was also during this time that Stark met a physicist who became his wife and, for several years, labmate. Stark has described Mary Beck as "the glue that holds one's life together."

STANFORD

Stark's work on carbamylation to identify the amino-terminal residues of proteins and aspartate transcarbamylase attracted the attention of Arthur Kornberg, who recruited him to Stanford University in the early 1960s. There, in the 1970s, Stark's group developed Northern blotting. At that time, RNA was detected by separating an RNA mixture in a tube gel, freezing the gel, and "putting it in a device like an egg slicer and cutting it into 100 or so pieces," says Stark. Each gel piece was hybridized with a complementary RNA probe to see which gel piece contained the RNA in question. The method, Stark says, was "ridiculously cumbersome." His group decided to do better.

They had figured out in 1975 how to make chemically reactive cellulose that would covalently

bind to DNA and RNA (3). Stark's group then made chemically reactive cellulose paper onto which they could attach RNA molecules from a gel. They then probed the entire paper with the complementary nucleic acid chain (4). "It actually worked the first time we tried it," says Stark.

Stark's sense of humor came through when they named the technique "Northern blotting" as a joke on Southern blotting, which Edwin Southern at Oxford University had developed for DNA detection (5). Similarly, Stark's group did the first demonstration of the idea of transferring proteins out of gels for detection (6, 7).

It was also at Stanford that Stark's group discovered PALA, an abbreviation for *N*-phosphonacetyl-L-aspartate (8). The molecule is the analog of aspartate transcarbamylase's transition state. Stark's group discovered that PALA was a strong inhibitor of aspartate transcarbamylase and that it could enter mammalian cells to block pyrimidine nucleotide biosynthesis.

With PALA, Stark and colleagues went on to discover the giant polypeptide CAD that contained aspartate transcarbamylase, carbamyl phosphate synthetase and dihydro-orotase, all involved in pyrimidine synthesis. By studying CAD, Stark's group was one of the first to show gene amplification in mammalian cells.

AN AMERICAN IN LONDON

In 1983, after 20 years at Stanford, Stark landed in London at the Imperial Cancer Research Fund. His research interests had moved from protein biochemistry to cellular and molecular biology, and he was interested in interferon-dependent signaling, an area in which he worked in collaboration with Ian Kerr at the U.K. Medical Research Council.

"London is a wonderful place to live," says Stark. "We were very privileged, because we owned a house in California that we were basically able to trade for a nice house in central London." Stark says that the environment at ICRF was also special. "My lab was completely funded. I didn't have to write any grants. All I had to do was show up for a review every five years," he explains. "It was heaven for somebody like me who wanted to primarily do research."

Part of his group in London worked on mechanisms of gene amplification, and the rest worked on interferon signaling pathways, research that later led to the discovery of the JAK-STAT pathway (9). The group also developed an approach called validation-based insertional mutagenesis (10).

But Stark's idyllic world was in for a nasty surprise nine years later. "I realized I was going to have to retire in the British system in a couple of more years!" he says. Stark would have had to have stopped working in 1995 at age 62.

BACK IN THE U.S.

Determined not to be forced out, Stark found another position in 1992 at the Cleveland Clinic Foundation, where a vacancy popped up after Bernadine Healy moved to become head of the National Institutes of Health under President George H.W. Bush. Twenty years later, his laboratory still continues to forge ahead on interferons, STAT1 and NFκB research.

His group has found that the mutagenesis approach they have developed can be powerful. "It is a way to upregulate gene expression randomly in a population of cells," explains Stark. "If upregulation of a protein in one cell out of millions in a population gives you an interesting phenotype and you have a way to find that cell by selection or something else, then that can lead to a novel research project."

For instance, Stark's group has an interest in lysine methylation of transcription factors, a mechanism that affects gene expression. With the mutagenesis approach, "we found upregulation of a demethylase that affected the function of NFκB," says Stark (11). "We've also used that method a lot in finding new mechanisms of drug resistance" (12).

Immersed as he is, Stark still manages to have a life outside of science. "I like to cook. I enjoy sports, mostly now as a viewer rather than a participant!" he says. "I love classical music. I did sing together with Mary a lot. We were in choruses in New York and California." The Starks also are enthusiastic concert and theater goers and collect art pieces, such as Japanese prints and Inuit sculptures.

But Stark continues to be leery of retirement. He has reduced his load of administrative work so he can have more free time to spend with his family. But he is absolutely certain of one thing: "I don't want to give up science," he says. "I don't want to quit."

Rajendrani Mukhopadhyay (rmukhopadhyay@asbmb.org) is the senior science writer for ASBMB Today and the technical editor for the Journal of Biological Chemistry. Follow her on Twitter at www.twitter.com/rajmukhop.

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ASBMB's new mentoring committee gets to work

BY FRED MAXFIELD

The American Society for Biochemistry and Molecular Biology has established a new committee on mentoring, which will coordinate society activities related to various aspects of mentoring both from the perspective of the mentor and the person being mentored. The committee will coordinate its activities with established committees, including the Education and Professional Development Committee and the Minority Affairs Committee.

The committee will contribute a monthly column to ASBMB Today, written either by a member of the committee or by an invited contributor. Our focus will be on career development, especially from graduate school through a first professional position in academia or elsewhere. At times we also may consider other aspects of mentoring ranging from precollege education through the later stages of a career. In addition, the committee will organize events at ASBMB annual meetings, such as roundtable discussions and workshops. We will solicit suggestions for topics to be considered at such events. Podcasts and a presence on social media sites also are being considered, although some committee members will need mentoring from junior colleagues for some of these activities.

The establishment of the committee underscores the importance of mentoring, and it also acknowledges that the nature of mentoring is changing. I feel privileged to have worked with outstanding mentors as a graduate student (Harold A. Scheraga) and as a postdoc (Ira Pastan). Each had a profound impact on my own career development. Many scientists have similar memories from their own training.

It is clear that the expectations and needs of trainees have changed significantly since my own training in the 1970s, but it is not so clear that the mentorship provided always has kept up with these changes. The availability of jobs when the research enterprise was in a period of rapid expansion meant that the main role of a mentor was to make sure that trainees would have enough publications to advance to the next stage of their careers. As the availability of research positions and the funding for these positions has been reduced, trainees have faced a greater range of career options, and they need guidance to choose among these. Additionally, changes in the larger society, such as a greater awareness of the importance of work–life balance and the recognition of the importance of diversity in the work force, add new dimensions to mentoring.

We look forward to working with members of the ASBMB to develop programs to improve mentoring as an important component of professional development. Suggestions or comments for the committee can be sent to mentoring@asbmb.org.

The members of the committee are Karen Allen (Boston University); Kate Carroll (The Scripps Research Institute, Florida); James Keen (Thomas Jefferson University); Jon Lorsch (Johns Hopkins University); Fred Maxfield (committee chairman, Weill Cornell Medical College); Melissa Moore (University of Massachusetts); Geeta Narlikar (University of California, San Francisco); and Melissa Starovasnik (Genentech Inc.).

Committee members


Allen


Carroll


Keen


Lorsch


Maxfield


Moore


Narlikar


Starovasnik

Fred Maxfield (frmaxfie@med.cornell.edu) is a professor and chairman of the department of biochemistry at Weill Cornell Medical College.

Attn: Lipid community!

This article announces our new Web editor, Jordan Scott. Jordan is taking over for Katie Ward, who has guided the Lipid Corner through its initial growth and has done a simply marvelous job. Jordan certainly has big shoes to fill, but it seems she's off to a great start! This is her article of introduction and touches on some of the changes she is planning on incorporating. So a huge thanks goes to Katie, and a big welcome to Jordan!

—DAN RABEN

BY JORDAN SCOTT

You may or may not have stumbled upon the website for the Lipid Research Division of the American Society for Biochemistry and Molecular Biology: The Lipid Corner. As the new editor, I would like to encourage you to browse the website and check out what it has to offer. This online forum for goings-on in the lipid community provides us researchers with a platform for the following:

- **HIGHLIGHTING NEW RESEARCH PUBLICATIONS IN THE LIPID FIELD.** These publications draw from the broad area of lipid research and encompass novel and exciting reports perhaps not on your normal literature search radar.
- **SEARCHING FOR JOB OPPORTUNITIES.** The Lipid Corner posts job opportunities in the lipid field. Please contact us if you have an opening in your lab or at your institution.
- **RESOURCES.** The site provides links to lipid-research-related databases and others, including relevant webinars and recorded lectures.
- **LISTINGS OF LIPID-RELATED CONFERENCES.** We keep up-to-date listings and a calendar of upcoming lipid-related conferences. (Don't forget to register for Frontiers in Lipid Biology in Banff, Canada, this September.)
- **SHOWCASING NEWS AND ACHIEVEMENTS.** We post announcements of awards and achievements, new hires and other news about lipid community members. Recently posted are the 2012 Avanti awards honoring George Carman of Rutgers University and the young investigator winner, Peter Espenshade of Johns Hopkins University School of Medicine.

Additionally, I would like to draw your attention to a few new things that the website will offer:

- **A BIMONTHLY PERSPECTIVES SECTION**, which will include reviews of recent, novel publications and other news in the field written by members of the lipid community. We plan to include topics from lipid research to training and mentoring in the lipid field.
- **A LINK TO THE NEW ASBMB LIPID DIVISION LINKEDIN MEMBER PAGE.** We hope that this will help lipid researchers network and stay abreast of their colleagues' work.

As a graduate student in Rob Stahelin's laboratory at the University of Notre Dame, I study the mechanistic activation and regulation of peripheral membrane-binding proteins. I employ biophysical tools such as surface plasmon resonance in tandem with cellular assays in these studies. The more I delve into my particular area of research, the more I realize my need for a greater understanding of lipid signaling networks and the broader lipid research field. My vision for the Lipid Corner is that it will be used as a tool and forum for research and networking for both students and senior investigators. The integration of research, news, calendar items and job opportunities is important for each of us, and we are grateful that the ASBMB has provided this platform.

Finally, we ask you, kind readers and lipid scientists, to notify us of anything that you believe would be helpful to other lipid researchers. Whether it is a new job listing, website or publication, we would be happy to showcase it for the lipid community. If you have not seen the website, please check it out for a snapshot of the current lipid research community. If you are a loyal reader, stay tuned to www.asbmb.org/lipidcorner for monthly updates. XXXX

Jordan Scott (jscott7@nd.edu) is the Lipid Corner's Web editor and a graduate student at the University of Notre Dame.

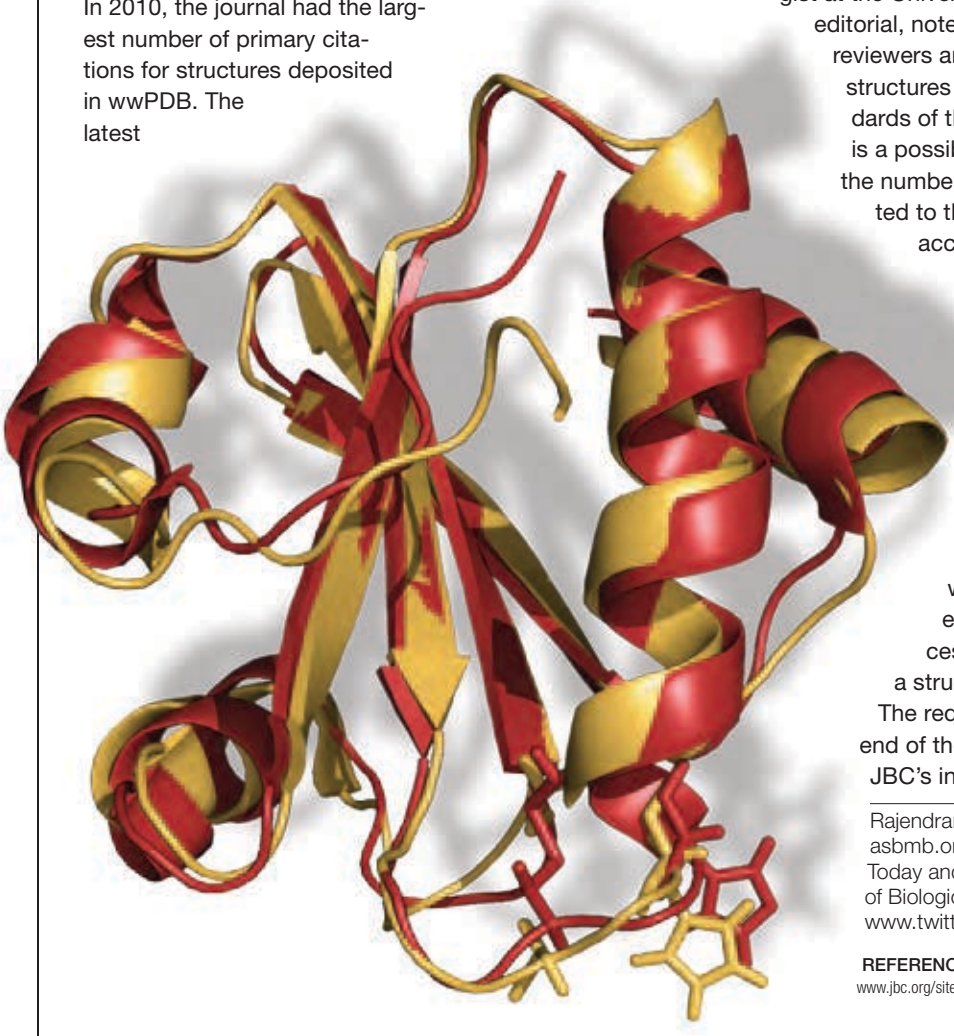
jbc THE JOURNAL OF BIOLOGICAL CHEMISTRY

Structure papers to require PDB validation reports

BY RAJENDRANI MUKHOPADHYAY

Attention, structural biologists! The Journal of Biological Chemistry soon will have a new requirement: When you submit a manuscript with an X-ray protein structure, you also will need to submit a validation summary report from one of the three World Wide Protein Data Bank centers. The report summarizes the results of an analysis of experimental data and geometry of reported structures by the wwPDB. The report will be used by JBC reviewers to confirm the accuracy and quality of the structures.

The JBC is an important forum for structural biology. In 2010, the journal had the largest number of primary citations for structures deposited in wwPDB. The latest move comes after a yearlong series of discussions among JBC associate editors and an editorial published last December to ask reviewers, authors and readers whether validation reports should be requested. The overall response was a resounding yes, with many saying that the report submission should be mandatory.



JBC Editor-In-Chief Marty Fedor says this new requirement is consistent with the journal's history of publishing high-quality structures. Fedor, who is based at The Scripps Research Institute, mentions the resistance of some biologists in 1978 when the JBC made it a requirement that structures be deposited into the PDB prior to manuscript submission. But now, "no one can imagine going back to the days before PDB depositions were required," she says. "We feel this new requirement is going to be a similar step along the same path of taking advantage of the tools available to curate these kinds of database depositions and making sure they meet certain standards of quality before they are disseminated to the community at large."

JBC Associate Editor Norma Allewell, a structural biologist at the University of Maryland who wrote the JBC editorial, notes the reports will make the task of reviewers and editors easier and will ensure that structures reported in the JBC meet the standards of the scientific community. "While there is a possibility that this requirement may reduce the number of structural manuscripts submitted to the JBC, it ensures that those that are accepted merit publication in the JBC," she says.

wwPDB member Helen Berman at Rutgers University says the organization is delighted by the JBC's move. With the report in hand, a reviewer can "be assured that the technical aspects of the crystallographic determination are fine," she says. In the cases in which errors are found, "at least the errors get caught early on in the process, and you don't have a situation that a structure has to be retracted."

The requirement will be implemented by the end of the summer and will be noted in the JBC's instruction to authors.

Rajendrani Mukhopadhyay (rmukhopadhyay@asbmb.org) is the senior science writer for ASBMB Today and the technical editor for the Journal of Biological Chemistry. Follow her on Twitter at www.twitter.com/rajmukhop.

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www.jbc.org/site/home/editorials/macromolecular.xhtml

THE JOURNAL OF LIPID RESEARCH

Marine microorganisms an unexpected source for anti-inflammatory fatty acids used to treat lipid disorders?

BY MARY L. CHANG

A hot area of lipid research today is focused on n-3 polyunsaturated fatty acids, better known by the abbreviation PUFAs. They have been shown to have positive anti-inflammatory effects on blood and the heart and are being considered in the development of medication and nutritional supplements. The PUFA eicosapentaenoic acid, or EPA, is already used to treat hyperlipidemia and arteriosclerosis; another PUFA, docosahexanoid acid, or DHA, is known to have an important role in eye and brain development and has been suggested to be linked to normal brain function.

Fish oils are now the major commercial sources of these two PUFAs; it is expected that the increasing global demand for these PUFAs will exceed the amount currently available through these traditional sources. To keep up with this increased demand, microorganisms and plants are being looked to as possible alternative sources. Thraustrochytrids, filament-producing marine microorganisms, are known to produce and store high amounts of PUFAs in lipid droplets, so the pathways they use to generate them are being investigated as part of the search for an alternative source of PUFAs.

In a paper entitled "The analysis of Δ12-fatty acid desaturase function revealed that two distinct pathways are active for the synthesis of polyunsaturated fatty acids in *Thraustochytrium aureum* ATCC 34304" (doi: 10.1194/jlr.M024935), Takanori Matsuda of Kyushu University in Japan and research colleagues studied and identified two active and distinct PUFA-synthesizing pathways in this one species of thraustrochytrid. By disrupting the gene that codes for a Δ12-fatty acid desaturase, a key enzyme in the production of PUFAs, Matsuda et al. were able to show that a desaturase/elongase pathway (also known as the standard pathway) is active in this species. The loss of this Δ12-fatty acid desaturase decreased the number of all types of lipids produced; however, normal cell growth was not affected when the enzyme was not working. Interestingly, their results also suggested DHA is primarily produced by a different PUFA synthase pathway. Their findings suggest genetic modification of these microorganisms for direct production of beneficial PUFAs by one or both of these identified pathways may be possible in the future.

Mary L. Chang (mchang@asbmb.org) is managing editor of the JLR and coordinating journal manager of MCP.

MCP MOLECULAR & CELLULAR PROTEOMICS

The evolution of unstructured protein interactions

BY RAJENDRANI MUKHOPADHYAY

The lock-and-key hypothesis of protein structural biology was held as dogma last century until examples started to crop up of proteins with flexible structures that could not be analyzed by conventional X-ray crystallography. In the past 15 years, the existence of proteins that don't have any definite structure has been established. In a recent Molecular & Cellular Proteomics paper, a trio of European researchers analyzed the role of intrinsically disordered proteins in the evolution of interaction networks in three model organisms (1). "We and others noticed that there is a significant presence of unstructured proteins in interaction networks," says Patrick Aloy at the Institute for Research in Biomedicine and the Catalan Institution for Research and Advanced Studies. He added that he and his colleagues wanted to understand "the role played by these proteins in the evolution of protein interaction networks."

The researchers compared the molecular interaction networks in human, fly and yeast and discovered that, despite their abundance, interactions involving disordered proteins were less conserved than those that included structured proteins. "Despite being very abundant, protein interactions involving at least one unstructured protein are much less conserved than one would expect by chance," says Aloy. He says that their results support the hypothesis that maintaining disordered proteins "gives a clear evolutionary advantage—it facilitates the change of interaction partners during evolution." Aloy says his group is now investigating "the structural and functional effect of disease-causing mutations that occur in unstructured regions" to see if there are any biomedical applications.

Rajendrani Mukhopadhyay (rmukhopadhyay@asbmb.org) is the senior science writer for ASBMB Today and the technical editor for the Journal of Biological Chemistry. Follow her on Twitter at www.twitter.com/rajmukhop.

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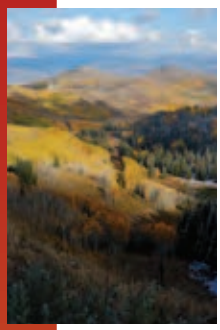

Transcriptional Regulation: Chromatin and RNA Polymerase II

OCTOBER 4–8 • Snowbird Ski and Summer Resort (Snowbird, UT)

Raymond Trievel, *University of Michigan,* and
Ali Shilatifard, *Stowers Institute for Medical Research*

KEYNOTE
Ramin Shiekhattar, *The Wistar Institute*

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Post-Translational Modifications: Detection and Physiological Role

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Gerald W. Hart, *Johns Hopkins University School of Medicine,* and Lauren E. Ball, *Medical University of South Carolina*

KEYNOTE
Donald F. Hunt, *University of Virginia*

Early Registration & Abstract Submission: August 1

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Advice for new grads entering the job market

'In this age of rapid technological changes, you have to be open to continuous training — to be ready to reinvent yourself'

BY NESTOR CONCHA

The caps and gowns have been returned, and the diplomas are in the mail. New grads nationwide are on the hunt for jobs that will both pay the bills and yield personal rewards. Here are some thoughts on how these emerging professionals should approach this challenge.

Have a plan, and expect it to evolve

First and foremost, it is important to identify your personal, long-term goals. The answer is not static, of course, and it may take awhile to arrive at a satisfactory one. At the same time, contemplate that any goal is a tentative one, and it will be rewritten many times over. Serendipitous (not random) opportunities will be important factors that will influence your goals. But even a plan that carries intrinsic uncertainty is preferable over not having a plan at all.

Your plan is a blueprint to guide the activities that are under your control: the specific actions that you will execute and that will move you closer to your goal. At the same time, the plan will provide the context and the background against which to identify opportunities, to influence people and to position yourself in circumstances that may not be totally under your control but will allow you to realize your goal.

In summary, there is an immediate result of your activities but also an important influential aspect on everything that surrounds those activities. Drawing the plan is a most personal endeavor, and the seriousness of it calls for not only a hard introspection but also consultation with a network of mentors, friends, colleagues and family members.

Assess your experience and your motivations

The next aspect to reflect on: the training you have received. This, too, will change. Indeed, it should change.

For biochemistry and molecular biology graduate students, the formative years in graduate school, followed by a few more years as postdoctoral trainees, lay down the path to a career as scientist. There is no better time in a young scientist's life. During these years, we get ever so close to the pinnacle of the scientific endeavor: the seducing prospect of being the first to describe an as-yet-unknown phenomenon, the rigor of scientific inquiry, the love (and frustrations) of experimentation, and the testing and falsifying of hypotheses.

We form a vision of ourselves — the incredibly appealing vision of becoming an authoritative voice in the area of research that happens to be also of profound personal interest. In this vision, we become leaders of labs filed with bright students and postdocs. Some will realize that vision, but most will not. The reality is that the open positions at universities are very competitively fought over and that funding for research is scarce.

You have options, so keep an open mind

You have been trained to do academic research because there is no better way, but it does not follow that academic research institutions are the only places where intellectually challenging science is being done and that only academic labs have the interesting problems to be tackled.

If discovery and challenge is what you are after, look into the past at Bell Labs, where scientists of varied fields, working together, came up with probably the most far-reaching set of discoveries that we enjoy today. Far closer to the present are ubiquitous high-tech companies at which intelligent development and use of technology has brought us new ways of working and communicating.

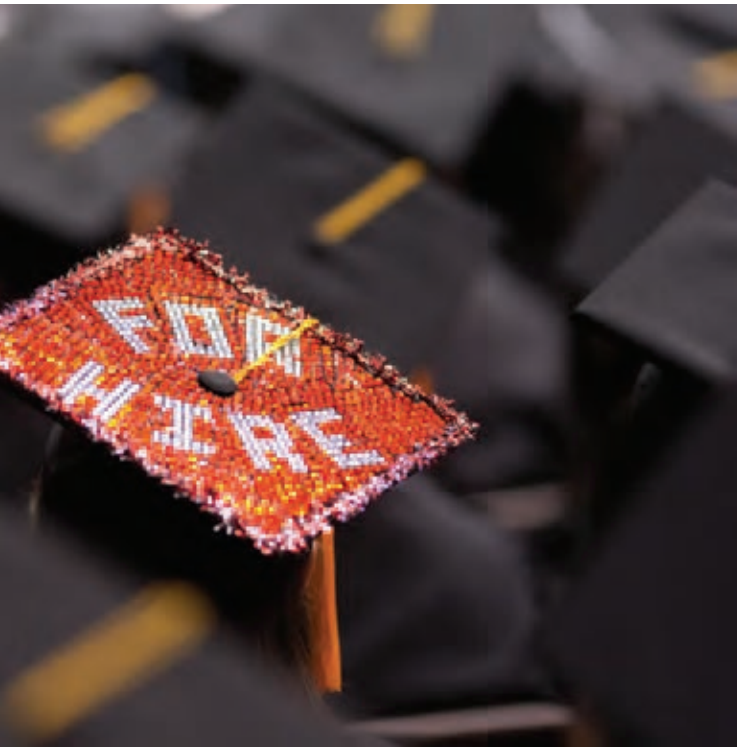

PHOTO: THOMAS CAMPBELL, UNIVERSITY OF HOUSTON

The future is even more promising: Intricate biological pathways, rare and complex diseases, and new medicines are at the frontier and many nonacademic labs and institutions are hard at work trying to unravel them, diagnose them and discover them. In other words, there are many opportunities to perform intellectually challenging work, be part of discoveries and perform otherwise rewarding activities in the company of respected colleagues.

Internships, co-ops, summer programs and the like provide terrific opportunities for both students and employers to get know one another. For the organization, these arrangements help identify talent and complete small projects; for the students, they provide the chance to sharpen interpersonal and technical skills.

Develop a top-notch résumé and work on interviewing skills

You want to end up on the short list of candidates. Here are some pointers:

1. It is of utmost importance to have a list of contacts who will help you find open positions.
2. Put together a well-prepared, succinct résumé highlighting your achievements, their impacts and your skills. Consider, as nonsensical and perverse as it may seem, that a list of citations does not speak for itself and that, although it is the most important section, it is not the only section the hiring manager will evaluate.
3. If a telephone interview is offered, underscore your interpersonal skills and leadership ability and demonstrate that you are able to communicate complex thoughts in simple terms. (There is a chance that a nonscientist, a person in human resources perhaps, may be making the call.)
4. Articulate the impact of your work, why it was important to pursue, what is the big picture and where your piece of work fits in.
5. Practice, practice, practice.
6. Be prepared to talk about these points during a face-to-face interview.
7. Devise a well-prepared seminar — paying careful attention to both the content and the delivery. It is unfortunate, but not uncommon, for people to present an attitude of almost contempt for the audience. It may not be deliberate, but don't make that mistake.
8. Pay attention to your audience's needs. Who might attend? Are they all experts in the same field, or will there be others who may not be familiar with certain terms and experimental approaches? Find out, and tailor the presentation. You want people to come out of your seminar not only with an understanding and appreciation of your work and scientific skills, but also with a sense that you, not your supervisor, understand the context and the long-term implications of pursuing your line of research. You want them to be confident that you have the reins, the knowledge to do the science and the skills to lead others through the arts of persuasion and communication.

Embrace change, for it is inevitable

In this age of rapid technological changes, you have to be open to continuous training — to be ready to reinvent yourself. You need to be open to carve your own future according to your plan and to be ready to grab the chances of making your mark and making a living.

Those opportunities may come in the form of doing research in an academic institution; doing research aimed at drug discovery in big and small pharma, startups, biotechs and contract research organizations; offering technologies to customers; or working with customers to find what their needs are to develop new technologies.

Just be ready to contribute where the contribution will be most impactful — for you and for society.

Nestor Concha (Nestor.O.Concha@gsk.com) is a research scientist at GlaxoSmithKline.

Reaching out to minority science students

BY MICHAEL F. SUMMERS

The future of science and engineering research in the U.S. is dependent on the quality and depth of the future talent pool. The demographics of this pool are changing rapidly, particularly at the doctoral level, where international students are making increasingly greater contributions. Science Ph.D.s issued to students holding temporary visas increased from 27 percent of all degrees awarded in 1989 to 37 percent in 2009; in the physical sciences and engineering, Ph.D.s issued to non-U.S. citizens rose from 16 percent to 42 percent and from 33 percent to 55 percent, respectively. Although there are numerous clear advantages to international graduate-level education, the significant decline in the proportion of U.S.-educated undergraduates who pursue advanced degrees in science, technology, engineering and mathematics (STEM) is cause for concern.

Ethnic minorities comprise an important and growing population in the U.S. (1) that will need to increasingly contribute to the science enterprise. Unfortunately, racial minorities have been historically underrepresented in STEM fields (2, 3), a problem that is not due to a lack of early interest (4). In fact, similar percentages of white, Asian-American and underrepresented racial minorities, or URMs, begin higher education with aspirations of pursuing STEM degrees, but the URM students leave STEM fields at rates that significantly exceed those of their white and Asian-American peers (5, 6).

There are several ways that research faculty members can help plug the holes in the leaky URM STEM pipeline. At scientific conferences, extra effort can be made to visit the research posters or presentations of URM students and postdocs. In the classroom, we can reach out to individuals who are underrepresented, letting them know that they are on our radar and that our expectations of them are just as high as our expectations of the other students in the class. But perhaps the greatest contributions can be made by providing extended research opportunities and serving as mentors to talented and motivated undergraduates.

An approach that has worked well in our laboratory is to recruit matriculated undergraduates into the laboratory the summer after their freshman year (7). Students are required to commit to two sequential summers of full-time research activities (with no summer classes or other summer job distractions) and 10 hours per week of lab activities during the intervening academic year. Although the more common summer-only research opportunities are great for providing exposure to nonmatriculated students, these and other short-term research activities can place a significant burden on the graduate students and postdocs who train the undergraduates (7). Based on our experience, most students will continue to work in the lab until they graduate. This approach has thus far been a win–win for the lab: The undergraduates receive valuable laboratory experiences and mentoring, and the graduate students and postdocs benefit by the long-term commitment of extra hands and the opportunity to strengthen their mentoring skills.

The mentoring, networking and experiences associated with extended undergraduate research activities could have a significant impact on the URM STEM pipeline and thereby help ensure that the science and engineering enterprise in the U.S. will have the talent pool necessary both to compete and to collaborate at the global level.

Michael F. Summers (summers@hhmi.umbc.edu) is a professor in the department of chemistry and biochemistry at the University of Maryland Baltimore County.

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- **Dale Sanders** John Innes Centre, Norwich, UK
- **John D Scott** Howard Hughes Medical Institute, University of Washington, Seattle, USA

Further information:

Conference: Stuart Pitson
stuart.pitson@health.sa.gov.au

Registration/Exhibition: Sally Jay
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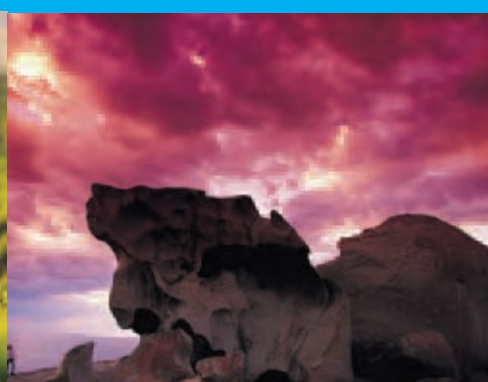

READER COMMENTS ONLINE

A tribute to midlevel scientists

Dr. (Lynn) Zechiedrich's essay is on target, but the emphasis was geared toward scientists who are stuck in a midlevel position or toward scientists who chose not to progress to the next level. I would like to add another choice: to step down. I marched up the ladder, tenured with external grants and my own lab, but with a heavy teaching load and no (teaching assistants). While those of us who gravitated toward (primarily undergraduate institutions) due to the emphasis on teaching, the odd aspect of working at a PUI is that the institutions expect the same level of funding and research productivity as Research I institutions. I found no time to be in the lab, to think of new ideas, to enjoy science. Instead of being stuck in a midlevel job, I was stuck in being a professor. The choice was to leave the life of a professor. I am back in the lab, pipetting and also writing more. Thus, rather than a fall-back position, I chose to move down, a rewarding change. Thank you for shedding light on midlevel scientists.
—MAUREEN SHUH, OCHSNER CLINIC FOUNDATION

Since the location of the Gala Dinner of the 1973 (International Union for Biochemistry) Congress in Stockholm had to be changed at the last minute, table sizes and protocol seating arrangements were modified as well, and I found myself, as a young postdoc, seated by mistake at the right side of congress president and Nobel prize winner Hugo Theorell. I was understandably thrilled and nervous, even more so due to the fact that Theorell had been a mentor of my mentor, Britton Chance, who gave with him the name to an enzymatic mechanism, the Theorell–Chance kinetic mechanism. And desperately wishing to ask a "clever" question I said: "What has been decisive for you, Professor Theorell, to receive the Nobel prize?" Humbly, Hugo Theorell answered: Years ago, a sergeant had planned an exercise with 100 soldiers outside the city. While he was instructing his men, a lady came, weeping. Minutes before, in that field where the exercise was planned, she had lost a ring of great personal value to her. Moved by the tears (but possibly also by the beauty) of the young woman, the sergeant decided the exercise of the day: Each soldier had to explore one meter of ground for the entire length of the field; before sunset, the ring had to be found. And, indeed, the ring was found! A soldier picked it up from the grass and brought it to the sergeant who, on his turn, brought it to the lady. Full of joy, she asked to meet the soldier who had made her so happy; shaking his hand, she thanked him very warmly and asked what she could do for him. The soldier bashfully answered: "I have no personal merit, madam; without the other 99 soldiers that have explored the field as carefully as I did, the ring could not have been found." Nurturing a culture of respect and esteem for those who are not always in the limelight will pay justice to science, which requires many more than 100 solders to allow one of them to go to the podium. —ANGELO AZZI, TUFTS UNIVERSITY

Words well chosen and expressed. The National Institutes of Health runs on the talent of the middle. Unfortunately, not all senior scientists are as egalitarian as you about giving credit where credit is due. —ANONYMOUS

Very well written! A sincere acknowledgement to the many scientists who work with deep enthusiasm.
—DONATELLA TOMBACCINI, UNIVERSITY OF FLORENCE

Are we doing a good job of teaching the groundbreaking research of our predecessors?

I have a poster of H.A. Krebs in my office (actually it is a poster of the Warburg bath I used every day of my graduate work with HAK). Students often ask who it is, and some are very surprised to hear that HAK was a real person! I wonder if all the cancer researchers who have rediscovered the Warburg effect also realize that he was a person.

—MALCOLM WATFORD, RUTGERS UNIVERSITY

What's new on Wild Types

Here's a snapshot of ASBMB Today science writer Rajendrani Mukhopadhyay's blog. Follow it at wildtypes.wordpress.com.

- **Kinase for secreted proteins found**
- **A salute to scientists**
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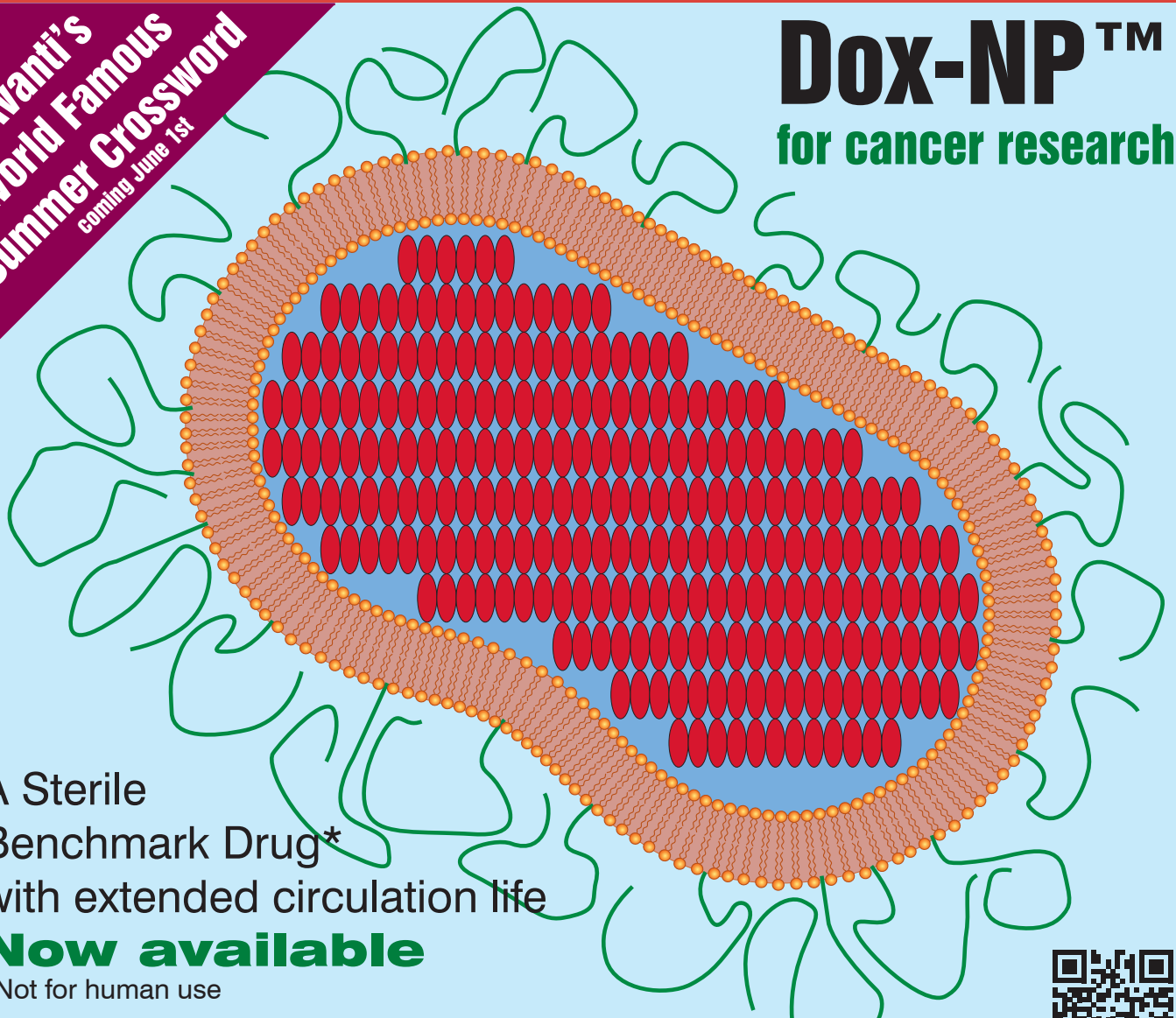

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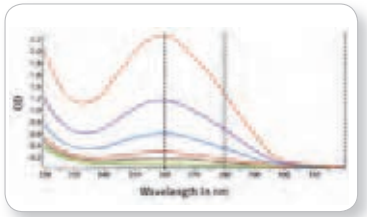

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