ASBMB today

Vol. 12 No. 2 February 2013

The other MALARIA PARASITE

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ASBMB TODAY PRESENTS THE FIRST INSTALLMENT IN THE ESSAY SERIES

DERAILED but UNDETERRED

American Society for Biochemistry and Molecular Biology

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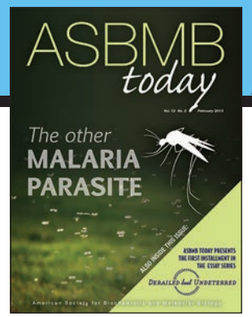

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ASBMB today

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Biochemistry and Molecular Biology

www.asbmb.org/asbmbtoday

editor's *note*

Derailed *but* Undeterred

Dear readers,

It gives me great pleasure to present this issue to you, as it debuts the first essay in our special series "Derailed but Undeterred." To my knowledge, this is the first personal essay series in the magazine's history.

As firsts often are, this one was terrifying. I had to summon up quite a bit of bravado even to suggest during one of our weekly ASBMB Today staff meetings that we solicit stories of failures, heartbreaks, illnesses and near-misses. I was relieved when it turned out my team was intrigued by the concept. But that relief deteriorated into apprehension when we put out the call for submissions and then turned to absolute disappointment when we had not received a single essay a few weeks later. I became certain this idea was, indeed, derailed, and I was feeling anything but undeterred.

Then it happened: The essays began trickling in, and they were more compelling than I'd imagined they would be. It turned out that people at all stages of their careers were willing to share publicly their fears and defeats. Furthermore, they were willing to share how they managed and overcame those fears and defeats.

While their stories vary widely in content and style, all the writers featured in this series send one message loud and clear: You have to have guts. You have to have guts to do science, to make it in science, to leave science and to return to science. You have to have guts to ask for and accept help. You have to have guts to keep going when darker days likely are ahead. You have to have guts to embark on a journey for which there is no map.

I do hope you will enjoy these tales of resilience, adventure and hard work. If you find them as inspiring as I have, perhaps you'll consider submitting an essay of your own that describes an obstacle or hardship that you have overcome or are facing. I've extended the submission deadline to March 31, because there are many other stories out there that need to be told.

Angela Hopp
Editor, ASBMB Today

president's *message*

On deck chairs and lifeboats

BY JEREMY BERG

Frequently, when relatively modest actions are proposed in the face of serious adversity, skeptics compare these adjustments to "rearranging the deck chairs on the Titanic." The implication is that the actions are pointless in the face of the larger challenge. Despite the saying, we know of no actual rearranging of deck chairs on the Titanic; however, we do know that there was a lifeboat policy (women and children first) that had tremendous impact on who survived. Even seemingly modest policies can influence events greatly.

The rearranging the deck chairs analogy has been raised repeatedly regarding the NIH policy of not allowing second (A2) amendments (i.e., second resubmissions) to grant applications, hereafter referred to as the No A2 policy. This policy grew out of the National Institutes of Health's Enhancing Peer Review initiative (1). The driving issue was that the percentage of funded R01 applications awarded upon initial submission (A0) had dropped from about 60 percent during the NIH budget-doubling period (1999 – 2003) to less than 30 percent in fiscal 2007 (2). Concomitantly, the percentage of grants that were funded in response to A2 applications increased from 10 percent during the doubling to more than 30 percent. The conclusion (supported by many specific anecdotes) was that study sections were queuing applications, providing outstanding scores to A2 applications while downgrading A0 applications, because the latter would have additional opportunities for funding. A consequence of this behavior was that outstanding research projects were being put into a holding pattern while they waited their turn to be given top scores.

The recommendation in the initial Enhancing Peer Review report (3) was that the NIH should "consider all applications as being new." The goal of this recommendation was to allow study sections to focus on the merits of a proposal without consideration of whether it would have additional chances for submission. Many in the scientific community reacted negatively to this recommendation (4), in part because it included the provision that reviewers would not receive access to comments about earlier submissions for the same or similar projects.

In response to this feedback, NIH leaders elected not to implement this recommendation. Instead, they decided to address the concern that outstanding projects were taking too long to be funded by reducing the number of allowable amendments from two to one (5). While shortening the time to funding for some outstanding applications, the No A2 policy also has the potential to eliminate applications (and applicants) from consideration if they are not successful after the first and final amendment.

This policy change also was met with considerable resistance from the scientific community. A petition containing more than 2,000 signatures (6) was submitted to the NIH expressing concern about the potential impact of the policy on investigators who submit applications that score very well but not well enough to be funded at the A1 stage. Key to the argument in the petition is the question of the level of discrimination of which the NIH peer-review system is capable. The petition claims that peer review cannot distinguish between a fifth percentile application and a 20th percentile application.

Based on an analysis I initiated while I was at the NIH (7), it is possible to evaluate this assertion quantitatively. Using about 400 competing renewal (type 2) R01 grants funded in fiscal 2006, I examined subsequent productivity as a function of the percentile scores given to the applications. To quantify productivity, I used the number of citations from 2007 to 2010 for research papers (as opposed to review papers), corrected for the time dependence for citations.

The data based on individual grants show considerable scatter with a correlation coefficient of $r = -0.09$, indicating a modest decrease in the productivity metric as the percentile score increases. The scatter may be influenced by many factors, including the limitations of this metric for determining true scientific merit, different publication and citation patterns for different research fields and, of course, limitations of the peer-review system in predicting subsequent productivity. Some of the scatter can be reduced through the use of running averages; i.e., by averaging productivity over grants with similar percentile scores. Using a running average over 10 grants reduces the scatter and produces a correla-

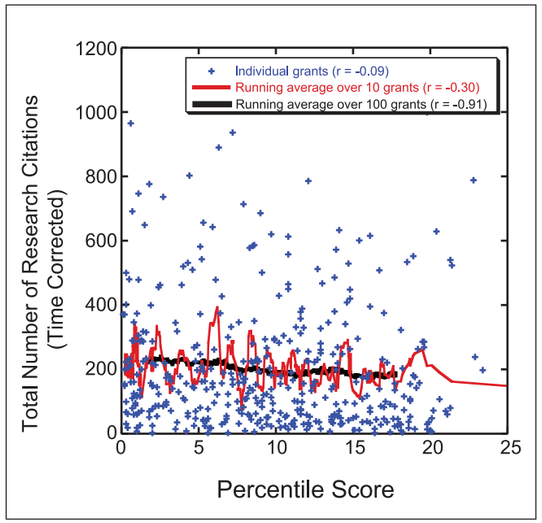

Figure 1. Research productivity as a function of percentile score for more than 400 competing renewal R01 NIGMS grants funded in FY06.

tion coefficient of r = -0.30. Using a running average over 100 grants produces a nearly straight line with a correlation coefficient of r = -0.91. The reduction in the productivity metric from the best-scored grants to the worst-scored grants (in this group, in the 15th to 20th percentile) is about 20 percent.

Is there any model for the uncertainty in scoring that accounts for the scatter observed in these data? In an attempt to answer this question, two options were considered. In the simpler model, the grants were ranked according to the productivity metric, and these rankings were converted to the effective percentile scores within the population. A random adjustment was made using a normal distribution with a given standard deviation, and the observed correlations between the rankings determined by these adjusted percentiles and the rankings determined by peer review were calculated. Calculations with standard deviations up to 30 percentile points revealed that this model underestimated the level of scatter in the data, indicating that other sources of scatter are important. The second model adds an additional source of productivity differences, dividing the applications into two classes, the more productive half and the less productive half. A constant percentile adjustment was included to account for the difference in the expected productivity between these two classes. Simulations showed that this model could account for the observed scatter with a standard deviation of 10 percentile points (as shown in Figure 2).

Thus the latter model suggests the uncertainty in scoring a competing renewal application is associated with a standard deviation of about 10 percentile points. Scores for new (type 1) applications are substantially more uncertain based on similar analyses.

With these estimates available, we now can model the potential impact of the No A2 policy in quantitative terms. Suppose that the overall standard deviation in scoring applications is 10 percentile points and that applications are funded up to the 12th percentile. What percentage of the applications that are truly in the top 12 percent will receive scores that are worse than the12th percentile? The results of simulations for standard deviations in scoring ranging from zero to 20 percentile points and funding cutoffs from 8 percent to 20 percent are shown in Figure 3.

These simulations reveal the answer to be 29 percent; that is, 29 percent of the applications that are actually in the top 12 percent of all applications would not be scored well enough to be funded. If we further assume the same scoring behavior applies to the unfunded applications resubmitted as A1 applications, this still leaves 8 percent of the top applications unfunded after two submissions. For a standard deviation of 15 percentile points and a funding cutoff of the 10th percentile – assumptions that are perhaps more likely, given the inclusion of new in addition to competing renewal applications and the current fiscal situation — the percentage of top applications still expected to be unfunded after two submissions is 14 percent.

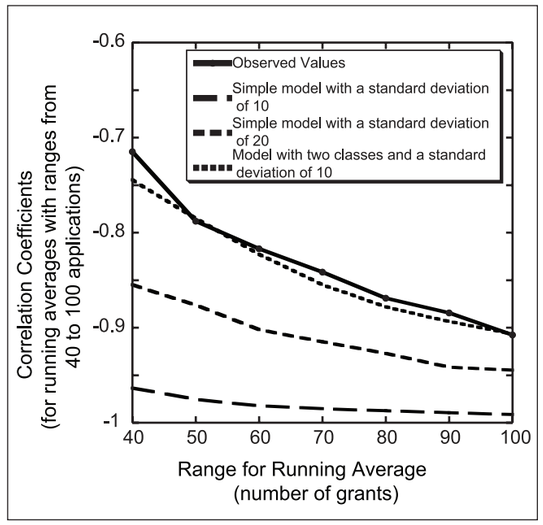

Figure 2. A model with two classes and a scoring uncertainty associated with a standard deviation of 10 percentile point accounts for the observed scatter in productivity.

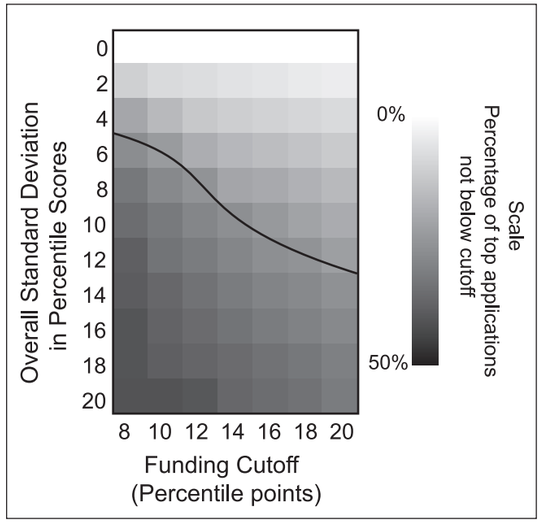

Figure 3. The results of simulations showing (via a gray scale) the percentage of applications that are actually better than the funding cutoff but are anticipated to score worse than the funding cutoff. The contour line shows the points where 25 percent of the top applications are expected to score worse than the cutoff.

On her Rock Talk blog, NIH Deputy Director for Extramural Research Sally Rockey recently posted some data regarding the impact of the No A2 policy (8). The data presented demonstrate that the fraction of R01 applications funded as A0 applications has increased. More specifically, the pool of awards that previously would have been expected to fund A2 applications is now about equally divided between A0 and A1 awards. Thus, while it is true based on simple arithmetic that the fraction of A0 and A1 grants had to increase (because funding at the A2 stage is no longer an option), the distribution of these additional awards between the A0 and A1 pools could have been less favorable if all the decrease in A2 awards had been reflected in an increase in A1 awards. Further, the blog post presents data indicating the time to funding for new investigators (whose grants were funded) is the same as that for established investigators whose new (as opposed to competing renewal) grants were funded. Nonetheless, based on the comments on Rock Talk and other blogs (9, 10, 11) many members of the scientific community remain concerned about the implications of the policy. Some have stated that going back to allowing A2 applications would increase the amount of meritorious science funded. However, the laws of arithmetic still apply: modifying the No A2 policy would not increase the total number of applications that could be funded.

Another compelling question is what happens to the applicants who have applications that are not funded after the A1 level. There are two schools of thought supported by anecdotes but (as of yet) little data. The first school believes that it should be relatively easy for any competent investigator to recraft his or her application so it passes the NIH filter used to determine if an application is sufficiently different to be counted as new. The NIH has provided some guidance about this filter (12) but, to my knowledge, has not provided the fraction of applications that have been returned because they are deemed to be too similar to a previous application. This school also believes that some fraction of the new applications being funded at the A0 stage are, in fact, appropriately recrafted proposals that were not funded previously. The second school believes many investigators whose applications are not funded after A1 submission are dropping out of academic research because they are not able to (or do not wish to) develop research projects sufficiently distinct to be considered new. I have no doubt that both events are occurring in specific cases, but data are needed. To that end, I have written to the NIH on behalf of the American Society for Biochemistry and Molecular Biology's Public Affairs Advisory Committee encouraging the NIH to do such analyses and make the results available.

Remarkably, the journal Nature published an editorial on this subject entitled "An Unhealthy Obsession" (13). The editorial, which acknowledges that the concerns about the impact of the No A2 policy are well-founded, suggests that the U.S. biomedical research community is unwise to continue to push for further reconsideration of the policy when the real issue relates to the historically low pay lines. The editorial is correct that the community must advocate as effectively as possible for growth in the NIH budget. We have been reaching out to ASBMB members to encourage them to contact their members of Congress and have provided (via an email to members) a useful tool that makes it very convenient for them to do so.

Thanks to the nearly 1,400 members who have participated, this effort has resulted in more than 4,400 letters to 349 members of the U.S. House and Senate. We need even greater participation in the future, and there simply is no good reason for any appropriate ASBMB member not to join the effort. With that said, this is not an excuse

for not challenging the NIH to develop policies that best support the biomedical research enterprise.

To return to the Titanic analogy, we are certainly in waters full of icebergs in this current climate, and we need to do everything we can to help the captain and crew steer clear of them. That does not mean, however, that we should neglect to urge careful examination of the policies that determine how access to the limited number of seats in the lifeboats is determined. The long-term health of the biomedical research enterprise depends on it.

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

REFERENCES

1. http://enhancing-peer-review.nih.gov/
2. http://nexus.od.nih.gov/all/2012/11/28/the-a2-resubmission-policy-continues-a-closer-look-at-recent-data/
3. http://enhancing-peer-review.nih.gov/meetings/NIHPeerReviewReportFINALDRAFT.pdf
4. http://www.faseb.org/portals/0/pdfs/opa/2008/NIHPeerReviewSelfStudy.pdf
5. http://grants.nih.gov/grants/guide/notice-files/NOT-OD-09-003.html
6. http://www.asbmb.org/asbmbtoday/asbmbtoday_article.aspx?id=12158
7. https://loop.nigms.nih.gov/index.php/2011/06/10/productivity-metrics-and-peer-review-scores-continued/
8. http://nexus.od.nih.gov/all/2012/11/28/the-a2-resubmission-policy-continues-a-closer-look-at-recent-data/
9. http://www.nature.com/news/2011/110329/full/471558a.html
10. http://scientopia.org/blogs/drugmonkey/2012/10/16/return-of-the-a2-revision-for nih-grants
11. http://writedit.wordpress.com/2012/11/28/a2-nevermore/
12. http://public.csr.nih.gov/aboutcsr/NewsAndPublications/PeerReviewNotes/Documents/PRNMay20125302012.pdf
13. http://www.nature.com/news/an-unhealthy-obsession-1.11953

CALL FOR NOMINATIONS: 2014 FASEB EXCELLENCE IN SCIENCE AWARD

The Federation of American Societies for Experimental Biology is seeking nominations for its 2014 Excellence in Science Award that recognizes the significant accomplishments of women scientists. We look forward to another list of nominees that reads like a *"Who's Who"* of international science, containing the names of outstanding women in science who have accomplished scientific work of lasting impact and have contributed substantially to training the next generation of scientists.

Nomination Procedures:
Nominators and their candidates must be members of a FASEB member society. Self-nominations will not be accepted.

Submissions must include all of the following documents uploaded individually in PDF format.

1. Nomination letter, setting forth in *detail:*
- contributions to the field that represent the nominee's outstanding achievement in science;
- leadership and mentorship;
- evidence of national recognition;
- honors and awards
- synopsis of selected bibliography

2. Full curriculum vitae, including *all* publications
- The CV must document all publications, leadership roles, mentorship, teaching, honors and awards
- 5 reprints
- 3 letters of support from peers
- 3 trainee letters of recommendation

For complete award details go to http://bit.ly/ecOK9W.

For questions, please contact:
Linda Stricker
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Bethesda, MD 20814-3998
Tel. (301) 634-7092
Email: lstricker@faseb.org

All nominations must be submitted on the FASEB Excellence in Science Award website by March 1. PAPER SUBMISSIONS WILL NOT BE ACCEPTED.

'How Scientists Can Save the World'

We hope you'll attend the public affairs session at the annual meeting in April

BY BENJAMIN CORB

Whether it's by conducting research that leads to breakthroughs, treatments and cures for the costly diseases that ravage the population; providing cutting-edge medical care for an aging population; feeding a global community that is taxing our current resources; or identifying new, sustainable sources of energy, the biochemists and molecular biologists of today — and those training for tomorrow — hold the keys to unlocking solutions to some of the biggest problems facing the nation and the world in the 21st century. These global challenges coincide with the greatest fiscal challenges the U.S. has faced since early in the 20th century and at a time when U.S. policymakers are making crucial decisions about the nation's ability to support and invest in science.

We seek to shine an appreciative, enthusiastic and supportive light on the scientists who toil every day...

The scientific community should embrace its leadership role and advocate strongly for the future of the research enterprise. The American Society for Biochemistry and Molecular Biology public affairs symposium at Experimental Biology 2013, titled "How Scientists Can Save the World," will focus on how individual investigators can ensure scientific progress. With the adage about catching more flies with honey than vinegar in mind, we seek to shine an appreciative, enthusiastic and supportive light on the scientists who toil every day in university and industry laboratories across the nation and world.

Helping to deliver this message will be two individuals who exemplify what determination and enthusiasm can do for the scientific enterprise. First will be Craig Mello, a biologist and professor of molecular medicine at the University of Massachusetts Medical School. Mello won the 2006 Nobel Prize in physiology or medicine along with Andrew Z. Fire for the discovery of RNA interference. Mello's research breakthroughs have not only revolutionized molecular medicine but also have launched a multibillion-dollar RNAi therapeutics industry built on his initial findings. Additionally, Mello is a proven advocate for federal support for investments in biomedical research and has participated in congressional briefings in the past. Mello is a staunch advocate for National Institutes of Health funding and for scientists to have their voices heard in the political discourse.

Joining Mello will be former U.S. Rep. Patrick Kennedy. During the Democrat's time representing Rhode Island in Congress, Kennedy was a vocal supporter of federal investment in biomedical research, particularly in the areas of drug abuse, addiction and neuroscience. Influenced by his own struggles with addiction, Kennedy long has supported federal efforts to better understand addiction to help other Americans overcome it. His support for basic research was emboldened as his father, the late U.S. Sen. Edward (Ted) Kennedy, struggled with and ultimately died of brain cancer in 2009. Additionally, Patrick Kennedy is a member of the board of directors of one of Washington's most revered biomedical funding advocacy groups, Research!America.

Join us for an informative and inspirational discussion on the important role scientists play in advancing the nation's scientific enterprise, solving our most pressing problems and maybe even saving the world.

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

Five decades after the discovery of cytochrome P-450

Tsuneo Omura, professor emeritus at Kyushu University, was honored late last year for his contributions to the field of cytochrome P-450 research at a symposium and ceremony in Fukuoka, Japan, on the 50th anniversary of his seminal work. Omura's 1962 communication with Ryo Sato in the Journal of Biological Chemistry reported that a pigment in liver microsomes that bound carbon monoxide to give an absorbance maximum at 450 nm was a heme protein. Omura and Sato named the protein a cytochrome, specifically cytochrome P-450 (for pigment 450). That report was followed in 1964 by two more papers, both now considered JBC Classics. Omura was issued a letter of recognition from the JBC editor Martha Fedor and Co-editor Herb Tabor at the Fukuoka event by F. Peter Guengerich of Vanderbilt University, who serves as an associate editor for the JBC and who is widely known and respected for his own work on cytochrome P-450, which he spoke about at the symposium.

Dawson's group among the first supported by new Parkinson's biomarker program at NINDS

DAWSON

The National Institute of Neurological Disorders and Stroke last month announced a new initiative aimed at accelerating the identification of biomarkers for Parkinson's disease. So far, the Parkinson's Disease Biomarkers Program has funded nine research teams. Among them is a group led by member Ted Dawson, a professor at Johns Hopkins University. Dawson's team is focusing on the early clinical signs of the movement disorder, including changes in cognition and sleep, to see how they're connected with potential biomarkers in cerebrospinal fluid and blood. "Our goal is to accelerate progress toward a robust set of biomarkers for Parkinson's disease by supporting researchers who have strong leads or innovative approaches, bringing them together, and making it easier for them to share and analyze data across studies," Story Landis, director of the NINDS, said of the new program. The initiative also includes an online data-sharing platform where PDBP investigators and all other interested researchers can deposit and access data and request biological samples. Find out more at http://pdbp.ninds.nih.gov/.

Matrix biology society gives Hudson its highest honor

HUDSON

Billy Hudson of Vanderbilt University won the 2012 Senior Investigator Award from the American Society for Matrix Biology. Hudson received the award, the organization's highest honor, late last year at the ASMB's annual meeting in San Diego. Hudson, who is director of the Center for Matrix Biology at Vanderbilt and founder of the science-outreach Aspirnaut program, was recognized for his contributions to our understanding of type IV collagen, found in the basement membrane that underlies all epithelial cells. Hudson also determined the primary structure of the collagen molecule NC1, which combines in a roped structure three chains of collagen, stabilizing a network that serves as part of the kidney-filtration barrier. More recently, Hudson's team found a novel chemical bond and the enzyme responsible for the bond reinforcing collagen IV networks in connective tissue.

Three members win national medals for science, technology

Three members were recognized by President Obama and issued the federal government's highest honors in their fields: the National Medal of Science and the National Medal of Technology and Innovation. Leroy E. Hood, founder and president of the Institute for Systems Biology in Seattle, and Lucy Shapiro of Stanford University School of Medicine both won the National Medal of Science. Robert Langer of the Massachusetts Institute of Technology won the National Medal of Technology and Innovation. In a statement, Obama said, "I am proud to honor these inspiring American innovators. They represent the ingenuity and imagination that has long made this nation great — and they remind us of the enormous impact a few good ideas can have when these creative qualities are unleashed in an entrepreneurial environment."

IN MEMORIAM:

Rita Levi–Montalcini

Neurologist Rita Levi-Montalcini passed away Dec. 30 in Rome at the age of 103. She was best known for her discovery of nerve growth factor, for which she shared the Nobel Prize in physiology or medicine with Stanley Cohen in 1986. Her research improved our understanding of the way cell growth factors function and of how diseases such as dementia, diabetes and cancer progress. Born 1909 in Turin, Italy, to Jewish parents, Levi–Montalcini faced oppression due to her gender and religion. She was forced to leave the University of Turin in 1938 amid rising anti-Semitism but continued with her research in a home laboratory. She joined Washington University in 1946 and went on to establish a research unit in Rome in 1962. She continued to split her time between Rome and St. Louis until she retired from the university in 1977. After retiring, she stayed active in science, and she continued to contribute to important discoveries, such as identifying the role of mast cells in pathology. She received numerous accolades during her life, including the National Medal of Honor and election into the National Academy of Sciences.

IN MEMORIAM:

Elwood Jenson

Elwood Jenson died of pneumonia Dec. 16 in Cincinnati at the age of 92. He is known worldwide for his work with hormone receptors; in particular, he isolated and discovered the importance of estrogen receptors in breast cancer. His work led him to be bestowed with honors such as membership in the National Academy of Sciences in 1974 and the Lasker Award in 2004 for outstanding contributions to basic and clinical medical research. Jenson received his bachelor's degree from Wittenburg College and his Ph.D. in organic chemistry from the University of Chicago. He joined the faculty at the University of Chicago in 1947 and was an original member of the research team at the Ben May Laboratory for Cancer Research, where he became director in 1969. He left the university in 1990. However, Jenson continued to be engaged actively in research as a visiting scholar and professor at a number of prestigious institutions. Jensen joined the University of Cincinnati in 2002 and continued with his research until last year..

– Compiled by Kyeorda Kemp

Please submit member-related news and accolades to asbmbtoday@asbmb.org.

A Science Revolution

UNDERGRADUATE UPRISINGS AT THE ANNUAL MEETING
APRIL 20 – 24 IN BOSTON

THE BIOCHEMISTS ARE COMING!
Annual meeting orientation for undergraduates

11:30 A.M. TO NOON SATURDAY, APRIL 20

The word is out: Biochemists and molecular biologists are invading the Boston Convention Center armed with their latest research findings. Undergraduates, especially those attending a scientific conference for the first time, are invited to an orientation session that will help them navigate the scientific talks, poster presentations and social events.

AN INTERCONTINENTAL CONGRESS
The 17th annual undergraduate research poster competition

1 P.M. TO 4:30 P.M. SATURDAY, APRIL 20

Hear ye! Hear ye! Calling all undergraduate first authors for the annual poster competition. This is your opportunity to engage fellow scientists in heated discussions. This event is mandatory for all travel award winners.

DECLARATION OF INDEPENDENCE: A WORKSHOP
Beyond College: Coping with Some Common Challenges

4:45 P.M. TO 5:45 P.M. SATURDAY, APRIL 20

College is almost over. What will you do with your forthcoming independence? The ASBMB Education and Professional Development Committee will discuss some common pitfalls and ways of avoiding them.

BOSTON TEA PARTY: BOTTOMS UP!
An undergraduate breakfast with Helen M. Berman

7 A.M. TO 8 A.M. SUNDAY, APRIL 21

Throw a few breakfast beverages back with an award-winning scientist! No destruction of tea is required. All undergraduate attendees are invited to join Helen M. Berman of Rutgers University, winner of the Delano Award for Computational Biosciences, for a free breakfast to discuss science and scientific careers. Register by Feb. 15 at www.asbmb.org/breakfast. Space is limited, and Undergraduate Affiliate Network members are given registration priority.

BOSTON TEA PARTY: ROUND 2
An undergraduate breakfast with Olke C. Uhlenbeck

7 A.M. TO 8 A.M. MONDAY, APRIL 22

Another chance to schmooze with an award-winning scientist! All undergraduate attendees are invited to join Olke C. Uhlenbeck of Northwestern University, winner of the 2013 ASBMB Fritz Lipmann Lectureship, for a free breakfast to discuss science and scientific careers. Register by Feb. 15 at www.asbmb.org/breakfast. Space is limited, and Undergraduate Affiliate Network members are given registration priority.

FOR DETAILS ABOUT THE COMPLETE UNDERGRADUATE PROGRAM, VISIT WWW.ASBMB.ORG/REVOLUTION2013

One small step for the future

Training future academic clinicians for multidisciplinary research teamwork

BY BRUCE J. BAUM AND FREDERICK P. OGNIBENE

Increasingly, we hear that future science must take on a team approach (1), without classical, single-discipline academic silos. This future likely will involve public–private partnerships linking academia and industry with each other and the public sector (2, 3). A key to the formation of any successful multidisciplinary team is communication, including the appreciation for and understanding of each other's expertise. Through its new, yearlong Medical Research Scholars Program, the National Institutes of Health is trying to seed the fields of translational research by training one necessary segment of future biomedical science teams, health professional students, across the entire spectrum of research, from basic discovery to epidemiology and back. The overarching goal, in the spirit of the NIH Roadmap, is to help "advance science and enhance the health of the nation" (4).

Since its founding, the NIH has been committed to the training of future biomedical researchers and clinician–scientists. As a result, many American basic scientists received their Ph.D.s through NIH-sponsored training programs, as did many double-degreed clinician–scientists. When one of us (Baum) completed his Ph.D. in biochemistry in the mid-1970s through such a training program, the future looked bright for an academic research career, and it was. However, right now the future seems uncertain for all stripes of young biomedical scientists. As Bob Dylan sang in 1964, "The times they are a changin'."

A major accelerator for change in biomedical research occurred in 2003, when then-NIH Director Elias Zerhouni published a paper in the journal Science announcing the NIH Roadmap (5). Two of the three major themes described were "research teams of the future" and "reengineering the clinical research enterprise" (5). Since then, translational research and multidisciplinary science have become catchwords, while the country's current economic woes have led to concerns about the financial support available for and the preeminence of American biomedical science (6, 7). Not surprisingly, the bidirectional research emphasis and economic challenges have sparked concern about career opportunities available for young scientists and students, whether they are focused on either the basic or clinical science ends of the biomedical research continuum (8, 9).

Clinical Research Center

IMAGE CREDIT: NATIONAL INSTITUTES OF HEALTH

The MRSP evolved from two past highly successful yearlong intramural NIH training programs that ran in parallel: the Clinical Research Training Program, which existed for 15 years, and the Howard Hughes Medical Institute-NIH Research Scholars Program, which existed for more than 25 years. These two programs allowed more than 1,400 medical, dental and veterinary students to experience the spectrum of health-related science, albeit in a nonintegrated way. Impressively, the majority of alumni from these two programs, who have been tracked after completing all of their clinical training, are engaged in research. Both programs, however, ended with the close of the 2011 – 2012 academic year, and in their place emerged the MRSP, a single program in which student–scholars are exposed to all facets of biomedical research.

Importantly, the MRSP is also a public–private partnership, with financial support coming jointly from the NIH common fund (i.e., the Roadmap initiative) and generous private-sector partners, particularly Pfizer Inc. and the Helmsley Charitable Trust. Our objective was to develop a dynamic training experience for the selected students, who typically participate between their third and fourth years of health professional school. The initial 2012 – 2013 MRSP class has enrolled 45 students, with an ultimate annual training capacity goal of about 70.

We think that by providing focused and rich opportunities for students to become engaged actively in research early in their clinical careers, we may help foster an appreciation of the entire process of scientific discovery. Further, we anticipate that individuals trained in the context of team science will recognize and be better prepared for the variety of long-term career pathways spanning the range of biomedical research. To achieve this goal, in addition to closely mentored research training, the MRSP provides an academic curriculum highlighting the diverse ways that scientific careers develop, training in human subjects research, and teaching rounds utilizing patients enrolled in NIH research protocols. Will this pedagogical experiment succeed? Only time will tell, but clearly traditional scientific training strategies must change.

The MRSP represents one small step in preparing individuals for a future in science quite different from the departmentally based and narrowly focused training most young scientists currently receive. While much of the outcry about multidisciplinary teams for translational research has focused on clinical scientists in training (9, 10), the need for new training models clearly exists across the research spectrum. The kinetics of successful translational research endeavors are bidirectional (5, 11) and so must be the training of America's future translational research scientists.

About the MRSP

- Medical, dental and veterinary students, who are U.S. citizens or permanent residents, are eligible to apply.
- Applications are accepted annually from Oct. 1 through Jan.15.
- The 2012 – 2013 student stipend is $33,700 per year.
- Housing is available on or adjacent to the NIH campus.
- Health insurance is provided.
- Relocation expenses are provided.
- There is a student education fund for elective courses and conference attendance.
- A weekly dinner is held with NIH and university-based senior scientists.
- Each student has a dedicated senior NIH adviser.
- Mentored research occupies about 85 percent of students' time.
- Additional academic activities include
  a) scientific lectures (basic to clinical),
  b) a journal club focused on clinical research issues,
  c) patient rounds illustrative of translation from basic science to clinical protocol,
  d) training in academic leadership,
  e) Pfizer-provided training in the drug-development process and
  f) elective NIH graduate courses and lectures.

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REFERENCES

1. Disis, M. L. and Slattery, J. T. *Sci. Transl. Med.* **22**, 1 – 4 (2010).
2. Editorial. *Nat. Med.* **18**, 469 – 470 (2012).
3. Bornstein, S. R. and Licinio, J. *Nat. Med.* **17**, 1567 – 1569 (2011).
4. Zerhouni, E. A. *JAMA* **295**, 1352 – 1358, (2005).
5. Zerhouni, E. A. *Science* **302**, 63 – 72, (2003).
6. Gura, T. *The Lancet* **380**, 1371 – 1372 (2012).
7. Sun, G. H. et al. *N. Engl. J. Med.* **367**, 687 – 690 (2012).
8. Kaplan, K. *Nature* **485**, 535 – 536 (2012).
9. Roberts, S. F. *et al. Acad. Med.* **87**, 266 – 270 (2012).
10. Edelman, E. R. and LaMarco, K. *Sci. Transl. Med.* **135**, 1 – 4 (2012).
11. Nussenblatt, R. B. *et al. J. Transl. Med.* **12**, 1 – 3 (2010).

Retrospective

Robert J. Cotter (1943 – 2012)

BY GERALD W. HART AND PHILIP A. COLE

Bob Cotter was not only a pioneer in the development of mass spectrometry and its application to difficult biological problems, but also he was an outstanding teacher, scholar and citizen of the larger scientific community as well as a fantastic resource and colleague for the Johns Hopkins University community. Bob will be remembered mostly for his inventive applications of mass spectrometry to biomedical science, his novel instrument designs and his leadership within the mass-spectrometry community. He will be sorely missed.

Bob grew up in Massachusetts and graduated from the College of the Holy Cross in 1965. He obtained his Ph.D. in physical chemistry at Johns Hopkins University, where he worked on gaseous ions with Walter Koski. After completing his Ph.D., Bob took a teaching position at Gettysburg College, where after three years he was denied tenure and his contract was terminated. Bob overcame this setback by re-entering basic research in 1978, initially as a senior postdoc in the Johns Hopkins Medical School Department of Pharmacology and Molecular Sciences, where he worked with his future wife, Catherine Fenselau, who also is a world-leading researcher in mass spectrometry. Bob soon was promoted to the faculty because of the exceptional promise evidenced by his inventions of clever new methods to analyze biomolecules in mass spectrometry. Bob had a highly productive career at Johns Hopkins, where he rose to the rank of full professor in 1992, co-authoring two books on time-of-flight mass spectrometry and more than 334 papers during his career. Bob remained at Johns Hopkins until his passing.

Bob is most well-known for his invention of the curved-field time-of-flight ion separation method, known as the reflectron, which was commercialized by Kratos. He helped to develop miniaturized time-of-flight mass spectrometers for use by NASA in the exploration of space, in particular in efforts to find life on Mars. His contributions to biomedical research are legion, but his most recent work contributed to our understanding of the histone code, antigen presentation and the regulation of cell division.

Bob's love of science and infatuation with time-of-flight mass spectrometry is best illustrated by the lyrics to a song he composed called "Time-of-Flight":

Time-of-flight
It's all right
Measures every ion in sight
Start pulse here
Stop pulse there
Looks at masses
Everywhere
Our resolution's growing every day!
'Cause those peptides and proteins are making big ions

So keep your eye on my flight tube
Gonna stand the world on its ear
And you'll see just how much we've grown
When we start mapping
Your proteome!

Time-of-flight
Line of sight
Reflectrons make the energy right
We use UV
And matrices
Any wavelength
That you please
Our resolution's growing every day!
'Cause those peptides and proteins are making big ions
Those peptides and proteins are making big ions

Time-of-flight, it's all right
Yes, and it's out of sight
Today!

The loss of Bob will affect adversely the research programs of his many collaborators. His expertise and insights greatly enriched the scientific value of many diverse areas of research and led to many discoveries that would not have been possible without his involvement.

Left: Bob Cotter, sporting his lab's Middle Atlantic Mass Spectrometry Facility shirt, in 1985. Right: Cotter entertaining in 2006.

Bob received many well-deserved awards over the years, but some of the most prestigious were the American Society for Mass Spectrometry's Award for a Distinguished Contribution in Mass Spectrometry (2011), the American Chemical Society's Frank H. Field and Joe L. Franklin Award for Outstanding Achievement in Mass Spectrometry (2011), and the American Chemical Society Divison of Analytical Chemistry's Award in Chemical Instrumentation (2009). Bob served as president of ASMS from 1998 to 2000 and held multiple positions within the United States Human Proteome Organization.

He started a musical group, the Pharm Boys, which played easy-listening songs at Christmas, and he directed and acted in humorous skits that lampooned his colleagues and himself.

Bob received worldwide recognition for his incredible record of achievement. But he was more than the sum of his many accomplishments. He was a delightful colleague, and he particularly loved department social events. He started a musical group, the Pharm Boys, which played easy-listening songs at Christmas, and he directed and acted in humorous skits that lampooned his colleagues and himself.

Bob loved to tell the true story of how he learned that his promotion to full professor had gone through. In those days, the department faculty contributed financially to the departmental holiday party, with an assistant professor giving $20, an associate professor $35 and a full professor $50. Bob, an associate professor at the time, was spotted by the department administrator in the hall armed with her checklist of who owed what. She nonchalantly asked Bob for a $50 contribution. Irritated that he was being asked for more than the expected amount, Bob complained that associate professors had to pay only $35. The administrator shot back that Bob had just been promoted, disarming Bob from a further reply except for handing over the required larger amount.

We all have lost a great friend, teacher and intellectual leader.

Gerald W. Hart (gwhart@jhmi.edu) is a professor at Johns Hopkins University and an associate editor for both the Journal of Biological Chemistry and Molecular and Cellular Proteomics. Philip A. Cole (pcole1@jhmi.edu) is a professor at the Johns Hopkins University.

The other MALARIA PARASITE

Researchers turn their attention to Plasmodium vivax, an ill-understood parasite that causes most malaria cases outside of Africa.

BY RAJENDRANI MUKHOPADHYAY

The year 2010 saw 216 million cases of malaria and an estimated 655,000 deaths from the disease, according to the World Health Organization's 2011 World Malaria Report. Ninety-one percent of the deaths occurred in tropical regions of Africa, and an overwhelming 86 percent of the dead were children under 5 years old. The most likely culprit of those cases was the parasite Plasmodium falciparum. Given its lethality, much research has been done over the past 40 years to try to wipe out the pathogen.

But P. falciparum is not the only parasite that causes deadly malaria: Plasmodium vivax is another that puts about 3 billion people living in other parts of the world at risk of contracting malaria. But because of the intense focus on P. falciparum's ravages in Africa, malaria researchers say efforts to understand P. vivax malaria have been sorely neglected.

Malaria researchers say that the ignorance has to be rectified. P. vivax is rampant in Asia, South America and the southern Pacific. Ivo Mueller at the Walter and Eliza Hall Institute of Medical Research in Australia rattles off a few numbers to make the point: In Brazil, P. vivax accounts for 90 percent of malaria cases. In China, P. vivax causes between 80 and 90 percent of malaria cases. "There is no way, if you do malaria research outside of Africa, for you to ignore that parasite," Mueller says.

But working with P. vivax is much more challenging than working with P. falciparum. Lee Hall, chief of parasitology and international programs at the National Institute of Allergy and Infectious Diseases, says the obstacles to studying P. vivax became grimly apparent when the Bill and Melinda Gates Foundation's call to arms in 2007 for malaria eradication got researchers thinking deeply about how to achieve the goal. "There are a lot of scientific and technical hurdles that are still significant impediments. The clinical aspects too are quite challenging," he says. If malaria eradication is to be achieved, says Hall, the scientific, technical and clinical issues surrounding P. vivax have to be understood. And therein lies the problem.

NEGLECT OF A PARASITE

Malaria is a disease defined by chills, sweating and fevers brought on by the bursting of red blood cells and the possible release of toxins produced by Plasmodia parasites. Five parasites have been identified so far to cause malaria in humans: P. falciparum, P. vivax, P. malariae, P. ovale and P. knowlesi. The parasites are transmitted from person to person by the Anopheles genus of mosquito.

Current distribution analyses of pathogenic Plasmodium species in humans shows that P. falciparum is more prevalent in tropical regions, while P. vivax is more prevalent in South America. Both parasites are prevalent in southeastern Asia and the western Pacific.

P. malariae can occur in all areas stricken with malaria, but its appearance is usually low. P. ovale is widespread mostly in tropical Africa, whereas P. knowlesi infection so far is known to occur only in certain forested areas of southeast Asia, such as in Malaysia.

Throughout the 20th century, P. falciparum infections were known as "malignant" malaria. In contrast, P. vivax infections got slapped with the unfortunate adjective "benign." The word gave the impression that P. vivax didn't send its victims to the grave. But that is not true. "The fatality rate with falciparum tends to be higher, but it doesn't mean that vivax malaria is a benign disease," says Mueller. "Vivax kills as well, just not as often."

The notion that P. vivax wasn't as dangerous as P. falciparum twisted its clinical record. There is speculation among malaria researchers that, as a result of colonial rule and medical standards of the day, medical doctors in India and other regions in the 19th and 20th centuries were not allowed to attribute the cause of death to P. vivax malaria, says Rhoel Dinglasan at the

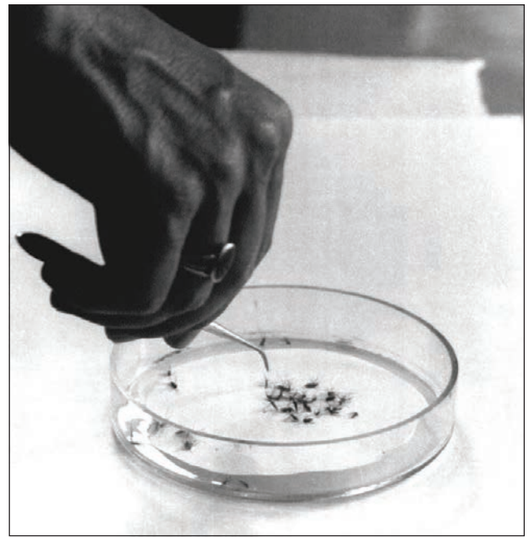


IMAGE CREDIT: PHILIP BOUCAS/WORLD HEALTH ORGANIZATION

A mosquito-eradication campaign in Iran showed that mosquitoes eventually developed resistance against insecticides. This image was taken in 1958 in Iran when a World Health Organization team went to help the Institute of Parasitology and Malariology in Tehran to organize field tests in the city of Shiraz, where mosquitoes were reported to be resistant.

IMAGE CREDIT: WORLD HEALTH ORGANIZATION

In the microscopy laboratory at Cambodia's National Center for Malaria, personnel look at blood slides for malaria.

Johns Hopkins School of Public Health. They had to list a different infection simply because the conventional wisdom was that a P. vivax infection could not be lethal.

P. vivax's neglect is also compounded by the fact that it is a trickier organism to study than P. falciparum. It has, thus far, eluded all efforts to be cultured stably in vitro. "We've been able to culture Plasmodium falciparum since the mid- to late 1970s. Because we can culture it, we have a huge arsenal of molecular and other tools," says Mueller. The availability of P. falciparum in in vitro cultures means researchers can isolate large amounts of the parasite at close to 100 percent purity.

The lack of in vitro systems for P. vivax forces malarial researchers to purify the parasite from blood samples taken from patients. To confound matters, P. vivax infects only reticulocytes, which are young red blood cells that make up about 1 percent to 2 percent of a person's total blood cell count. So the amount of parasite circulating through an infected person's system is very low. The best researchers can do is to get about 80 percent purity with their preparations.

The lack of culturing methods also means that drug development against P. vivax is hard, says Mueller. For P. falciparum, in vitro assays allow researchers to screen libraries of potential drugs against the possible targets in the parasite. P. vivax lacks those in vitro assays, so drug screening is hard to do.

In short, malarial researchers studying P. vivax are in a tough spot. "Progress in vivax research is slower than in falciparum research," says Mueller. "It takes more effort and more money to get the same kind of results as you would get for falciparum."

DRUGS AND VACCINES

In the current effort to eradicate malaria (there were other malaria eradication campaigns in the 20th century that failed), the Gates Foundation and other agencies have devoted resources in the past five years to develop new drugs to treat malaria cases and vaccines to halt the transmission of the parasites. For drugs and vaccines against P. vivax, the challenges are several-fold. One is P. vivax's biology.

The parasite has several stages in its lifecycle that happen in different places in the mosquito and human bodies. The human blood circulation system is one such location. To date, clinicians have been able to treat P. vivax's blood stages with common malarial drugs, because the parasite has not yet acquired the same kind of resistance P. falciparum has. But it may not remain so easy. "We can still treat vivax in many parts of the world with chloroquine, although choroquine resistance in vivax is rising," notes Mueller.

Unlike P. falciparum, which lives out the human part of its lifecycle in the blood, P. vivax has a dormant stage while it is in the human liver. Even if the blood-circulating form of P. vivax gets cleared out by drugs, the parasite can continue to lurk hidden deep inside the liver, and the person carrying the dormant P. vivax doesn't show any symptoms of malaria. Then, by an unknown mechanism, the parasite bursts forth anywhere between a few months to several years after initial infection, infects the reticulocytes and causes the patient to relapse with malaria. Mosquitoes pick up the parasites from infected people and spread them, continuing the cycle of transmission.

Mario Henry Rodriguez-Lopez at the National Institute of Public Health in Mexico says this dormant form of P. vivax is a major problem. He describes how patients get treated with chloroquine for the blood forms but 10 percent of those patients end up relapsing, because the dormant P. vivax emerges from the liver and sets off another cycle of infection. In contrast, P. falciparum doesn't have a dormant stage, so it always can be targeted in the blood with drugs, assuming it hasn't acquired resistance to those drugs.

A drug called primaquine attacks P. vivax when it's in the liver, but the drug has some serious drawbacks. Primaquine can't be administered to children and pregnant women and can be toxic to people with a deficiency in glucose-6-phosphate dehydrogenase, an enzyme found in red blood cells. In developed countries, patients with P. vivax infections can be tested for the deficiency, but in developing countries, where resources are scarce, testing for the enzyme deficiency is an added economic and public health burden.

The second problem with primaquine is related to dosing. Like an antibiotic, it needs to be taken for seven to 14 days, even if the symptoms of infection are gone. "You try to get somebody to take a seven-day drug when they no longer feel sick! We don't manage to do that," says Mueller. He adds that a drug being developed, tafenoquine (an analog to primaquine), needs to be taken for only a couple of days. But it still doesn't get around the problem of the patients who have the enzyme deficiency.

With the current limited arsenal of drugs, a country like Mexico faces the following scenario: "In the last six or seven years, we haven't had any falciparum cases. But what remains is Plasmodium vivax," says Rodriguez-Lopez, because the dormant liver form eludes treatment and keeps spreading.

Malaria eradication efforts in the 20th century focused on killing mosquitoes to stop the transmission. In Africa, P. falciparum is transmitted mainly through the mosquito Anopheles gambaie. But going after just the mosquitoes has proved to be ineffective. There are 500 known Anopheles species; to date, 40 of them have been studied, and all 40 carry Plasmodium. Even though it has a penchant for Anopheles gambaie, P. falciparum lets other Anopheles mosquitoes carry it. P. vivax appears to be even more promiscuous and can be carried by several mosquito species. Going after all Anopheles mosquitoes would be akin to herding cats.

One angle researchers, including Dinglasan at Johns Hopkins, have taken with vaccine development is to block the transmission of P. vivax. He and his group have been searching for ligands in the microvilli of the mosquito midgut, where the parasite stays during one part of its lifecycle. They identified a protein called alanyl aminopeptidase N and are pursuing it as a vaccine antigen to prevent transmission broadly, irrespective of the mosquito or parasite species. The idea is to immunize people with alanyl aminopeptidase N so that they develop antibodies against the molecule. When the mosquito sucks up blood from these immunized people, the blood will contain those N antibodies, which will interfere with the parasite's development in the mosquito midgut.

But Dinglasan and others are still not sure how effective the strategy will be, because there are too many cautionary tales in malaria eradication. Already, Dinglasan says, with the vaccine his group is pursuing, they have data to show that the antibodies elicited against the antigen have different effects on the different parasites. "The molecule we're targeting for the vaccine blocks 98 percent of the vivax parasites from invading the mosquito midgut, but there is enough variation or polymorphisms in the phenotype of invasion that they can potentially bypass" the antibodies, he says. "The same concentration of antibody blocks 100 percent of falciparum infections in mosquitoes in Cameroon, but it doesn't block 100 percent of the vivax infections in mosquitoes in Thailand."

Another vaccine-development approach is to exploit P. vivax's fondness for the Duffy antigen, a membrane glycosylated protein on red blood cells that acts as a nonspecific receptor for chemokines. People missing the Duffy antigen for genetic reasons appear to be resistant to P. vivax. This is interesting, says Hall, because "the population in large parts of Africa is Duffy negative. That explains why you don't find a lot of Plasmodium vivax in large parts of Africa."

The parasite expresses a Duffy antigen binding protein, and this is another protein that Hall says researchers are going after in hopes of developing a vaccine. "By interfering with binding of the Duffy binding protein to the Duffy antigen, the idea is you can block invasion and possibly have a malaria vaccine against vivax," explains Hall. "We'll find out whether it works." He cautions that the parasite's invasion is a complex process that involves other antigens, so the Duffy antigen tactic may not pan out.

OUTLOOK

If the Gates Foundation's 2007 call for complete malaria eradication is to be achieved, malaria researchers say they have an uphill battle ahead of them in understanding the ways in which the other malarial parasites function. But Dinglasan, Rodriguez-Lopez and Mueller say it's encouraging that funding agencies now are giving more emphasis to these parasites. And some progress is being made.

In 2012, the P. vivax genome was sequenced and shown to have more polymorphisms than that of P. falciparum. The diversity of single-nucleotide polymorphisms, for example, suggests that P. vivax is more functionally variable. The genome, says Hall, can act as a roadmap for exploring biochemical and molecular mechanisms to halt P. vivax.

But researchers focused on the disease outside of Africa insist that more needs to be done to tackle P. vivax and give the parasite the same level of attention as P. falciparum. Dinglasan says, "I am a card-carrying member of the malaria-eradication bandwagon. I clearly acknowledge that if we are ever to meet the goal of eradication, we cannot simply focus on falciparum malaria."

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.

DOUBLE VISION

The protein art of Maja Klevanski

Most biochemists look to the Protein Data Bank for structural data, but Maja Klevanski looks to it for artistic inspiration. Klevanski, a graduate student at the University of Heidelberg, first got the idea of translating the ribbon models of protein structures into art when she was preparing her diploma thesis at Harvard University.

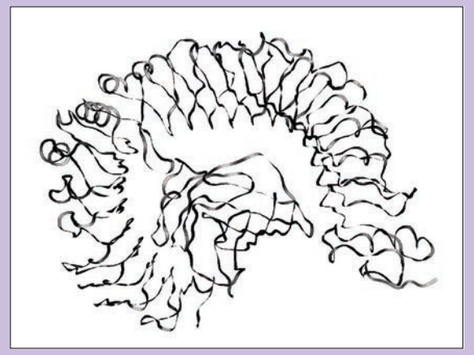
She was searching for something to contribute to a professor's birthday symposium when she started noticing images in the protein structures he had published: a birthday present, then a cat bringing a birthday cake. She made a simple animation of the images using PowerPoint so that she could contribute something to the celebration. "It was not very artistic in the beginning," she recalls.

But over time, her method has become more elaborate. To find her images, she rotates protein structures until she begins to see something interesting and then begins a painstaking process of drawing over the structure, redrawing and tweaking the rotation until the image in her mind is fully realized on the page.

Last year, a collage of her work titled "Nature playing chess" reached the top 10 in the illustration category of the 2012 International Science and Engineering Visualization Challenge. She says she hopes to publish a book one day that combines her art with the science behind it. "But, first of all, I have to finish my Ph.D.!" she says.

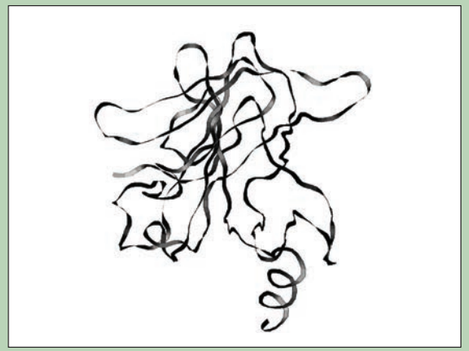
You can find more of her work at her website, where she also takes requests to re-imagine your favorite protein: www.protein-art.com.

– Cristy Gelling



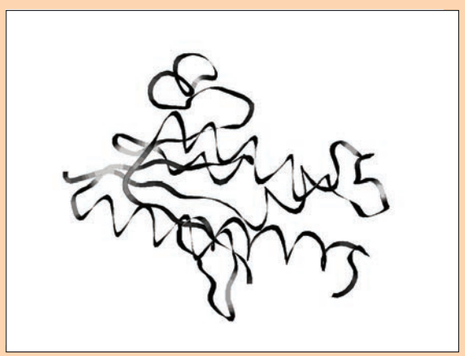
TLR4-MD-2 Complex

Bullfighting



p53

Dancing Couple



Taq Polymerase (Fragment)

Mouse on the Sofa

CDK5-p25 Complex

Dragon with House

THE USES OF METABOLIC ADVERSITY

BY WENDY KNAPP POGOZELSKI

“Sweet are the uses of adversity.”

– William Shakespeare, “As You Like It”

Blurred vision was the first sign that something was wrong. The front row of the freshman chemistry class I was teaching looked strangely fuzzy. Then, over the next few days, I was gripped by an unquenchable thirst and was constantly fatigued. Seemingly overnight I lost eight pounds. I recognized the symptoms of diabetes, but I was young(ish), slim(ish) and an avid kick-boxer. Mine was not the typical diabetic profile.

Despite my suspicion that I was experiencing raging hyperglycemia, the diagnosis — “You have diabetes” — was devastating. It marked the beginning of a lifestyle that is an enormous challenge. However, the journey has led me to an increased understanding of biochemistry, has enhanced my teaching and ultimately has cast me in a new role of helping others.

It turned out that I had developed latent autoimmune diabetes in adults, or LADA, a subset of type 1 diabetes. LADA is due to an autoimmune reaction to pancreatic glutamate decarboxylase, or GAD65. While LADA has a slower onset than classic type 1, formerly known as juvenile diabetes, the two diseases follow a similar course and require injections of insulin.

Fortunately, I felt equipped to manage my condition. I teach metabolism to undergraduates using an approach that emphasizes insulin-dependent pathways as a unifying theme and one that offers an everyday context. I knew that carbohydrates, whether whole grain or highly processed, could raise my blood glucose to dangerous levels, so my response to the diagnosis was to reduce greatly carbohydrates in my diet. In addition, I was careful to monitor my blood sugar levels and insulin doses. The result was that my hemoglobin A1c (glycosylated hemoglobin, a measure of blood sugar control), was 5.4 percent, within the normal 4 percent to 5 percent range. My doctor said that I was his “best patient ever” and that I was achieving the blood sugars of a nondiabetic person.

Despite satisfaction with my glycemic control, my physician wanted me to see a dietitian. To my surprise, the dietitian was appalled by my diet. She said, “You have to eat a minimum of 130 grams of carbohydrates a day.” I protested, but she recruited the rest of the medical team to endorse her position: “We all say you have to eat more carbs. The American Diabetes Association gives us these guidelines.” One member of the team said, “I want you to eat chocolate. I want you to enjoy life.”

As someone raised to be cooperative, and because I found it easy to embrace medical advice to eat chocolate, I agreed to eat more carbohydrates. The result was that my HbA1c rose above 7 percent. My blood sugar levels were frequently in the 200 to 300 mg/dl range (far above the normal level of about 85 mg/dl), even when I supplemented with extra insulin. My former dose of seven units of insulin per day increased to 30 units per day. The loss of control was immensely frustrating. My physician attributed my initial success to what is called the diabetes honeymoon. Often, when someone first begins taking insulin, there is a short-lived period during which β-cells seem to recover a bit and secrete insulin. Regardless, it was clear that the dietitian’s approach was not yielding the success I desired. I felt confused and uncertain as to what to do.

I decided to investigate for myself what my best diet should be. I studied the literature, I sought out researchers and physicians, and I attended countless metabolism-related talks. In addition, I connected with hundreds of people with diabetes. The most important contribution to my achieving clarity, however, was evaluating literature based on a molecular understanding of how metabolism works.

In my quest for answers, I found to my surprise that many dietitians and physicians were unable to explain the basis for the dietary recommendations they endorsed. Some did, however, express a desire for a better understanding or review of what they’d once learned. And in the general public, I encountered scores of diabetics and nondiabetics who also wanted tools to make sense of conflicting nutritional information.

I began to use what I had learned not only to expand and improve my teaching and research but also to step into the role of a nutrition explainer. First I was determined to see that none of my students would lack understanding of processes such as gluconeogenesis and the many pathways affected by insulin. I created new lecture topics and problem sets based on diabetes and nutrition applications. My students responded positively and appreciatively. There was a palpable increase in attention in class. Students came to my office to chat about things that they had read. My class evaluations praised the use of nutritional context and often said, “This material could have been rather dull without all these great applications.” I even heard (frequently) “I love metabolism!”

Beyond my student population, I engaged a world of bloggers, physicians and other people with diabetes, many of whom were eager to understand more deeply how things work metabolically. I now find myself being interviewed, quoted in papers, and invited to speak to groups of people, including physicians, who want to deepen their understanding of metabolic pathways. I am asked to share my nutrition-based teaching applications with other professors and with textbook publishers. In these efforts, I try to avoid dispensing nutritional advice; instead, I attempt to show how nutrient composition affects metabolic pathways so that my audience feels better able to evaluate nutritional recommendations.

Five years later, diabetes is still an immense

My doctor said that I was his “best patient ever” and that I was achieving the blood sugars of a nondiabetic person.

Beyond my student population, I engaged a world of bloggers, physicians and other people with diabetes, many of whom were eager to understand more deeply how things work metabolically. I now find myself being interviewed, quoted in papers, and invited to speak to groups of people, including physicians, who want to deepen their understanding of metabolic pathways.

mental and physical challenge, but I am grateful for the insight and tools that my education and training have provided me. Most importantly, if I am able to further the use of molecular science to help others find optimal dietary strategies, and if I can help the next generation, then my adversity will have had a positive outcome.

Wendy Knapp Pogozelski earned a B.S. from Chatham University and a Ph.D. in chemistry from Johns Hopkins University under the direction of Thomas Tullius. She spent two years as an Office of Naval Research postdoctoral fellow working at various sites in radiation biology. She is a professor of chemistry at the State University of New York (SUNY) College at Geneseo, where she has been since 1996. She teaches biochemistry, emphasizing medical and nutrition-based applications. Her current research focuses on radiation effects on mitochondrial function and mitochondrial DNA as well as on understanding how dietary strategies affect biochemical pathways.

jbc THE JOURNAL OF BIOLOGICAL CHEMISTRY

The role of frataxin in the neurological disorder Friedreich ataxia

BY RAJENDRANI MUKHOPADHYAY

Friedreich ataxia is a rare genetic autosomal recessive disease that damages the nervous system and causes movement problems. The disease is named after the German physician Nikolaus Friedreich, who was the first to describe it in the 1860s. It usually begins in childhood, typically between the ages of 5 and 15, and worsens with age. The condition causes the degeneration of nerve tissue in the spinal cord, especially in the sensory neurons that direct muscle movement of the arms and legs.

The disease involves deficiencies in the protein called frataxin. The protein has homologues in both eukaryotes and prokaryotes, but its function is still unresolved. In a recent Paper of the Week in the Journal of Biological Chemistry, a team led by Elena Hidalgo at the Universitat Pompeu Fabra in Spain identified a frataxin homologue in the mitochondria of fission yeast. The investigators found that cells missing the gene for the protein were sensitive to growth under aerobic conditions, had increased levels of total iron, showed signs of oxidative stress and consumed less oxygen compared with wild-type cells. These signs closely mimic the problems associated with reduced frataxin levels in cells from Friedreich ataxia patients. Proteomic analysis showed that when cells were missing the frataxin homologue iron in the cytosol was less readily available, causing the activation of a regulator of the iron-starvation gene expression program.

The data suggest that the frataxin homologue is important for iron and reactive oxygen species homeostasis. The investigators say their strain of fission yeast missing the frataxin homologue will make a new model for studying the molecular basis for Friedreich ataxia.

To hear a podcast discussion about this paper with Hidalgo, go to www.jbc.org/site/podcast or find the JBC podcast site on iTunes.

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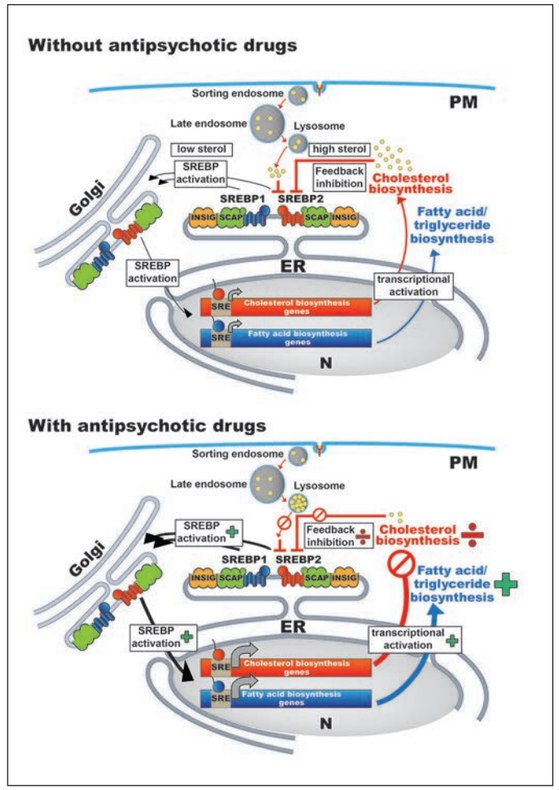
JLR THE JOURNAL OF LIPID RESEARCH

The metabolic effects of antipsychotics

BY MARY L. CHANG

While it's been known for years that the use of atypical antipsychotic medications is associated with various cardiovascular side effects, researchers still don't have a clear picture of how these drugs might lead to such risk factors as weight gain, diabetes and high cholesterol.

Antipsychotics have been around since the 1950s and have been essential in the treatment of schizophrenia and other psychiatric disorders. More recently, they also have been prescribed for use in dementia. In 2011, antipsychotic drugs were prescribed to about 3.1 million Americans at a cost of $18.2 billion, according to the market research firm IMS Health.



In their findings presented in "Atypical antipsychotics alter cholesterol and fatty acid metabolism in vitro" in the February issue of the Journal of Lipid Research, Alberto Canfrán-Duque and colleagues at Hospital Ramón y Cajal in Madrid compared the effects of clozapine, risperidone and ziprasidone, three atypical (also known as second-generation) antipsychotics, with those of haloperidol, a first-generation antipsychotic, on intracellular lipid metabolism in three human cell lines. The team's in vitro results indicated that all four drugs reduced de novo cholesterol biosynthesis, which seems to fly in the face of all the negative metabolic issues experienced by patients.

Canfrán-Duque et al. suggest reduced cholesterol synthesis may lead to a homeostatic feedback mechanism and thus transcriptional activation of fat synthesis. Further, their theory confirms previously published results from others implicating antipsychotics in the trapping of low-density lipoprotein-derived cholesterol in endosomes and lysosomes. While de novo cholesterol biosynthesis in the cell lines decreased in the presence of antipsychotics, biosynthesis of complex lipids like triglycerides and phospholipids increased, explaining the metabolic problems in patients taking antipsychotics.

All four antipsychotics targeted the same enzymes while inhibiting cholesterol biosynthesis, but different drugs had different activity levels against these enzymes, and the mechanisms by which the antipsychotics affect these enzymes still remain to be elucidated.

In a commentary in the same JLR issue, Silje Skrede, Vidar Martin Steen and Johan Fernø of the University of Bergen and Haukeland University Hospital summarize how antipsychotics may increase lipid biosynthesis and cause metabolic problems (see figure). Skrede et al. stress that the new theory put forth by Canfrán-Duque et al. may be relevant to mouse models and human studies and may lead to important research on how intracellular cholesterol biosynthesis and homeostatic activation of fat synthesis cause abnormal lipid levels and obesity.

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MCP MOLECULAR & CELLULAR PROTEOMICS

Where do sperm cells get their energy?

BY RAJENDRANI MUKHOPADHYAY

For decades, researchers have been debating whether sperm cells get their fuel, molecules of ATP, from mitochondrial oxidative phosphorylation or glycolysis. In a recent Molecular & Cellular Proteomics paper, a group of researchers described a series of experiments that seem to suggest that, apart from the ATP derived from sugars, sperm may also get their ATP from fatty acids metabolized in mitocondrial and peroxisomal pathways."We reasoned that the field of sperm metabolism would advance if we knew which metabolic enzymes are present in human sperm," says Alexandra Amaral, who, along with Rafael Oliva at the University of Barcelona, spearheaded the study. Their work advances our understanding of the cellular physiology of sperm, which in turn may have some bearing on the development of a male contraceptive pill and better in vitro fertility techniques.

The investigators tackled proteomic analyses of the tail of human sperm, because previous studies indicated many sperm metabolism proteins are located there. (The head region of sperm is taken up with paternal genetic material and the sperm's nucleus.) By identifying all the proteins in the tail, the investigators hypothesized, they could tease out which were the ATP-producing pathways in the cell.

Amaral, Oliva and colleagues isolated active sperm cells from semen samples taken from healthy men. They took the tails from the cells and ran the tail proteins out on SDS-PAGE gels. They then cut out the protein bands from the gel and analyzed them by liquid chromatography–mass spectrometry. "Our rationale was that the analysis of tail preparations would permit us to identify minor proteins that are usually masked by more abundant proteins in whole-cell analyses," says Oliva.

The team discovered a number of proteins that had not been previously described. Some were peroxisomal proteins, which came as a surprise to the investigators, because the conventional wisdom was that sperm didn't have peroxisomes. Some peroxisomal proteins are known to be involved in the oxidation of very long-chain fatty acids.

Amaral says, "We were able to show that sperm might be able to use fatty acids as fuel and that lipidic beta oxidation may contribute to sperm motility."

Fatty acids located inside the sperm cell as a source of ATP rarely figured in the sperm energy-origin debate. The investigators say that their data contradict a common concept in the literature that sperm cells need to have external substrates for energy production through either oxidative phosphorylation or glycolysis. The finding of peroxisomal proteins suggests sperm may be able to get energy from internal sources of substrates, such as the long-chain fatty acids, to guard against external energy-source fluctuations.

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Not for the faint hearted — but if you feel the calling …

BY JIM KEEN

In this time of continuing limited resources, most of us in the academic science community are straining to see a brighter horizon and hopefully even some upward funding foothills beyond the fiscal cliff and canyon of still uncertain size. If the tenured academic position was ever a guaranteed job for life (highly debatable), those days are long, long gone. Rather, someone considering a traditional academic research and teaching position had better have passion and a calling. If you do, and if you're not faint of heart, what can you expect? Here's a small collection of tips for those setting out on the exciting high-wire act.

Starting your research program

Essential to success in a new academic position is the development of an independent, substantial research program. This process has many moving parts, but it begins with the identification of important, unanswered questions in your field, the development of a well-formulated plan of attack to address the questions, and obtaining sound preliminary experiments to show feasibility of the plan. Usually this program will continue or branch from one of your completed research projects, but ideally it will benefit from the integration of perspectives derived from all your training experiences and result in a uniquely personal approach.

Managing your time and your human resources

Interaction with students is what draws many to an academic setting, so a commitment to teaching probably comes naturally. Teaching also provides an opportunity to identify trainees with whom you will enjoy mentoring and with whom you will enjoy working. Taking on a doctoral or even master's degree student is a substantial commitment, and during the first year or two, your students will require more of your time and focus than you might expect (or remember!). But hopefully they will become independent and reward your effort with their own creativity and perspectives. Some graduate programs are now facilitating joint sponsorship of students, which may lessen the financial and time burdens. This also brings into focus the fact that one does not work alone, so being an astute human-resources manager is a useful trait as well. Attracting the best co-workers to your lab requires being a keen judge of capability and compatibility, conveying clear performance expectations and providing a rewarding work environment so colleagues at all levels share in the discovery process. When personal HR functions work well, it's great! When they don't, it can be a real drain. It often is worthwhile to have faculty colleagues interview prospective hires until your own lab can provide enough co-interviewer perspectives. Workshops to develop management skills, probably not part of the graduate curriculum, are also useful.

Keeping your research program going

Many young investigators report that getting a renewal for that first grant is even more difficult than getting it in the first place, as mechanisms supporting initial applicants don't apply and productivity after only a few years may be modest. So getting a running start is important, along with perseverance. It's also vital to temper the inclination to branch out with the awareness that keeping a primary program going while getting sufficient preliminary results to convince review panels to fund a second direction takes energy, time and often some luck.

Getting pulled in multiple directions

Most academic institutions strategically are developing interdisciplinary, collaborative research efforts to make the faculty sum greater than its component parts. Recruitment of interactive junior faculty members is often a tactic, and on stepping aboard, a new faculty member with unique experience may be sought to contribute to multiple research programs. This can be intellectually broadening, exciting and flattering — if it doesn't materially dilute efforts toward the new faculty member's own program. Should ongoing collaborations emerge, you should position yourself to become a recognized co-principal investigator on efforts (and grants!) and not a dependent associate whose contributions are hazy to the research community and to institutional promotion committees.

Asking for and accepting help

Formalized mentoring programs for junior faculty members are becoming widespread, sometimes leaving older faculty members bemused, as a random conversation at the bench or over coffee usually constituted mentoring when they were younger. Yet most of today's new faculty members welcome active guidance, and both younger and older participants are reporting these programs to be rewarding. A new lab has myriad needs, many of which will become apparent in unexpected ways and will have difficult timeframes, so having a strong department chairperson on your side willing and able to make your case to higher administration is important.

Paying attention

It's helpful to listen carefully for information you may not exactly want to hear but need to know. For example: Consider reaching out to review panel officers who can fill you in on the details of applications that failed to meet the funding bar, or examining teaching critiques that contain important feedback about your performance. Though doing so might make you uncomfortable initially, there are surely things to learn to make your next efforts go more smoothly.

Doing your community service

It's also important and rewarding to be a good institutional citizen, perhaps through participation in curriculum development, graduate training, seminar planning or other committee work. Of course, if wrangling is a theme at your institution, it can distract you from your core efforts or, worse, have the same effect as seeing how sausage is made, as the saying goes.

In some ways, the junior faculty position is the ultimate meritocratic and entrepreneurial position for our business-focused times: a position with great independence of thought and few rigid limits to expansion when supported by truly creative thinking and execution, inner drive and an appropriate amount of self-promotion. Increasingly, a shrinking safety net makes the high-wire performance an intense experience. For many, it continues to be a fantastic experience to step into an empty lab and know that you can pretty much ask any scientific question that is important to you and have the unparalleled excitement of leading your own discovery team, perhaps in close collaboration with others, in a quest for answers that will benefit humanity.

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Accreditation 1.0 is here

BY PETER J. KENNELLY

We are pleased to announce the public release of version 1.0 of the description for the American Society for Biochemistry and Molecular Biology's bachelor's degree-certification program. We invite all interested parties to read and provide feedback regarding the guidelines and invite interested programs to serve as beta testers by applying for ASBMB-recognized status by June 1. Students enrolled in the inaugural set of recognized programs will be eligible to participate in the degree-certification process during the 2013 – 2014 academic year. In the meantime, we will be piloting the assessment instrument that will be used to determine student eligibility for degree certification, with the 2013 – 2014 assessment serving as the beta version.

Find out more about the degree-certification program

On the Web: Visit hwww.asbmb.org/accreditation/

At the annual meeting: Attend an open meeting with members of the degree-certification working group at 12:30 p.m. April 22 in Room 257B of the Boston Convention and Exhibition Center during Experimental Biology 2013.

What's in it for me?

The degree-certification program was constructed to meet many of the goals expressed by members of the biochemistry and molecular biology community. The original seed was planted by industry representatives seeking a vehicle to help them better evaluate candidates for entry-level jobs. Further impetus came from the publication of the "Vision and Change" report from the National Science Foundation and the American Association for the Advancement of Science and the Teagle Foundation's report "Biochemistry/Molecular Biology and Liberal Education."

A degree-certification program offered an avenue by which the ASBMB could play an active role in shaping this next stage in the evolution of pedagogy for the molecular life sciences. Each student participating in the certification program will have the opportunity to obtain a national credential that is performance-based and independent of institutional name recognition. Educators will gain access to an independent assessment process that will provide external feedback and meet the growing demands of administrators and accreditation bodies. Programs will have access to a set of expectations from an eminent international scientific advisory board regarding curriculum and infrastructure to help buttress requests for needed personnel and physical infrastructure. Graduate programs, medical schools and employers will have an objective measure of student learning and preparedness.

Each student ... will have the opportunity to obtain a national credential that is performance-based and independent of institutional name recognition.

Will this work?

It is up to you, the BMB community, whether this long-awaited effort succeeds or fails. No program of this nature, even when well-constructed (we hope!), can flourish and gain credibility without buy-in from the constituencies it is intended to serve. During the past several years, we have been the recipients of regular inquiries regarding when this program would go live and how it would be structured. News of our effort even has attracted inquiries from overseas about whether we intend to go international. So now the ball is in your court. Please review the guidelines, provide your feedback, apply for recognition for your program and respond to announcements about the assessment exam. We have built it. Will you come?

Peter J. Kennelly (pjkennel@vt.edu) is a professor and the head of the department of biochemistry at Virginia Polytechnic Institute and State University and chairman of the ASBMB Education and Professional Development Committee.

The sphingolipid connection in muscle weakness

BY MARIANA NIKOLOVA-KARAKASHIAN AND MICHAEL B. REID

The metabolism of sphingolipids is subject to regulation and generates bioactive metabolites that mediate the cellular response to stress. Emerging research suggests that sphingolipids also influence the force of skeletal muscle contraction (1). These studies add to the well-characterized role of sphingolipids in the regulation of glucose uptake by muscle (2). A complex and essential role is becoming apparent for specific bioactive metabolites, such as ceramide, sphingosine and sphingosine-1-phosphate and a distinct set of related metabolic enzymes.

Cancer, aging and other pro-inflammatory processes are associated with a persistent decline in the force of muscle contraction.

Contraction of skeletal muscles is caused by neurally activated sarcolemmal action potentials, which propagate throughout the cells, causing calcium release from intracellular stores and activation of myofilament proteins. In part, the amplitude of these calcium transients determines the force of contraction.

Sphingosine and sphingosine-1-phosphate have opposing effects on calcium transients. Sphingosine (and to a lesser extent dihydrosphingosine and phytosphingosine) directly binds to and inhibits the sarcolemmal calcium channel. In contrast, sphingosine-1-phosphate acts via G(i)-coupled, agonist-specific surface receptors S1P3 and S1P2 to increase cytosolic calcium levels from both extracellular and intracellular pools.

Cancer, aging and other pro-inflammatory processes are associated with a persistent decline in the force of muscle contraction. Several findings suggest that sphingolipids – more specifically ceramide – promote muscle weakness:

(i) Direct exposure to sphingomyelinase or cell-permeable ceramide depresses the force of intact fiber bundles from murine diaphragm ex vivo (3).

(ii) TNF, a systemic mediator of weakness, causes abrupt accumulation of C18, C20 and C22 ceramides in muscle.

(iii) Exercise can ameliorate muscle weakness and also alters sphingolipid metabolism, a complex effect that varies with exercise duration and muscle type.

The mechanisms by which sphingolipids regulate muscle force have begun to emerge. Beyond modulating calcium, sphingolipids appear to stimulate oxidant production and depress myofilament function. Sphingomyelinase exposure increases ceramide levels, increases cytosolic oxidant activity and depresses the force of muscle fiber bundles. Antioxidant pretreatment blunts the force decrement, identifying oxidants as downstream mediators of sphingomyelinase action. Studies of permeabilized fibers suggest these oxidants depress force via effects on myofilament proteins (4).

At the same time, key questions remain unanswered. More and more data suggest that sphingosine rather than ceramide is the direct mediator of weakness. Systematic analyses of the enzymes that mediate ceramide turnover in muscle will help resolve this dilemma. Furthermore, skeletal muscle fibers have a highly specialized structure. Subcellular localization of the enzymes that regulate sphingolipid metabolism appears to be critical but remains to be defined. Such studies may reveal novel aspects of sphingolipid metabolism and identify downstream targets that are specific to muscle.

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REFERENCES

1. Nikolova-Karakashian, M. N. & Reid, M. B. *Antioxid. Redox. Signal.* **9**: 2501 – 2517 (2011).
2. Chavez, J. A. & Summers, S. A. *Cell Metab.* **5**, 585 – 594 (2012).
3. Ferreira, L. F. et al. *Am. J. Physiol. Cell. Physiol.* **3**, C552 – C560 (2010).
4. Ferreira, L. F. et al. J. *Appl. Physiol.* **9**, 1538 – 1545 (2012).

Great achievements in science and technology in ancient Africa

BY SYDELLA BLATCH

Despite suffering through the horrific system of slavery, sharecropping and the Jim Crow era, early African-Americans made countless contributions to science and technology (1). This lineage and culture of achievement, though, emerged at least 40,000 years ago in Africa. Unfortunately, few of us are aware of these accomplishments, as the history of Africa, beyond ancient Egypt, is seldom publicized.

Sadly, the vast majority of discussions on the origins of science include only the Greeks, Romans and other whites. But in fact most of their discoveries came thousands of years after African developments. While the remarkable black civilization in Egypt remains alluring, there was sophistication and impressive inventions throughout ancient sub-Saharan Africa as well. There are just a handful of scholars in this area. The most prolific is the late Ivan Van Sertima, an associate professor at Rutgers University. He once poignantly wrote that "the nerve of the world has been deadened for centuries to the vibrations of African genius" (2).

Here, I attempt to send an electrical impulse to this long-deadened nerve. I can only fly by this vast plane of achievements. Despite this, it still should be evident that the ancient people of Africa, like so many other ancients of the world, definitely had their genius.

Math

Surely only a few of us know that many modern high-school-level concepts in mathematics first were developed in Africa, as was the first method of counting. More than 35,000 years ago, Egyptians scripted textbooks about math that included division and multiplication of fractions and geometric formulas to calculate the area and volume of shapes (3). Distances and angles were calculated, algebraic equations were solved and mathematically based predictions were made of the size of floods of the Nile. The ancient Egyptians considered a circle to have 360 degrees and estimated π at 3.16 (3).

Eight thousand years ago, people in present-day Zaire developed their own numeration system, as did Yoruba people in what is now Nigeria. The Yoruba system was based on units of 20 (instead of 10) and required an impressive amount of subtraction to identify different numbers. Scholars have lauded this system, as it required much abstract reasoning (4).

Astronomy

Several ancient African cultures birthed discoveries in astronomy. Many of these are foundations on which we still rely, and some were so advanced that their mode of discovery still cannot be understood. Egyptians charted the movement of the sun and constellations and the cycles of the moon. They divided the year into 12 parts and developed a yearlong calendar system containing 365 ¼ days (3). Clocks were made with moving water and sundial-like clocks were used (3).

A structure known as the African Stonehenge in present-day Kenya (constructed around 300 B.C.) was a remarkably accurate calendar (6). The Dogon people of Mali amassed a wealth of detailed astronomical observations (7). Many of their discoveries were so advanced that some modern scholars credit their discoveries instead to space aliens or unknown European travelers, even though the Dogon culture is steeped in ceremonial tradition centered on several space events. The Dogon knew of Saturn's rings, Jupiter's moons, the spiral structure of the Milky Way and the orbit of the Sirius star system. Hundreds of years ago, they plotted orbits in this system accurately through the year 1990 (7). They knew this system contained a primary star and a secondary star (now called Sirius B) of immense density and not visible to the naked eye.

Metallurgy and tools

Many advances in metallurgy and tool making were made across the entirety of ancient Africa. These include steam engines, metal chisels and saws, copper and iron tools and weapons, nails, glue, carbon steel and bronze weapons and art (2, 8).

Advances in Tanzania, Rwanda and Uganda between 1500 and 2000 years ago surpassed those of Europeans then and were astonishing to Europeans when they learned of them. Ancient Tanzanian furnaces could reach 1800˚C – 200 to 400˚C warmer than those of the Romans (8).

While the remarkable black civilization in Egypt remains alluring, there was sophistication and impressive inventions throughout ancient sub-Saharan Africa as well.

Architecture and engineering

Various past African societies created sophisticated built environments. Of course, there are the engineering feats of the Egyptians: the bafflingly raised obelisks and the more than 80 pyramids. The largest of the pyramids covers 13 acres and is made of 2.25 million blocks of stone (3). Later, in the 12th century and much farther south, there were hundreds of great cities in Zimbabwe and Mozambique. There, massive stone complexes were the hubs of cities. One included a 250-meter-long, 15,000-ton curved granite wall (9). The cities featured huge castlelike compounds with numerous rooms for specific tasks, such as iron-smithing. In the 13th century, the empire of Mali boasted impressive cities, including Timbuktu, with grand palaces, mosques and universities (2).

Medicine

Many treatments we use today were employed by several ancient peoples throughout Africa. Before the European invasion of Africa, medicine in what is now Egypt, Nigeria and South Africa, to name just a few places, was more advanced than medicine in Europe. Some of these practices were the use of plants with salicylic acid for pain (as in aspirin), kaolin for diarrhea (as in Kaopectate), and extracts that were confirmed in the 20th century to kill Gram positive bacteria (2). Other plants used had anticancer properties, caused abortion and treated malaria – and these have been shown to be as effective as many modern-day Western treatments. Furthermore, Africans discovered ouabain, capsicum, physostigmine and reserpine. Medical procedures performed in ancient Africa before they were performed in Europe include vaccination, autopsy, limb traction and broken bone setting, bullet removal, brain surgery, skin grafting, filling of dental cavities, installation of false teeth, what is now known as Caesarean section, anesthesia and tissue cauterization (3). In addition, African cultures preformed surgeries under antiseptic conditions universally when this concept was only emerging in Europe (2).

Navigation

Most of us learn that Europeans were the first to sail to the Americas. However, several lines of evidence suggest that ancient Africans sailed to South America and Asia hundreds of years before Europeans. Thousands of miles of waterways across Africa were trade routes. Many ancient societies in Africa built a variety of boats, including small reed-based vessels, sailboats and grander structures with many cabins and even cooking facilities. The Mali and Songhai built boats 100 feet long and 13 feet wide that could carry up to 80 tons (2). Currents in the Atlantic Ocean flow from this part of West Africa to South America. Genetic evidence from plants and descriptions and art from societies inhabiting South America at the time suggest small numbers of West Africans sailed to the east coast of South America and remained there (2). Contemporary scientists have reconstructed these ancient vessels and their fishing gear and have completed the transatlantic voyage successfully. Around the same time as they were sailing to South America, the 13th century, these ancient peoples also sailed to China and back, carrying elephants as cargo (2).

People of African descent come from ancient, rich and elaborate cultures that created a wealth of technologies in many areas. Hopefully, over time, there will be more studies in this area and more people will know of these great achievements.

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REFERENCES

1. Kresge, N. "A history of black scientists." *ASBMB Today.* February 2011.
2. Van Sertima, I. "The Lost Sciences of Africa: An Overview." *Blacks in Science: Ancient and Modern.* 7 – 26 (1983).
3. Woods, G. *Science in Ancient Egypt* (1988).
4. Zaslavsky, C. "The Yoruba Number System." *Blacks in Science: Ancient and Modern.* 110 – 127 (1983).
5. Lynch, B. M. & Robbins, L. H. *Science* **4343**, 766 – 768 (1978).
6. Adams, H. "African Observers of the Universe: The Sirius Question." *Blacks in Science: Ancient and Modern.* 27 – 46 (1983).
7. Brooks, L. *African Achievements: Leaders, Civilizations and Cultures of Ancient Africa.* (1971).
8. Shore, D. "Steel-Making in Ancient Africa." *Blacks in Science: Ancient and Modern.*157 – 162 (1983).
9. Asante, M. et al. "Great Zimbabwe: An Ancient African City-State." *Blacks in Science: Ancient and Modern.* 84 – 91 (1983).

Science Olympiad and the ASBMB

Inspiring the next generation of scientists

BY GERARD J. PUTZ AND JENNY KOPACH

If you're visiting a college campus on a Saturday in March, you might be surprised to find it crawling with packs of 12- to 18-year-olds in goggles and lab coats, hurrying from one building to the next. These industrious kids aren't early college students: They're team members from Science Olympiad, one of the largest, oldest and most prestigious science, technology, engineering and math after-school programs in the country.

Just like a football team, these Science Olympians practice weekly (if not daily), hone their skills and prepare to demonstrate their aptitude against equally matched peers. And to the victors go the spoils — medals, trophies, scholarships and rewards for achievement that in many cases carry scientific interest from classroom to career.

A tall but doable order

The educational landscape is well-populated with single-discipline K – 12 STEM competitions, but Science Olympiad is unique in that it combines all the major science specialties, including life sciences, chemistry, physics, engineering, Earth and space science, and inquiry.

In the fall 2012 issue of the Enzymatic newsletter, American Society for Biochemistry and Molecular Biology Undergraduate Affiliate Network Chairwoman Marilee Benore underscored a common problem facing K – 12 education: Students often pursue science with little knowledge of the options open to those with scientific knowledge and training. The solution? Have students interact with working professionals in Science Olympiad settings. Inspiring students to follow college and career paths into biochemistry and molecular biology is a tall order, but once they see how their event preparation connects with your real-world experience, they will begin to see themselves following the same path (see chart).

By collaborating with Science Olympiad students, you can educate students and teachers about common BMB topics found in Science Olympiad events, illustrate BMB concepts that may seem complex to middle- and high-school students, and advocate for college majors and careers in BMB.

BMB Career Path	Aligned Science Olympiad Event
Epidemiologist	Disease Detectives
Cancer researcher	Designer Genes
Pharmaceutical scientist	Microbe Mission
Molecular biology professor	Protein Modeling
Medicinal biochemist	Anatomy & Physiology
High school science teacher	Forensics
Plant biologist	Water Quality & Food Science

A step beyond show and tell

Many students are aware of current events with links to the biochemistry and molecular biology world — the chemistry of the teenage brain, cancer research that affects their families, the story of Henrietta Lacks' HeLa cells (required reading in some high schools now), food safety in school lunches and the political stem-cell debate.

Science Olympiad events are exemplary models of real-world applications of science and the STEM careers offered on each path. For instance, Science Olympiad has worked with the Centers for Disease Control and Prevention since 1999 on the Disease Detectives event. Within the CDC, scientists were charged with creating K – 12 workforce-development outreach programs that would add to the pool of eligible STEM professionals. Covering topics like pandemics, disease outbreaks, food-borne illness and resulting effects on population, the CDC found that the Science Olympiad Disease Detectives event is an effective way to motivate students to investigate careers in epidemiology.

Similarly, the Milwaukee School of Engineering's Center for BioMolecular Modeling worked with Science Olympiad to develop the cutting-edge Protein Modeling event for high-school participants. In this event, students use computer visualization and online resources to guide them in constructing physical models of proteins and learn about how protein structure affects its function. This event

is linked to current and relevant topics for student engagement, and national winners receive generous scholarships to the engineering school.

The ASBMB member perspective

ASBMB member Shannon Colton, a program director at the Center for BioMolecular Modeling, says Science Olympiad events have helped the engineering school engage more than 9,000 high-school students.

"The students are excited to be on the cutting edge of science, and educators appreciate a new topic to connect the real world of science with what the students are learning," Colton says. "Team coaches welcome assistance from experts, and we encourage ASBMB members to reach out and make connections. We have found that working with high-school students reignites our passion for this work and reminds us why we chose this route initially."

Many students are motivated to follow a direct career path once they've been successful in Science Olympiad events.

Case in point: Emily Briskin, a sophomore at Yale University. Briskin participated in the Disease Detectives and Microbe Mission events, was a gold medalist on her Centerville High School Science Olympiad team and attended President Obama's White House Science Fair in October 2010. Today she's studying molecular, cellular and developmental biology, along with French. "I am interested in global health and microbial disease, and I hope to eventually get my master's in public health and perhaps work at the CDC. I am involved in Community Health Educators, a group that goes into middle-school classrooms to discuss important public health topics."

Get involved

Science Olympiad provides an organized and meaningful volunteer activity for scientists in every U.S. state. Simply align your talents with the appropriate grade level and degree of involvement, reach out to the school coach or Science Olympiad state or tournament director, and you'll be making a difference before you know it. You can tailor your volunteerism and outreach to your region, your position and your schedule:

- UAN members on college campuses can volunteer at Science Olympiad tournaments or with teams.
- More experienced ASBMB members can serve as Science Olympiad team mentors in their communities or at Science Olympiad tournaments and can contribute content.

Another plus: As Science Olympiad is an after-school program, it does not compete with teachers' limited daily instructional time or with district curriculum requirements.

For more information about public outreach opportunities, contact Geoff Hunt at ghunt@asbmb.org.

Gerard J. Putz (gjputz@soinc.org) is the president and co-founder of Science Olympiad. Jenny Kopach (jrkopach@soinc.org) is the vice-president of marketing communication and a national executive board member of Science Olympiad.

SCIENCE OLYMPIAD IN BRIEF

Science Olympiad is a national nonprofit organization founded in 1984 and dedicated to improving the quality of K – 12 science, technology, engineering and math education, increasing interest in science among all students, creating a technologically literate workforce and providing recognition for outstanding achievement by both students and teachers.

Modeling athletic teams, the Science Olympiad teams prepare throughout the year for tournaments. There are three divisions of competition:

Division A: grades K – 6

Division B: grades 6 – 9

Division C: grades 9 – 12

Science Olympiad tournaments (350 annually) consist of 23 team events and are 100 percent aligned to the National Science Education Standards. Each of the 6,400 U.S. teams (roughly 200,000 students) participates in events that require a variety of skills including research and study, lab work and experimentation, and design and construction of devices.

#overlyhonestmethods

Even if you're not on Twitter, you might have heard or read something about a hashtag that last month yielded a steady stream of tweets that exposed, and indeed rejoiced in, the sausage-making that science can be sometimes.

It all started with a researcher doing what lot of people do on social media: blowing off steam. That one tweet, by a post-doc who goes by the handle @dr_leigh, has been edited below because, well, you'll know why when you read it. The others are a sampling of the thousands of tweets from scientists in all fields that followed @dr_leigh's relatable public sigh.

@dr_leigh: we did experiment 2 because we didn't know what the (redacted) to make of experiment 1 #overlyhonestmethods

@ProteinWrangler: Plasmids were a gracious gift from the Miser lab after many emails, phone calls, & drunken reminders at conferences. #overlyhonestmethods

@ProfLikeSubst: Most of samples died when they overheated on the deck of a modified tuna boat being driven by a drunk captain #overlyhonestmethods #tooreal

@Bashir_Course9: We actually did Exp 2 before Exp 1. The elegant reasoning written here is completely posthoc. @SciTriGrrl @dr_leigh #overlyhonestmethods

@JDFrenchie: We use intro level psych students as research subjects because we have no obligation to pay them. #OverlyHonestMethods

@cellularscale: We used software X because it is free. #overlyhonestmethods

@nikkismalls28: Any samples run will likely be contaminated, because we still haven't fixed what the intern messed up this summer #OverlyHonestMethods

@atomselectrons: This dye was selected because the bottle was within reach #overlyhonestmethods

@dr_leigh: incubation lasted three days because this is how long the undergrad forgot the experiment in the fridge #overlyhonestmethods

@paulcoxon: Scientific collaborators are carefully chosen by the quality of their research, and if their labs are near a beach #overlyhonestmethods

@SciTriGrrl: We study this signaling pathway because it has the best antibodies #overlyhonestmethods

@sonicgu: Crystals were obtained by the "I forgot the flask in the fume hood" technique. #overlyhonestmethods

@drugmonkeyblog: Two days to isolate the protein, five weeks to generate the hilarious double-entendre name for the gene. #overlyhonestmethods #flynerds

@SciTriGrrl: This project was started to prove someone wrong. They were not. Dammit. #overlyhonestmethods

@NellyPlants Plants were placed in darkness for 18 h rather than the usual 20 to avoid risk of getting snowed in and trapped in lab #overlyhonestmethods

@doc_becca: By "representative," we mean "best." #overlyhonestmethods

@chemverse0409: A 30 minute reaction time was chosen because that's how long it takes to get pizza and beer. #overlyhonestmethods

@short2thepoint: The experiment only worked when my hair was shorter than shoulder length #overlyhonestmethods #superstitions

@BadPhysics: Older centrifuge used as three PhDs were utterly baffled trying to program the new one. #overlyhonestmethods

Boston

ASBMB ANNUAL MEETING

April 20–24, 2013

www.asbmb.org/meeting2013

LATE-BREAKING ABSTRACT

DEADLINE: February 21, 2013

EARLY REGISTRATION

DEADLINE: February 22, 2013

HOUSING

DEADLINE: March 22, 2013

THEMATIC SESSIONS

Catalytic Mechanisms

Chemical and Systems Biology

Genome Replication and Repair

Glycan Regulation of Signaling Pathways
Lipids and Membranes

Mechanisms of Gene Transcription and Regulation

Mechanisms of Signal Transduction

Protein Modification, Trafficking and Degradation

RNA Function and Protein Synthesis

Transitions, Education and Professional Development

Triple Negative Breast Cancer

SPECIAL EVENTS

Professional Development for Graduate/Postdoctoral Trainees
Saturday, April 20

ASBMB Opening Reception
Saturday, April 20, immediately follows the Opening Lecture

Undergraduate Orientation: A Student's Guide to the ASBMB Annual Meeting
Saturday, April 20

17th Annual Undergraduate Student Research Poster Competition
Saturday, April 20

Beyond College: Coping with Some Common Challenges
Undergraduate workshop, Saturday, April 20

Undergraduate Breakfast with ASBMB Award Winners
Sunday, April 21, and Monday, April 22

ASBMB Welcome and Networking Reception
Sunday, April 21

ASBMB Thematic Fermentation Happy Hour
Monday, April 22

ASBMB Women Scientists Networking Event
Tuesday, April 23

Y.E.S. Mixer (Young Experimental Scientists)
Consult program for details