Vol. 16 / No. 2 / February 2017

ASBMB TODAY

THE MEMBER MAGAZINE OF THE AMERICAN SOCIETY FOR BIOCHEMISTRY AND MOLECULAR BIOLOGY

Sharing the whole HeLa genome

CONTENTS

NEWS

2
PRESIDENT'S MESSAGE
Facts about the MAC

4
NEWS FROM THE HILL
What is in the budget, Mr. President?

5
MEMBER UPDATE

7
JOURNAL NEWS
7 Another role for c-Myc, one of cancer's biggest players
8 Biochemical tricks of the hibernating bear
10 Scott syndrome
11 Sex and genetics affect fatty-liver development

2

8

FEATURES

12
SHARING THE WHOLE HELA GENOME

17
FOR BETTER AND FOR WORSE

12

John Arnst describes how a group at the National Institutes of Health works with the family of Henrietta Lacks to give researchers access to the HeLa genome.

17

PERSPECTIVES

22
MINORITY AFFAIRS
Imposter syndrome and diversity graduate students

26
NIH UPDATE
An experiment in program-based funding

28
DUE DILIGENCE
The myth of perfection

29
EDUCATION
29 Funding undergraduate work
30 The ASBMB Student Chapters welcomes its new chair!

31
OUTREACH
A note from the new Public Outreach Committee chair

32
ESSAY
32 What is service?
34 Biochemist, ethicist, pastor, chaplain

36
THE DO-OVER
Wish I did my Ph.D. in the U.S.

36

ASBMBTODAY
THE MEMBER MAGAZINE OF THE AMERICAN SOCIETY FOR BIOCHEMISTRY AND MOLECULAR BIOLOGY

ASBMB
American Society for Biochemistry and Molecular Biology
www.asbmb.org/asbmbtoday
PRINT ISSN 2372-0409

Facts about the MAC

By Natalie Ahn

People often tell me that they are unaware of the many activities carried out by committees at the American Society for Biochemistry and Molecular Biology (http://www.asbmb.org/AboutUs/). It is within these groups that members generously and unselfishly do most of the society's work promoting discovery, education, career development, advocacy and outreach. So I thought I'd tell you more about them, starting with the Minority Affairs Committee, also known as the MAC.

The MAC's goal is to advocate for ethnic and cultural diversity in science. Led by Takita Sumter of Winthrop University, who is the chair, and Sonia Flores at the University of Colorado Anschutz Medical Campus, who is the deputy chair, this very active group makes enormous contributions to the ASBMB, benefitting everyone.

To begin with, the MAC plays a major role in organizing our annual meeting. Members arrange the "Issues in Depth" scientific symposium, which focuses on a cutting-edge problem in biomedical research. At the 2017 ASBMB annual meeting in Chicago in April, the topic is "Antibiotics and Resistance," and speakers will address the pressing need for new knowledge and innovations in antibiotics discovery, resistance mechanisms and drug development.

The MAC presents the Ruth Kirschstein Diversity Award, honoring the former director of the National Institute of General Medical Sciences and the first woman to head an institute at the National Institutes of Health. Kirschstein was a major advocate for diversity in training scientists in biomedical, behavioral and clinical fields. This award recognizes individuals who have made great strides toward this goal.

The MAC reception at the ASBMB annual meeting is a popular event.

In 2016, the Ruth Kirschstein Diversity in Science award went to Avery August of Cornell University.

Also, the MAC organizes the welcome reception for everyone on the Sunday evening of the annual meeting, which is our biggest, most rollicking party. During that event, we showcase posters by minority graduate-student and postdoctoral travel awardees. Also, the MAC pairs minority trainees with established scientists to discuss career plans as well as how to navigate the meeting.

Recruiting underrepresented minority scientists to biochemistry and molecular biology is a major goal of our society. The MAC reaches out to minority students by representing ASBMB at national conferences focusing on career development and by awarding the Marion B. Sewer Distinguished Scholarship for Undergraduates. Named for our beloved late colleague, Marion B. Sewer at the University of California, San Diego, the scholarship recognizes individuals with high achievements in research who have demonstrated leadership in promoting diversity. The MAC also collaborates with the Student Chapters Committee to establish partnerships between minority-serving institutions and mentoring universities. The partnerships promote faculty interactions between neighboring institutions to enhance training in the biosciences and has increased the number of MSI student chapters nationally.

Finally, I must mention the IMAGE workshop, through which the MAC supports research careers by teaching grantwriting. IMAGE stands for "Interactive Mentoring Activities for Grantsmanship Enhancement." This is not your typical writing course. It is a full-bodied mentoring program, in which participants work with experienced reviewers for two whole days, formulating proposals by testing ideas and strategies, with continued mentorship throughout the submission process. Participants emerge with increased confidence in their proposal writing abilities; 85 percent of the 2013 cohort received funding after the workshop. The next IMAGE workshop is scheduled for July, and the MAC will present a summary of best practices in the "Grant Success Demystified" workshop at the annual meeting.

The ASBMB is committed to diversity and inclusion in science, which expands creativity and innovation by broadening viewpoints and promotes societal fairness and equality. Check out the MAC website at www.asbmb.org/minority/. Have new ideas or want to get involved? Contact Allison Goldberg at agoldberg@asbmb.org.

Natalie Ahn (natalie.ahn@colorado.edu) of the University of Colorado, Boulder, is president of the ASBMB.

What is in the budget, Mr. President?

By Benjamin Corb

The Budget and Accounting Act of 1921 requires the president of the United States to submit a budget to the U.S. Congress for each fiscal year. The law goes so far as to provide a deadline for the submission: It requires that "on or after the first Monday in January but not later than the first Monday in February of each year, the President shall submit a budget of the United States Government for the following fiscal year."

While it's not explicitly stated, it's commonly assumed that a new administration, as is the administration of President Donald Trump, will submit a budget request to Congress late. A late submission allows the new administration a chance to develop its own budget based on its funding priorities.

Thanks to a failed appropriations process last year, Trump has the task of providing a budget for fiscal year 2018 as well as providing guidance on the remainder of FY2017. This is a complicated dance that Trump's economic team must perform, especially when considering his team has been in place for less than a month. In December, Congress passed a continuing resolution to fund the government through most of April. The continuing resolution gives time to Trump's team to do the homework to deliver to Congress a framework for his administration's funding priorities. Today, we are assuming that homework is being done.

The time it takes Trump and his team to get the budgetary work done affects science and federal funding. In October, because the government was operating under a continuing resolution, the National Institutes of Health announced a reduction in noncompeting research awards by as much as 10 percent and that institute councils would hold back some funding decisions for grants until there was clarity for what lies ahead. The continuing resolution funds agencies at the level of 2016. However, both the NIH and the National Science Foundation were proposed to have increases in FY2017. Mr. Trump and Congress really should get working on FY2017!

As for FY2018, Trump has an opportunity to make a statement to the life-sciences community about what kind of president he'll be with his proposed budget. Former Vice President Joe Biden is known for saying, "Don't tell me what you value. Show me your budget, and I'll tell you what you value."

Trump's budget will give us an indication of what he values. If Trump provides Congress with a spending proposal to increase NIH and NSF funding, we may take away that while he may hold views on other scientific disciplines, like climate science, that are at odds with the views of most scientists, his administration may be friendly to the cause of biomedical research. A flat or weakened budget would provide us with evidence for what many suspect — that he is a president not interested in scientific progess.

February is federal budget season. Trump, the research community is watching for signs of your support. Please don't let us down.

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

Interested in science policy?

Follow our blog for news, analysis and commentary on policy issues affecting scientists, research funding and society. Visit **policy.asbmb.org**.

Ohsumi wins Breakthrough Prize

Yoshinori Ohsumi at the Tokyo Institute of Technology was one of the 2017 recipients of the Breakthrough Prize in Life Sciences. The prize is worth $3 million.

Ohsumi was honored for his groundbreaking work elucidating the molecular mechanisms of autophagy, the process by which cells deconstruct and recycle cellular components.

The Breakthrough Prizes were established in 2012 by Google co-founder Sergey Brin; CEO and co-founder of 23andme Anne Wojcicki; entrepreneur and venture capitalist Yuri Milner; Milner's wife, Julia, who is an artist and a photographer; Facebook founder Mark Zuckerberg; and his wife, philanthropist and pediatrician Priscilla Chan. The prizes recognize outstanding achievement in life sciences, fundamental physics and mathematics.

Ohsumi's work on autophagy also garnered him the 2016 Nobel Prize in physiology or medicine. In the December issue of ASBMB Today, John Arnst, ASBMB Today's science writer, explored in the cover story how Ohsumi's work opened up new avenues for investigation in cellular and molecular biology. See www.asbmb.org/asbmbtoday/201612/Feature/Autophagy/.

Fuchs wins Vanderbilt prize

FUCHS

Elaine Fuchs, the Rebecca C. Lancefield professor and head of the Robin Chemers Neustein Laboratory of Mammalian Cell Biology and Development at The Rockefeller University, is the 2016 recipient of the Vanderbilt Prize in Biomedical Science.

The Vanderbilt Prize in Biomedical Science, awarded since 2006, recognizes women who have significantly advanced medical research and have mentored other women in the scientific community.

A pioneer in the field of stem-cell research, Fuchs is being recognized for her novel use of reverse genetics as a tool to better understand skin diseases and cancer stem cells.

Fuchs will receive the prize on March 30, when she will deliver a lecture as a part of the Flexner Discovery Lecture Series.

Forsburg earns mentoring award

FORSBURG

Susan L. Forsburg, the Gabilan distinguished professor in science and engineering and a professor of biological sciences at the University of Southern California, has received the midcareer 2016 Nature Award for Mentoring in Science. Nature awards two prizes of $10,000, recognizing outstanding midcareer and lifetime contributions toward scientific mentorship. Forsburg's research explores how DNA replication contributes to genome stability, using the fission yeast Schizosaccharomyces pombe as a model. She mentors students and postdocs not just in her USC laboratory but more broadly in the community.

The prizes, which have been given out annually since 2005, focus on particular geographical regions each year. The 2016 awards are concentrated on the U.S. West Coast, specifically in the states of Washington, Oregon and California.

In memoriam: Klaus Kuettner

Klaus Kuettner, former chair of the department of biochemistry at Rush University from 1980 to 2002, died in May. He was 82.

Originally born in a part of Germany that is now in Poland, Kuettner immigrated to the U.S. around 1962 after obtaining his doctorate in biochemistry from the University of Berne.

In 1964, he joined Presbyterian–St. Luke's Hospital, which later merged with Rush Medical College, beginning his 52-year career at Rush.

Kuettner rose from a junior faculty position to chairman of the department of biochemistry, where he served as a mentor to both his students and his peers. As a researcher, Kuettner was highly regarded for his work on cartilage.

He is survived by his wife, Erzsebet, and his brother, Wolfdieter, as well as his two stepdaughters, Monica Adler–Werner and Vanessa Adler–Schecter.

Erik Chaulk (echaulk@asbmb.org) is a peer-review coordinator at the ASBMB.

CONTINUED ON PAGE 6

CONTINUED FROM PAGE 5

ASBMB members elected as AAAS fellows

The American Association for the Advancement of Science has elected 46 members of the American Society for Biochemistry and Molecular Biology as fellows for distinguished scientific achievement during their careers. Chosen by their peers, these members have demonstrated outstanding achievements in scientific research, education or leadership.

The AAAS is a nonprofit organization dedicated to the promotion of science through enhancing communication among scientists as well as promoting scientific education and policy. These new fellows will be recognized at the AAAS annual meeting this month.

Congratulations to the following individuals:

Section on agriculture, food and renewable resources

Alice C. Harmon, University of Florida

Section on biological sciences

Janet L. Stein, University of Vermont College of Medicine
Ali Shilatifard, Northwestern University Feinberg School of Medicine
Zu-Hang Sheng, National Institute of Neurological Disorders and Stroke
Martin A. Schwartz, Yale University
Karla J. F. Satchell, Northwestern University
Kathleen Postle, Pennsylvania State University
James C. Paulson, The Scripps Research Institute
Krishna K. Niyogi, Howard Hughes Medical Institute/University of California, Berkeley/Lawrence Berkeley National Laboratory
Mona Nemer, University of Ottawa
Michael S. Marks, Children's Hospital of Philadelphia Research Institute/University of Pennsylvania Perelman School of Medicine
Jane B. Lian, University of Vermont College of Medicine
Terri Goss Kinzy, Rutgers Robert Wood Johnson Medical School
Yibin Kang, Princeton University
Jerard Hurwitz, Memorial Sloan–Kettering Cancer Center
Timothy T. Hla, Boston Children's Hospital/Harvard Medical School
Wolf-Dietrich Heyer, University of California, Davis
Jack J. Hawiger, Vanderbilt University School of Medicine
Phyllis I. Hanson, Washington University School of Medicine in St. Louis
Wei Gu, Columbia University
Geoffrey L. Greene, University of Chicago
Max E. Gottesman, Columbia University
Joel M. Goodman, University of Texas Southwestern Medical School
Thomas E. Dever, National Institute of Child Health and Human Development
William A. Cramer, Purdue University
Xiaodong Cheng, University of Texas Health Science Center
Junjie Chen, University of Texas MD Anderson Cancer Center
David A. Brow, University of Wisconsin–Madison
David L. Brautigan, University of Virginia School of Medicine
Paul Babitzke, Pennsylvania State University
José M. Argüello, Worcester Polytechnic Institute
Steven R. Goodman, University of Tennessee Health Science Center
Ralph B. Arlinghaus, University of Texas MD Anderson Cancer Center

Section on chemistry

James B. Ames, University of California, Davis
Mark R. Chance, Case Western Reserve University
Catherine E. Costello, Boston University School of Medicine
Julie T. Millard, Colby College

Section on medical sciences

Peter Lobel, Rutgers Robert Wood Johnson Medical School
Christopher J. Molloy, Rutgers, the State University of New Jersey
David J. Tweardy, University of Texas MD Anderson Cancer Center
Edward T.H. Yeh, University of Texas MD Anderson Cancer Center

Section on neuroscience

Jesús Avila, CSIC–Universidad Autónoma de Madrid
Roger J. Colbran, Vanderbilt University
Yueming Li, Memorial Sloan–Kettering Cancer Center
Henry L. Paulson, University of Michigan
Benjamin L. Wolozin, Boston University School of Medicine

Another role for c-Myc, one of cancer's biggest players

By Courtney Chandler

Cancers involve a diverse range of genes and proteins that aid in their formation, progression and maintenance. One gene that has been implicated in many cancers is c-Myc. One cancer, a common liver cancer in children, didn't appear to involve c-Myc. But now, in a recent article selected as one of the Editors' Picks in in the **Journal of Biological Chemistry**, a team led by Edward Prochownik of the University of Pittsburgh has shown that hepatoblastomas are no different from most other cancers: Tumor progression requires c-Myc.

The c-Myc gene encodes a transcription factor, which is a protein that binds to DNA and promotes the expression of particular genes. When c-Myc is overexpressed in cancers, it effectively signals to turn on other genes at levels higher than normal. The products of these genes then can promote cancer development and progression.

Hepatoblastoma is the most common pediatric liver cancer. It often is diagnosed in children under the age of 3 and occurs with higher incidence in low-birthweight infants. Survival rates are greater than 80 percent if the tumor is removed completely with surgery but drop to as low as 20 percent if the tumor spreads beyond the liver.

On the surface, c-Myc generally doesn't appear to be involved in the formation of hepatoblastoma, although it has been seen at high levels in some tumors. Instead, hepatoblastoma is characterized by mutations in two key proteins: beta-catenin and yes-associated protein, abbreviated YAP. "In our work, we asked whether c-Myc was required for beta-catenin and YAP to induce hepatoblastomas in mice," explains Prochownik.

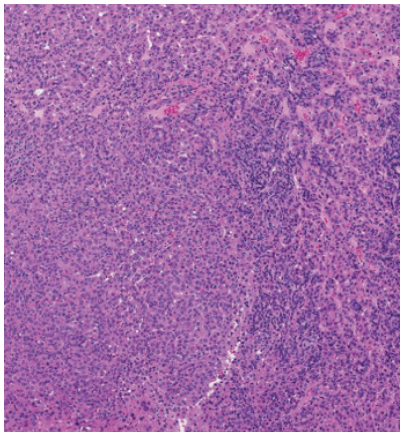


IMAGE PROVIDED BY EDWARD PROCHOWNIK

c-Myc's absence in the liver impairs tumor growth but not initiation.

The investigators asked if the two proteins lead to cancer by themselves or if they also need c-Myc. They used mice genetically engineered to lack the c-Myc gene in their livers and then used beta-catenin and YAP to induce hepatoblastoma formation. They observed that the mice lacking c-Myc in their livers survived much longer than mice with intact c-Myc.

The researchers used metabolic and molecular profiling to understand why the mice without c-Myc survived longer. Through techniques including RNA sequencing and mitochondrial analysis, they observed a role for c-Myc in supporting tumor growth. "The apparent role for c-Myc in supporting tumor growth was its ability to maximize certain crucial metabolic processes, such as protein synthesis and glucose uptake," says Prochownik. There were more cellular building blocks that made increased growth and cancer progression possible.

The work of Prochownik and colleagues indicates that c-Myc is involved in tumor progression but not initiation. Given c-Myc's involvement in a number of cancers, why is this news? "Our findings indicate that even tumors which do not superficially appear to involve c-Myc deregulation, such as hepatoblastomas, are nevertheless highly dependent on it," explains Prochownik.

This was somewhat surprising, as recent work from the same laboratory has shown that c-Myc is not required for the long-term replacement and maintenance of normal noncancerous liver cells. Prochownik's group believes that this disparity is due to the nature of cancerous cells. c-Myc is largely dispensable in normal cells that have relatively slow and highly controlled growth. However, in cancer cells that undergo rapid division and metabolism, c-Myc is required. c-Myc's role may be to allow cells to utilize nutrients and cellular precursors to permit the type of rapid proliferation that seldom would occur under normal circumstances.

c-Myc is possibly the most frequently deregulated protein in human cancer, making it a good target for therapeutics. The work of Prochownik and colleagues suggests that targeting c-Myc may prove useful even for cancers that don't appear to be initiated by c-Myc deregulation, such as hepatoblastoma. "Our data suggest that pharmacologic approaches specifically targeting c-Myc or some of the pathways it regulates might be viable targets for novel therapeutic interventions," says Prochownik.

Maybe in the future, one of cancer's most active players can be stopped.

Courtney Chandler (cochandl@umaryland.edu) is a biochemistry Ph.D. candidate at the University of Maryland, Baltimore.

Biochemical tricks of the hibernating bear

By Amber Lucas

Winter is in full swing, and many of us have fantasized about curling up in a warm cave and slumbering until the warmth of spring arrives, just like a bear. Bears have the ability to sleep away the harsh winter months when food is scarce. They can spend five to seven months in hibernation. During this time, bears do not eat, drink, excrete or exercise. Despite the length of inactivity, bears do not experience bone loss, muscle loss, heart complications or blood clots like humans do during extended bouts of inactivity.

In a recent paper published in the **Journal of Biological Chemistry**, Karen Gjesing Welinder at Aalborg University in Denmark and colleagues set out to understand how wild Scandinavian brown bears protect their health and save energy during hibernation.

"The bear's tricks for hibernation adaptations can inspire and teach us to prevent effects of the restricted mobility of astronauts and of long-term hospitalized patients," says Welinder. "Immobile people lose muscle and bone mass, get blood clots, atherosclerosis and cardiac diseases. Immobile bears do not. Our deeper understanding of the tremendous physiological placidity encoded in animal genomes might be exploited in healthier lifestyles and medical treatments."

To understand how bears maintain their health during hibernation, Welinder and colleagues decided to look for differences in the levels of blood constituents between hibernating and nonhibernating brown bears. The molecules circulating in the bloodstream play important roles in cellular defenses, nutrient transport and cell signaling. The researchers used a multitude of screening tools in this study to analyze the molecular components in the blood, including mass spectrometry-based quantitative proteomic, metabolomic and hematological analyses of blood cells.

The investigators discovered that the bears' secret to maintaining their health during hibernation lies in saving energy on protein synthesis. During hibernation, complex pathways with many proteins are turned down or eliminated and are replaced with a small number of proteins with broader specificity and wide ranges of func-

PHOTOS COURTESY OF OLE FROBERT, OREBRO UNIVERSITY HOSPITAL, SWEDEN

Researchers collect samples from anesthetized wild Scandanavian brown bears.

Analyses of blood taken from anesthetized wild bears help researchers understand the biochemistry of hibernation.

tions. This switch from complexity to simplicity allows bears to decrease the energy necessary to maintain important molecular processes for survival during hibernation.

Welinder and colleagues found that while the large majority of protein levels decreased during hibernation, the overall protein concentration increased due to dehydration and an increased level of serum albumin. The change allowed the bear to spend less energy synthesizing proteins to maintain functional protein concentration levels. Additionally, protein degradation was repressed by a 6 °C decrease in body temperature and an increase in expression of alpha-2-macroglobulin, a broadly acting protease inhibitor. This further saved energy on costly protein synthesis by decreasing protein turnover.

Researchers search for bears.

Welinder and colleagues found that even though protein expression decreased overall, there were a few select proteins that were drastically elevated during hibernation. Bile salt-activated lipase, which can hydrolyze both triglycerides and cholesterol esters, was elevated 32-fold during hibernation and allowed the bears efficiently to harvest energy from stored fat. Only the three central coagulation factors, fibrinogen, thrombin and factor Xa, were increased during hibernation; together, these factors facilitate wound healing, only permitting local formation of blood clots when needed. Furthermore, the immune response was simplified to a few antimicrobial proteins, such as lysozyme, which acts as the innate line of defense against infection.

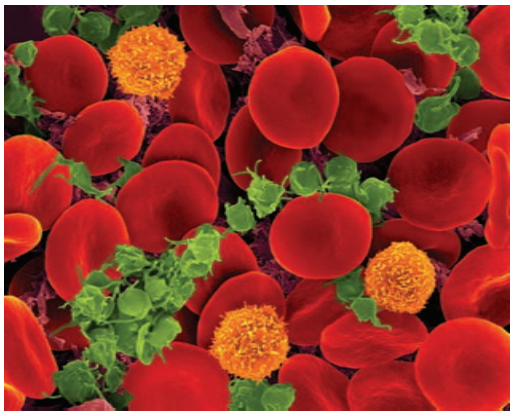
The sex hormone-binding globulin increased a dramatic 45-fold during hibernation, suggesting that this molecule must play a central role in the maintenance of hibernation. Welinder says the mechanism of action of sex hormone-binding globulin during hibernation still remains elusive.

Amber Lucas (allucas@andrew.cmu.edu) is a graduate student in the department of biological sciences at Carnegie Mellon University.

Scott syndrome and the smallest sample size

By John Arnst

Scott syndrome is a dysfunction of blood platelets, which are the tiny circulating discs that initiate coagulation. It's a rare bleeding disorder: There are only three known Scott syndrome patients worldwide. This dearth means that researchers must come up with ingenious ways to get the most data out of limited blood samples.



In a recent paper published in the journal **Molecular & Cellular Proteomics**, researchers have combined quantifications of the proteome, phosphoproteome and proteolytic cleavage sites to characterize platelet functions and modifications from blood samples from one patient. Of the three people worldwide with Scott syndrome, only one, who lives in the U.K., was available for blood donations when the researchers embarked on their study.

The disorder is homozygous recessive. Both copies of the inherited alleles that normally would code for anoctamin-6 are faulty in this patient.

Blood platelets lacking anoctamin-6, which is a channel protein for ions and phospholipids, are unable properly to localize the phospholipid phosphatidylserine, which normally stimulates the coagulation process. This dysfunction interferes with the platelets' production of thrombin, which is needed to convert the parent molecule fibrinogen to the sticky fibrin strands that anchor blood clots.

While there is a diagnostic test for prothrombin consumption that can verify Scott syndrome's thrombin-formation deficiency, this is not performed routinely, which may cause the disease to go undiagnosed.

The team of researchers, led by Johan P. Heemskerk at Maastricht University in the Netherlands and René P. Zahedi at the Leibniz Institute of Analytical Sciences in Germany, treated blood platelets from the Scott syndrome patient and from control blood donors with thrombin, ionomycin and a mixture of convulxin with thrombin. All of these compounds promote exposure to phosphatidylserine to some extent in control platelets but not in Scott syndrome platelets.

The researchers then extracted the proteins in the platelets that had been treated by the compounds and labeled them with isotopes. Then they fragmented the proteins into smaller peptides and used enrichment methods to purify the phosphopeptides and peptides that had been cleaved inside of the platelets.

This approach allowed the researchers to analyze simultaneously the proteome, phosphoproteome and N-terminome of each platelet sample. "You get a lot of information from a very small blood amount," says Heemskerk.

The proteomic analysis confirmed the absence of anoctamin-6 in the Scott syndrome platelets as well as the upregulation of the water-channel protein aquaporin-1. The upregulation of aquaporin-1 may be a compensatory reaction for impaired ion and phosphatidylserine transfer.

By examining the peptides with phosphorus groups in each sample, the investigators saw strong similarities between Scott syndrome platelets and control platelets that both were treated with thrombin. As thrombin causes only mild exposure to phosphatidylserine, this finding indicated that many other activation processes in the patient's platelets were unaffected.

The Scott syndrome platelets treated with ionomycin and the convulxin mixture, both of which cause high exposure to phosphatidylserine, showed an increase in the number of protein sites where phosphorus-containing groups were added.

However, the protease's consensus motif wasn't well-defined in research literature. The researchers were able to identify this motif and confirm that the Scott syndrome platelets showed a lower expression of calpain.

"I think it was the first time a study combined these three things to quantify the proteome, the phosphoproteome and the N-terminus protein from a blood sample using platelets that are from a patient, not from cell culture," notes Zahedi.

The approach will allow the researchers to interrogate more fully limited samples from Scott syndrome patients to look for spliced genes that might be producing low levels of anoctamin-6. Zahedi and Heemskerk plan to continue their work by examining the genetic variation of anoctamin-6 across various individuals and compare it with altered activation levels of platelets and altered expression levels of the proteome.

John Arnst (jarnst@asbmb.org) is ASBMB Today's science writer. Follow him on Twitter at twitter.com/arnstjohn.

Sex and genetics affect fatty-liver development

By Alexandra Nail

The obesity epidemic has accelerated the prevalence of liver disease in the Western world. Nonalcoholic fatty liver disease is caused by fat accumulation, also known as steatosis, in hepatocytes, the primary cell type in the liver. If left untreated, NAFLD can lead to end-stage liver diseases, such as cirrhosis and hepatocellular carcinoma.

Males and females develop NAFLD differently, and the molecular mechanisms by which genetic factors influence NAFLD development in both sexes are not fully understood. In a recent study published in the **Journal of Lipid Research**, Jake Lusis and colleagues at the University of California, Los Angeles, and at the University of Wisconsin–Madison used genetically identical strains of mice to determine how sex differences at the genetic level contribute to the development of hepatic steatosis.

In a previous study published in 2015, Lusis and colleagues analyzed 113 mouse strains to identify molecular pathways upregulated in males more susceptible to NAFLD. In the JLR study, the investigators evaluated 100 strains of female mice for NAFLD susceptibility. "In the past, studies focused on males and were often applied to women without any reflection on gender-specific differences," says Lusis. "We hope this study will prompt other researchers to include both genders in their work."

"In the past, studies focused on males and were often applied to women without any reflection on gender-specific differences," says Jake Lusis. "We hope this study will prompt other researchers to include both genders in their work."

To identify factors contributing to hepatic steatosis in females, Lusis and colleagues measured lipid accumulation in the liver and other tissues after mice were fed a diet high in fat and sucrose. This type of diet mimics a typical Western diet. Triglycerides, which make up the main component of fat, were lower in female livers compared with male livers. In addition, the locations where the mice stored fat and the differences in plasma lipids with respect to hepatic triglycerides correlated differently between the sexes. These data suggest that gender-based lipid metabolism influenced fatty-liver development.

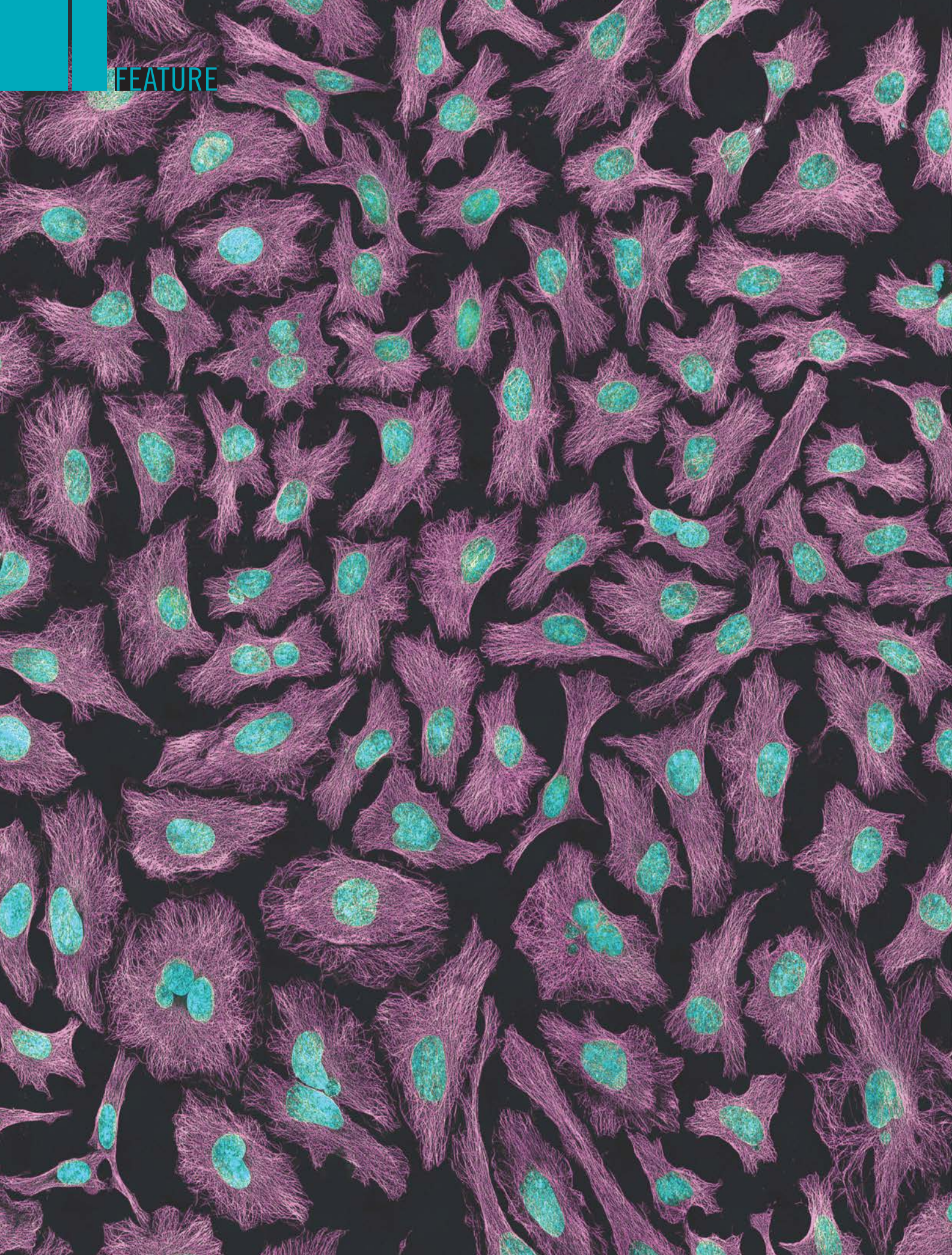
The investigators next did microarray analyses to identify gene expression profiles that correlated with hepatic triglyceride content. This technology relies on hybridization of gene-specific probes to quantify expression of numerous genes in multiple samples. Roughly two-thirds of the genes that correlated to hepatic triglyceride content were shared between sexes. A significant portion of these genes were associated with mitochondria, highlighting the importance of mitochondrial function in lipid metabolism for both sexes.

To determine how genetic variation might affect differences between the sexes in hepatic triglyceride accumulation, Lusis and colleagues carried out a genomewide association study. The study analyzed single nucleotide polymorphisms to identify genetic loci that associate with differences in hepatic triglyceride content and, consequently, NAFLD development. The investigators found a high correlation between S-phase kinase protein 1a expression and hepatic triglyceride levels in females. Previous work by Lusis and colleagues showed that glycerophosphodiester phosphodiesterase 1 is important for NAFLD development in males. Lusis notes, "Different genes might be more important for development of fatty liver in one sex than in the other."

To test whether sex hormones are responsible for sex-biased differences in hepatic triglyceride accumulation, the investigators removed the reproductive organs responsible for sex-hormone production from the mice. When normalized to body fat content, gonadectomized males on a high-fat, high-sucrose diet exhibited increased hepatic triglyceride content, whereas their female counterparts showed no differences. Previous studies had identified that ovariectomy increased insulin resistance in both normal and high-fat-fed females. Taken together, these data suggest that estrogen is protective against insulin resistance in females and that testosterone is protective against hepatic triglyceride accumulation in males.

Current strategies to control NAFLD include weight reduction, lifestyle changes, and pharmacological agents to increase insulin sensitivity or decrease cholesterol levels. So what's in store for the future for NAFLD research and treatment? "We hope that more detailed follow-up studies of the genes identified in our work will result in a better understanding of the disease process and will lead to the development of medications against NAFLD," says Lusis.

Alexandra Nail (alexandra.gjevre@uky.edu) is a Ph.D. student at the University of Kentucky.



Sharing the whole HeLa genome

Three years on, the agreement reached between the Lacks family and the National Institutes of Health is benefitting genome researchers

By John Arnst

In March 2013, a group of researchers at the European Molecular Biology Laboratory sequenced the genome of HeLa cells. With the last decades' advances in sequencing techniques, the sequencing was done easily. It was also done with good intentions.

The cancer cells, which were first taken from a lump removed from Henrietta Lacks' cervix months before her death from cervical cancer in 1951, are the most widely used cell line in the world. The cells are hardy and have helped develop many antitumor and viral treatments, including the polio vaccine. However, the genomic data published in 2013, which can be used to glean sensitive medical information about Lacks' descendants, was shared without their knowledge.

"It's like, 'Here we go again, being involved in research without our permission or our consent,'" says David Lacks Jr. He is a grandson of Henrietta Lacks, who was a black tobacco farmer and a mother of five. When Henrietta Lacks went to seek medical attention at Johns Hopkins Hospital for a small mass in her cervix in 1951, the gynecologist on duty, Howard Jones, took a biopsy of the tumor cells. After a diagnosis, the cells made their way to George Gey, the head of tissue culture research at Johns Hopkins, by way of a mutual colleague.

Henrietta Lacks wasn't asked for permission for her cells to be shared in this manner, although taking samples from patients without permission was a standard practice at the time. While her cells, which divided indefinitely at an unprecedented rate, went on to revolutionize medical research, the Lacks family was kept in the dark until researchers came looking to draw blood samples from family members in the 1970s. The HeLa cells generated billions of dollars of profit for biomedical industries, while the Lacks family was unable to afford medical care and health insurance.

These injustices were brought to the world's attention with Rebecca Skloot's bestselling 2010 book, "The Immortal Life of Henrietta Lacks." Before publishing the book, Skloot established the Henrietta Lacks Foundation, which now has awarded more than 50 grants for education-related, health-care and pre-approved emergency expenses to a number of members of Lacks' immediate family.

When the genome was put up on the European Nucleotide Archive in early 2013, "there weren't any policies that said the data couldn't be made available," says Dina Paltoo at the National Institutes of Health. Paltoo is the director of the scientific data shar-

CONTINUED ON PAGE 15

The image on the opposite page, which is the same image shown on the cover, is a multiphoton fluorescence image of HeLa cells. Microtubules are in magenta; DNA is in cyan. Image is courtesy of Tom Derrinck at the National Center for Microscopy and Imaging Research.

1920

Henrietta Lacks was born Loretta Pleasant on August 1, 1920, in Roanoke, Virginia to Eliza and Johnny Pleasant.

The world owes much to Henrietta Lacks. Lacks was a black woman whose cells were removed during a biopsy in 1951 and used for research without her knowledge or approval. A few months after Lacks' diagnosis of cervical cancer, she died at the age of 31. She never would know that, more than six decades later, her cells would continue to grow and provide a foundation for advancements in science and medicine.

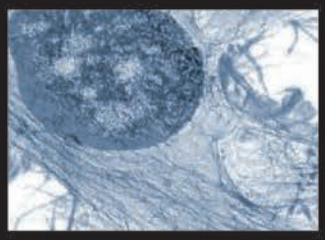
Lacks' cells revolutionized the field of medicine. Her amazing and immortal cells, commonly known as HeLa cells, have been used for decades in biomechical research. HeLa cells have been used to study, among other things, cancer, the effects of radiation and AIDS. HeLa cells led to the development of successful drugs in fighting human diseases, including leukemia, hemophilia, herpes, human papillomavirus, Parkinson's disease and influenza.

1941

On April 10, 1941, Henrietta Pleasant married David "Day" Lacks

1951

A biopsy of Henrietta Lacks' tumor was taken and sent to the lab of George Gey resulting in the creation of HeLa cell line.



1952

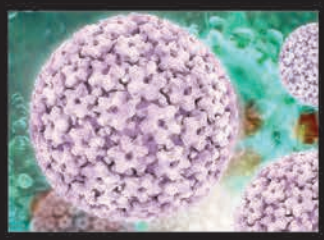
Scientists used HeLa cells to help develop the polio vaccine.

1973

Scientists used HeLa cells to study the behavior of salmonella inside human cells.

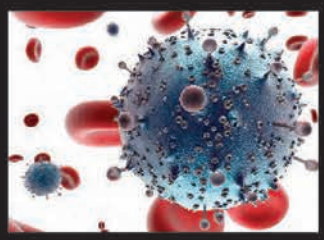
1984

HeLa cells were used by a German virologist to help prove that the human papillomavirus causes cancer.



1986

The virus infection mechanism of HIV was studied by scientists who infected HeLa cells with HIV.



1993

HeLa cells were used to study tuberculosis.

2013

The NIH announced an agreement with Henrietta Lacks' family to allow researchers access to the whole genome data of HeLa cells

CONTINUED FROM PAGE 13

ing policy division at the NIH's office of science policy. "This is pretty much the standard practice in the genomics community, and a lot of journals require that data has been shared before they'll publish the findings." A study about the genome and epigenome of the HeLa cells by researchers at the University of Washington was also about to be published in Nature.

After the genomic information was put up in a public database by the German researchers at EMBL, Skloot published an op-ed in the New York Times that garnered a significant amount of attention. NIH Director Francis S. Collins met up with the Lacks family to discuss their options.

"We could leave it out there as is, for the whole world to see, but the issue with that is when you sequence Henrietta Lacks' genome, you also include family traits of our genome as well," says Lacks. "We don't know what would be known 20 years from now with that sequence just being out there for anybody to use and how that would have an effect on us."

Reaching a consensus

The family came to the conclusion that the best way to handle the HeLa genomic sequence would be to have researchers apply to access it. "We didn't want it to be cut off, because the family is unanimously proud of what the cells have helped accomplish," says Lacks.

Collins and Kathy Hudson, who then was the NIH's deputy director for science, outreach and policy, put together a working group consisting of bioethicists, geneticists, clinicians and members of the Lacks family. According to the terms of the agreement in August 2013 that the family reached with the NIH, any researchers' plans to use the data had to meet certain criteria: The data should be used only for biomedical research purposes, the requesters must disclose any commercial plans that they would have for the data, and the requesters would agree to acknowledge the family and the contributions of the cells in any publications and presentations. The study from the University of Washington group, which had been put on hold, appeared in an issue of Nature that ran that month with a discussion of the agreement by Hudson and Collins.

The HeLa Genome Data Access Working Group and includes Lacks and Veronica Spencer, a great-grandchild of Henrietta Lacks. The group evaluates requests to access this data and then sends its findings to the advisory committee to the NIH director. That committee then makes a recommendation to Collins, who makes a final decision.

"The NIH director has also reached out to journals and has encouraged them to make sure that investigators that are pursuing publication are abiding by the HeLa genome data use agreement and are also acknowledging the agreement and the family appropriately," says Paltoo.

Fruits of the database

The NIH's database of genotypes and phenotypes, or dbGaP, currently contains five data sets related to the sequenced HeLa genome. So far, Collins has approved 47 requests from researchers from 20 different countries. The only rejected request was for a group that didn't want to share its findings. The two papers that caused the uproar were published after they were approved by the group.

One of those approved investigators is Andrew Adey at Oregon Health & Science University. As a graduate student, Adey was the first author on the University of Washington genome paper led by Jay Shendure.

Early in his career, Adey helped investigate what gives the HeLa cells the ability to divide in such an aggressive manner. The capability arose

CONTINUED ON PAGE 16

PHOTO PROVDED BY JERI LACKS-WHYE

David Lacks Jr. (left) and his cousin Jeri Lacks–Whye (right) often speak publically about the Lacks family's experiences with the HeLa cell line.

CONTINUED FROM PAGE 15

from the integration of DNA from the human papilloma virus into the genome of a cell in Henrietta Lacks that led to her cervical carcinoma.

"The viral foreign DNA integration that occurred in the HeLa genome happens in some subset of cervical carcinomas, but in this case it happened in a very unfortunate way," says Adey. "It happened to integrate in a location that activates a cancer gene, so it was really a perfect storm of events that happened in the cell that resulted in this extremely aggressive form of cancer and, ultimately, immortalization of the cell."

The E6 and E7 viral oncogenes were present on the inserted viral DNA that inhibit tumor suppressors, such as the well-known p53. The virus also inserted 30 copies of a regulatory enhancer near a proto-oncogene, MYC, which can cause unregulated cell division when hijacked. This interaction contributed to a much more aggressive form of cancer.

Adey and colleagues recently characterized the stability and heterogeneity of HeLa cells using a technique called combinatorial indexing. The technique allows them to perform single-cell whole-genome sequencing at a higher throughput than was previously possible by barcoding individual cells.

The researchers first applied the technique to cancer cells from an advanced adenocarcinoma and were able to identify subpopulations within the tumor. In future uses, "we'll be able to sample very low abundance subpopulations," says Adey. "We might be able to then infer and detect some aspects that could be targetable in a different way than the rest of the tumor."

In addition to all of the lifesaving medicines developed with HeLa cells, researchers trying to develop new medical technologies can use the HeLa genome as a powerful calibration tool.

"We're developing new technologies and tools to look at cancer as well as other aspects or other diseases," says Adey. "When we develop these tools, we want to test them out on something where we know the answer, so that's what we use HeLa for. We know exactly what it's going to look like."

Controlled access to the HeLa genomic data has also resulted in the development of a new analytical method by Shendure's group. The method involves chromosome-scale scaffoldings to assemble highly contiguous genomes from short reads. The reassembly is made possible by an algorithm that clusters fragments of the genome based on chromatin interaction data sets, which are useful for assigning, ordering and orienting the genomic sequences to chromosomes. The researchers first described the method, for which Shendure has also filed a patent, in a paper in the journal Nature Biotechnology in November 2013. In the paper, the researchers used the HeLa genome as one way to test the method to find interchromosomal rearrangements in cancer genomes.

Additionally, new insights into the effect of the genome's spatial organization on transcription, which has significant implications for aberrations that occur in diseases, have been made by Yijuan Ruan's group at The Jackson Laboratory Cancer Center in Bar Harbor, Maine.

While researchers use the HeLa cells to better understand countless aspects of cell biology, Lacks and Jeri Lacks–Whye, another one of Henrietta Lacks' grandchildren, have traveled to speak to audiences of up to 4,000 about their family and the broader issues raised in Skloot's book.

"Even though we speak a lot on the book, we're also starting to speak more on the issues that are encompassed in the book, like health, prosperity and precision medicine," says Lacks.

"Everybody is going to be sick at some point in time or affected by somebody who's sick," he adds. "We want to help scientists find cures."

John Arnst (jarnst@asbmb.org) is ASBMB Today's science writer. Follow him on Twitter at twitter.com/arnstjohn.

For better and for worse

'These proteins really have broadened my notion of the concept of prions,' researcher says

By Angela Hopp

Prion diseases — mad cow disease and Creutzfeldt–Jakob disease, for example — are downright terrifying.

You could be infected now and not even know it. The incubation period can last for decades.

You might have gotten it from an infected hamburger while in Europe years ago. Or maybe you acquired a random mutation last night while taking out the trash.

Once the infection gets going, maybe you'll think you're becoming a klutz. Later, you will notice a more serious tremor. Then, once amyloid plaques have turned your brain into a spongy mess, you will shake uncontrollably. A frozen, macabre smile will take over your face.

There is no cure.

That's why it's so easy to think of prions as evil proteins — and only that. But they're not all bad!

As a paper that appeared in the journal Cell on Oct. 6 underscores, some prions are, in fact, advantageous.

That paper, written by a research team at Stanford University, reported the discovery of 46 new prions in yeast. The team overexpressed every gene in the Saccharomyces cerevisiae genome, stopped to allow for reproduction over many generations, and then looked to see if the progeny showed signs of that initial overexpression. They did.

The work was led by Daniel Jarosz at Stanford University. Jarosz earned his Ph.D. in Graham Walker's lab at the Massachusetts Institute of Technology and completed his postdoctoral studies in the late Susan Lindquist's lab, also at MIT and the Whitehead Institute. He started his own lab at Stanford in 2013.

Jarosz spoke with ASBMB Today's executive editor, Angela Hopp. The interview has been edited for length, clarity and style.

What did you study in graduate school?

I started in chemistry, but I took this class from Gerry Fink on gene regulation. It really made me think: "Wow, there are some absolutely amazing things that are happening in biology that we don't understand mechanistically."

One of them that excited me initially was mutagenesis. It's clear in organisms from bacteria to humans that, in response to DNA damage, the production of mutations is an active process. It's more than just mistakes that are made by the replicative polymerase. Actually, there are genes that you can delete and organisms won't mutate anymore in response to the DNA damage. I wanted to understand how that works. The biochemical activity of one of those genes had been established one month before.

CONTINUED ON PAGE 18

CONTINUED FROM PAGE 17

Graham's lab had mostly approached this problem genetically. There were 20 years' worth of mutants with fascinating phenotypes sitting in the freezer. It became clear to me that, now that the problem was biochemically tractable, we would be able to understand the mechanism at an unprecedented level. That's exactly what my colleagues and I proceeded to do for several years. It was a truly exhilarating time.

So then you did a postdoc.

I think it's hilarious that I looked for labs all over but the ideal fit was directly across the street (in Lindquist's lab). The day that I interviewed there, someone was doing an autopsy on a patient with Parkinson's disease. He took me on a journey, slice by slice, through the brain, looking at the deposition of protein aggregates. The day ended with meeting someone who was making amyloid fibers in vitro and then doing single-molecule optical tweezers experiments to pull on them and extract spring constants. I thought: This is amazing! It was like its own small department. There even was someone who had his own lab in Arizona and came on sabbatical (to Lindquist's lab) and just decided he would rather remain as a senior scientist in (her) lab than go back to his own position. I was hooked by the end of the day.

Working with Susan was one of the great joys of my life. She is one of the most tenacious, brilliant and unfailingly kind people you could ever, ever imagine. (Author's note: Later, on the day of this interview, Lindquist died of cancer.)

What did you work on there?

I developed this way to look at the traits of wild yeast strains systematically and in high-throughput. I then began looking at whether protein folding — and in particular the Hsp90 chaperone — might affect their behavior.

Another central focus of the lab was prion biology, in particular these enigmatic entities like [PSI+]. These are phenotypes that were discovered decades ago that are heritable but don't follow Mendel's rules, so they didn't seem like mutations because they can be passed to all meiotic progeny, rather than half of them. They could be eliminated if you transiently treated the cells with a chemical — something that would never happen for a mutation. And they could be passed from one cell to another by mixing cytoplasm without mixing DNA. Quite unusual.

A string of really exciting studies in the 1990s established that those traits arose from prions. Since then controversy had raged over whether prions in yeast were just diseases, like PrP in mammals, or if they might have other phenotypes. Might they even be occasionally adaptive?

Several studies from Sue's lab had taken a stab at this question, showing that [PSI+] can produce some beneficial traits. But many others were detrimental. One of the key arguments in favor of the disease hypothesis had been that when people looked for prions in wild strains, they hadn't found them. They only had seen them in laboratory strains. With my colleague Randal Halfmann (now at Stowers Institute for Medical Research), we looked at many, many different wild strains and found that some of them did harbor prions that we knew about, including [PSI+].

But we also used this phenotyping platform to look more generally. Making no assumption about the molecular origin of the prion's phenotype, could we test whether there were traits in wild strains that had prionlike properties of inheritance? Properties that were totally different from what you would expect for a mutation?

We found that, even in a very limited experiment, this kind of inheritance was pervasive. It was fascinating and surprising.

Contemporaneously, I got excited by another prion in wild strains — [GAR+]. And it was totally crazy.

[GAR+] regulates a switch between fermentative and respiratory metabolism. It's conserved in (S. cerevisiae) and related species but also in fungi that are separated by hundreds of millions of years of evolution. It can be induced by a cross-chemical communication event in response to specific bacteria. And this provides benefit for both the bacterium doing the inducing and the yeast perceiving the signal. Despite this fascinating biology, [GAR+] was a real enigma mechanistically — it didn't form amyloid fibers, for example.

This is really what motivated the work that we just published — done largely in my lab at Stanford.

Tell me about that work.

A prion is a protein that exists in multiple conformations, and one of them is like a runaway train. It can self-template once it forms. We reasoned that if we just make more protein, we should be able to increase the odds that you get a conformational switch to set that runaway train in motion.

We used an army of robots to transiently overexpress every single protein in the yeast proteome. We then asked: If we stop overexpressing and look many, many generations later, is there a molecular memory of that past overexpression?

Molecular memory?

Is there a trait that's different in those cells whose ancestors saw overexpression compared to those cells whose ancestors either didn't see overexpression or just saw overexpression of GFP as a control?

If we see a difference, do those traits have the same unusual genetic properties that we ascribe to prions? Do they disobey Mendel's laws? Can they be erased with transient inhibition of chaperone activity? Can they be passed from one cell to another through cytoplasmic mixing?

PHOTO PROVIDED BY DANIEL JAROSZ

Daniel Jarosz

We identified dozens of new prions and only three old friends. And rather than being unusual, it looks like [GAR+] is actually the founding member of a very large class of protein-based, self-templating elements that can be heritable. Most of them don't form amyloid fibers. They don't have these long regions of asparagine- and glutamine-rich repeats. Instead, they tend to be intrinsically disordered proteins, highly enriched in transcription factors and RNA-binding proteins.

Spell out why this is important.

Obviously, prions have been exciting to people for a long time. They motivated a Nobel Prize. (Author's note: Stanley Prusiner won the 1997 prize in medicine or physiology for his discovery of prions.) They changed how we think about inheritance.

But people have thought of them as relatively rare. And we thought we understood what protein sequences can drive prions — again, mostly these asparagine- and glutamine-rich repetitive elements.

But [GAR+] was such an odd one out. And we could see that it was con-

CONTINUED ON PAGE 20

CONTINUED FROM PAGE 19

served for at least a couple of hundred million years.

It was found totally by chance by a lab in Canada in the late '70s, and they had no clue what they had found. They had two papers trying to follow up on the inheritance patterns, and after it didn't make too much sense to them, they dropped the project.

It seemed to me that the most fundamental thing about prion biology is this really unusual folding landscape — where there's a conformation that is kinetically inaccessible but thermodynamically really stable. There's a history to that folding landscape, where once you form the self-templating conformer, new folding events are going to be down this other pathway.

We reasoned that you could increase the likelihood that the initial misfolding event would happen just by making more protein. People have seen this before. So we had some precedent that would lead us to think that it wasn't a totally crazy idea.

But nobody had done it on the same scale as you?

No one had done it systematically. You know, we use many other models in the lab now, but yeast remains my favorite, because you can do almost anything you want with it. For example, we could overexpress every single gene in quadruplicate, transiently, and ask: What is the effect of that — the long-lasting effect of transient overproduction.

So you overexpress and overexpress…

And then you stop. And then we grow the cells for a long time. Then we asked, at least 100 generations later: Do the grandprogeny of those mothers that saw overexpression also have a difference in their behavior? Do they have some sort of a memory of their ancestors' experience?

How did you determine that?

Since we were doing it for many proteins, we had to be a little pragmatic. So the easiest thing to measure was simply growth rate. And we can do that in relatively high throughput. So we asked: How did those grandprogeny grow in the presence of a variety of different stressors?

So what do these prions you found look like?

They definitely don't form fibers. Most seem to form small oligomers.

So what are the big takeaways?

First, I think, for the prion field, it suggests that a nonamyloid type of prion biology is far from rare. Rather, it may be the predominant form of protein-based inheritance. We found behavior that resembles [GAR+] far more often than we found behavior that resembles [PSI+].

Before, most everybody thought prions equaled amyloid.

Even though the biochemistry involved for an amyloid prion and these (ones we found) is very different in detail, the proteins that have this behavior have similar functions. Amyloid prions turn out to be highly enriched in proteins that regulate information flow in the cell — in proteins that are transcription factors and that that regulate the biology of RNA.

And the same is true of the proteins that we uncovered in this screen. Even though they don't form amyloids, they don't have the same sequence bias, etc., they are also highly enriched in transcription factors and RNA-binding proteins. It raises an interesting question.

I think people who are dyed-in-the-wool believers in prions as selfish

Activision and aptitude

Daniel Jarosz acknowledges that he had "a maybe slightly unusual upbringing."

He grew up in Indianola, Washington, to parents who were anti-nuclear activists. He recalls going with them, when he and his sister were little, to protest. "They would sit in front of the trains that would bring nuclear warheads to the submarine fleet that was there and wear shirts that said, 'Only love will stop the train,'" he says. But, he adds, they'd always make sure only one of them risked arrest so that the other could look after the kids.

The elder Jaroszes, a construction worker and a housekeeper, were not alone in their activism. They were part of a small community focused on nonviolent action — "a crazy and wonderful collection of ex-hippies, nuns, priests, Buddhist monks, you name it," as Jarosz puts it.

A product of public school, Jarosz fell for science early on. In kindergarten, he recalls, he had to fill out a questionnaire. On it, he wrote that the thing he liked least about himself was that he had collected only three fossils.

His academic potential did not go unnoticed, and he was admitted at age 14 to the University of Washington, where he double majored in chemistry and biochemistry. Going to college early was an amazing experience, he says. "I wish that more people could have the opportunity to do it."

At UW, he initially was interested in physics, but an undergraduate research experience with a biochemist, American Society for Biochemistry and Molecular Biology member Rachel Klevit, set him on a new path.

He then enrolled in a Ph.D. program at the Massachusetts Institute of Technology. By then only 18 years old, but "sheepish" about his age, he had to decline when his peers invited him out for drinks. "I think they thought I just hated them," he says with a chuckle. Needless to say, his social calendar was not full: "It gave me more time to focus on my work!"

But he wasn't alone. He had a girlfriend, Mirna, who had gone through the early-admissions program at UW too. She had arrived at MIT a couple of years earlier. They're married now and have three children.

elements probably would say that there is something about those types of proteins that are safe harbors … but an equally plausible explanation is that this is a mode of regulation that's exploited in normal biology.

Is there anything else that our readers should know?

The other thing that is interesting is that, perhaps mercifully, given their connection to neurodegenerative disease, the N- and Q-rich sequences that drive canonical prion biology are relatively rare in our proteome. I'm fairly happy about that. Even though these could be beneficial occasionally, I'd rather not chance it too often.

In contrast, these sequences of the type that we discovered are actually more common in our proteome than they are in the yeast proteome, and indeed we, in the final experiment in the paper, were able to at least provide proof of principle that human homologues of these proteins can adopt conformations that self-template.

Are there any major misconceptions about prions?

I almost hesitate whether to call these prions at all. Prusiner, in his seminal 1982 paper, wrote what he meant by "prion:" proteinaceous and infectious. And it's very helpful for the field that he was so clear about this definition. So I feel as if we should call them prions. But, that being said, I think, in terms of their fundamental biochemistry, in terms of their often beneficial effects on cells, it's a loaded term. These proteins have really broadened my notion of the prion concept.

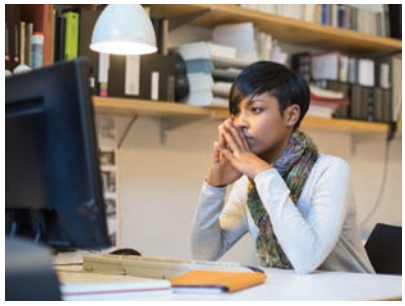
Angela Hopp (ahopp@asbmb.org) is the communications director for the ASBMB and executive editor of ASBMB Today. Follow her on Twitter at twitter.com/angelahopp.

Imposter syndrome and diversity graduate students

By Julia Omotade, Jamie King & Richard A. Kahn

In today's graduate education environment, "diversity students" — as defined in the notice NOT-OD-15-053 from the office of the director at the National Institutes of Health to include underrepresented minorities, students with disabilities and those from a disadvantaged background — must constantly navigate stereotypes and misperceptions. The stereotypes and misperceptions, which challenge the notion that their successes are due to merit alone, make these students particularly susceptible to a certain condition. Imposter syndrome is a condition where one feels inadequate or unworthy of his or her success or accomplishments despite evidence suggesting otherwise.

The term "imposter syndrome" was coined in 1978 by Pauline Rose Clance and Suzanne Imes at Georgia State University in a paper they published in the journal of Psychotherapy Theory, Research and Practice. "Imposter syndrome" quickly moved into the mainstream. We use the term to describe the chronic and potentially lifelong feelings of inadequacy and self-doubt that affect performance and professional outcomes. We believe that the anecdotal experiences highlighted in this article hold true among students across many institutions and fields and result in creating imposter syndrome in diversity graduate students. We hope this article will encourage open dialogue, without which the best intentions of programs designed to build, foster and retain diversity in the STEM disciplines may be undermined.



Perspectives from two URM students

Prior to entering graduate school, our strong work ethic and academic achievements gave us the confidence to believe that we were fully qualified to undertake graduate training at a top research institution. However, throughout our graduate careers, many of our achievements have been attributed to our inclusion in an ethnic group rather than hard work or talent. Recurring encounters began to compromise our perceptions that we were indeed competent and qualified to be successful scientists on our own merits. This was despite progression through our graduate programs with all other outward signs of success. Here are some of our experiences:

By Julia Omotade

Upon entering graduate school, I received a merit-based fellowship that the institution used to attract top applicants. Importantly, this fellowship is not associated with any diversity initiative. When several colleagues became aware of this fellowship, they asked how much "diversity money" I was receiving. Thus, instead of an accomplishment, this fellowship instantly was transformed in my mind into an automatically generated handout based on statistics or an attempt to meet a "diversity quota."

During my second year, I was selected to receive support from our institutional T32 training grant from the NIH. Despite the fact that this grant is reserved for talented and successful students, I heard comments from colleagues suggesting that I was selected primarily to document institutional diversity. Prior to hearing such comments, I had been humbled and extremely proud of my accomplishments. I had worked hard, been vocal in classes, made good impressions, and progressed well in my training and research. Though my academic record suggested that my merit rather than racial identification was the source for my accomplishments, I internalized the perception that my accomplishments were based on racial identification and began to believe the misperceptions surrounding my success.

Over the past decade, the NIH (and other institutions) has made a robust effort to increase racial and cultural diversity of the research workforce. Although these programs have been fundamental to increasing diversity on a national and institutional basis, my experience is that such awards often are interpreted as affirmative action and viewed as avenues through which unqualified individuals procure opportunities that they could not have secured on merit alone. For example, my deepest and most per-

sistent feelings of imposter syndrome arose from comments regarding my NIH predoctoral diversity fellowship, also commonly referred to as an F31. Although fellowship applications from URM students are reviewed using the same criteria and scoring matrix as nonminority fellowships, it became clear to me that these fellowships are regarded by my colleagues as less competitive. It is common for URM students to hear comments such as "I wish I could apply for the diversity fellowship" or "You're so lucky you can apply for the diversity F31." For a URM student, these comments instantly depreciate the competitiveness and value of these awards. I vehemently defended the competitiveness of my fellowship, but I internally began to believe that this award was inferior to the grants awarded to my non-URM colleagues.

By Jamie King

I attended a historically black college, which helped build the strong level of confidence that I had when I entered graduate school. During that time, I did not encounter colleagues who viewed designated diversity initiatives as handouts.

However, early in my graduate career, it became apparent that some people perceived these awards to be handouts. I recall specific comments while taking a highly stressful grant-writing course during which my colleagues and I felt the pressure of writing a strong, competitive fellowship application. When I expressed my anxiety to some colleagues, I was met with the comment, "Well, at least you can apply for the diversity one." In my mind, this meant that despite preparing an application with the same rigor and scientific standards as the others, any future success in funding would not be perceived as prestigious because of my status as a URM.

My sentiments may seem like an extreme interpretation of offhand comments. But the effect of these remarks was substantial. Those remarks became subconsciously magnified over time. In addition to negatively affecting my perceptions about my personal qualifications for fellowship applications, these feelings of imposter syndrome also spilled over into other aspects of my professional career, such as research seminars and symposia. On multiple occasions, I wondered if my audience was less inclined to provide feedback and engage in scientific discussions because they might think I was only there to fulfill a diversity quota.

Despite these experiences, I have learned to manage imposter syndrome by focusing on self-assertion and open dialogue with a supportive group of students, all with the goals of building and maintaining my confidence. Not all students who face imposter syndrome are equipped to identify it and manage it on their own. For this reason, it is important and necessary to address these issues openly in the graduate-student community.

A faculty member's perspective

By Richard A. Kahn

Any biologist worth his or her salt knows that diversity (be it genetic, intellectual, ethnic or other) strengthens the population. The NIH and other institutions are to be commended for their efforts toward increasing the diversity of students in the biological sciences through support of training grants, fellowships and research grant diversity supplements.

However, my co-authors have made me acutely aware of an issue that risks undermining the goals of such initiatives. As someone who has served on various selection committees, I am aware that ethnicity is a factor taken into consideration when making funding decisions. Indeed, many of us who have served on committees ranking program training grants, known as T32s, have been concerned that the NIH may be overemphasizing the importance of funding a large percentage of diversity students through these grants. As a result, there can be inflation in scoring URMs out of concern for how reviewers will factor this issue into the overall score. In a nutshell, the initiative to maximize diversity can lead to the perception that diversity students are recipients of merit-based awards largely due to their diversity status, not their talent. The resulting imposter syndrome that these misperceptions create could undermine the key goals of such programs: to increase diversity enrollment and improve long-term career outcomes.

I believe there remains the belief among a subset of our students and faculty that some diversity students are not as qualified and are recipients of affirmative action. I cannot speak to national numbers or those at other institutions or even other programs at Emory University where I work. However, my experience as the recruiter for the biochemistry, cell and developmental biology graduate program last year demonstrated that this was not the case.

Our applications were reviewed in three rounds to identify the top students, who then were invited for interviews. GRE scores, GPAs, research experience and letters were the criteria that I took into consideration. I did not pay attention to URM status, though training-grant eligibility was an important factor. Near the end of this process, I reviewed the group of applicants as we moved from 142 applications to 22 interviewees in three rounds of cuts. I determined the percentage of diversity students in each round. The percentage began at approximately 20 percent, increasing at each step and ending at approximately 30 percent. We found no differences between average GRE and GPA numbers between URM

CONTINUED ON PAGE 24

CONTINUED FROM PAGE 23

and non-URM candidates. Letters and research experience are harder to quantify, but nothing struck me as different between the two groups. These anecdotal data from one program at one institution support the conclusion that our diversity applicants are fully qualified without regard to ethnicity.

One conclusion is clear: No diversity student in our program need fear that he or she was offered admission primarily due to race or ethnicity. This conclusion is in stark contrast to the internalized feelings of imposter syndrome that my co-authors shared and that consistently arose in discussions with members of all graduate programs. Though I certainly was aware of the types of comments described above, I vastly underappreciated the negative impact they could have on our students.

The path forward

Though likely nonmalicious in the minds of the sources, the perceptions about diversity students described above are insidious and generate an impact regardless of intent. Moreover, the effects of the perceptions may be unconsciously magnified over time. Misperceptions surrounding awards procured by diversity students are pervasive — regardless of institution, field or stage in one's education. We believe most people are unaware they hold and convey such misperceptions. URM students repeatedly encounter race- or ethnicity-based misperceptions that question the quality and validity of their professional achievements. Though seemingly subtle and innocuous, such misperceptions are persistent. Their presence throughout one's graduate education may culminate in imposter syndrome that can negatively affect one's self-efficacy and career.

Students, faculty and administrators must be made aware of the issues of imposter syndrome and be willing to address them openly. We believe this is key to decreasing the susceptibility of diversity students to imposter syndrome. Comments that perpetuate imposter syndrome among our diversity students are often subtle, suggesting that awareness may go a long way toward change. Platforms for open discussion and raising awareness could include integrating seminars hosted by student or university organizations, such as black graduate student chapters, that are focused on defining and addressing diversity-specific imposter syndrome into existing graduate and professional development series.

Graduate programs or students may be able to counteract the effects of imposter syndrome by focusing on techniques to build confidence despite encounters with microaggression. By focusing on small victories or self-affirmations for success, individuals may be able to build confidence that can accumulate over time. However, any personal stride to regain confidence likely will be less effective without open discussions of the issues and ways for an individual to best respond. Graduate education is an ideal stage to identify the causes of imposter syndrome in diversity students and foster dialogue to combat the negative and far-reaching effects that may result. For mentors and leaders of graduate programs, it is important that when faculty members witness diversity-based microaggressions, they intervene and address them constructively.

While raising awareness of diversity-specific imposter syndrome at the local level is important, we believe institutes that fund diversity fellowships and grants also should help address this issue. In doing so, they hopefully will increase the impact of their well-intentioned and much-needed diversity programs. Some steps toward this goal might include de-emphasizing the importance of the percentage of diversity students supported by T32's and re-emphasizing the goal of supporting the top students overall. Reviewers and funders of diversity grants should focus on the real steps the graduate program is taking to support diversity more than its number of diversity students. Currently, each institute makes its own decisions as to how (and how much) to fund training grants, including diversity ones.

Transparency in funding of grants (number of applications, success rates and pay lines for all versus diversity applicants by NIH institution) provides important data that should be available for each institution and quickly could help dispel the aura of affirmative action. Alternatively, should an institute fund diversity fellowships at a significantly higher rate than others, the burden should be on it to provide an explanation. With transparency, the perceptions and comments that propagate imposter syndrome should decrease on their own. At the very least, transparency will provide evidence-based rebuttals that challenge such perceptions head-on.

Overall goals include increasing the demographic representation of our trainees and scientists at every level, creating a community that more accurately reflects our national population, and ensuring equal access to training and career opportunities. A key step in achieving these goals is to eradicate longstanding misperceptions. Only by identifying and discussing them openly can we hope to bring about these long overdue changes.

Julia Omotade (ofomota@emory.edu) and Jamie King (jlking3@emory.edu) are graduate students at Emory University. Richard A. Kahn (rkahn@emory.edu) is a professor of biochemistry at Emory University's School of Medicine, a former director of graduate studies, and a recruiter for the biochemistry, cell and developmental biology graduate program. The authors thank a large number of colleagues for providing input throughout the years regarding many of the ideas expressed in this article.

Upcoming ASBMB events and deadlines

FEB

Feb. 8: ASBMB annual meeting late-breaking abstract deadline
Feb. 16: PROLAB application deadline
Feb. 17: ASBMB annual meeting Outstanding Student Chapters Award deadline
Feb. 23: ASBMB annual meeting early registration deadline

MAR

March 6: Student Chapters Undergraduate Research Award deadline
March 15: Accreditation application deadline

APR

Apr. 22–26: ASBMB annual meeting, Chicago

ASBMB
American Society for Biochemistry and Molecular Biology

Promoting Research Opportunities for Latin American Biochemists

The American Society for Biochemistry and Molecular Biology, the International Union of Biochemistry and Molecular Biology and the Panamerican Association for Biochemistry and Molecular Biology have instituted a program (PROLAB) and committed funds to foster interactions among biochemists in Latin America, Portugal and Spain with those in the United States.

This program is open to postdoctoral fellows, graduate students and tenure-track faculty members (within five years of their training).

The application deadline is Feb. 16.

Learn more at *www.asbmb.org/pabmb*.

ASBMB
American Society for Biochemistry and Molecular Biology

IUBMB

PABMB

An experiment in program-based funding

By Anna Taylor & Bob Finkelstein

This is an exciting time for biomedical research. Our understanding of basic biological mechanisms is increasing exponentially, propelling innovation across the research landscape. Technological advances in DNA sequencing, imaging, bioinformatics and many other areas are accelerating progress across scientific disciplines and will enable the development of new diagnostic approaches and therapeutic interventions. This is particularly true in neuroscience where, for example, former President Barack Obama's BRAIN Initiative, announced in 2013, already is generating cutting-edge tools and discoveries (1). It is critical that funding for biomedical research, which comes primarily from the National Institutes of Health, continue to spur this progress. Our goal at the NIH should be to create a stable and flexible funding environment that allows investigators to pursue bold, creative research.

In the current fiscal climate, achieving this goal will be challenging. For more than a decade, the pool of talented investigators has increased continuously in size, and the number of grant applications submitted to the NIH has grown accordingly. In addition, the NIH budget has not kept pace with inflation (2). As a result, grant-application success rates have declined significantly (3). Researchers are struggling to obtain, and then maintain, stable predictable funding for their laboratories. The lack of stable funding makes it almost impossible for principal investigators to plan their scientific goals, lab-personnel needs and other variables.

To begin to address these issues, a subset of institutes at the NIH (e.g., the National Institute of Neurological Disorders and Stroke; the National Institute of General Medical Sciences; the National Cancer Institute; the National Heart, Lung and Blood Institute; the National Institute of Environmental Health Sciences; and the National Institute of Dental and Craniofacial Research) are piloting a new grant mechanism — the R35 award. Different institutes are experimenting with different forms of this mechanism, varying the award length, budget, eligibility criteria and other award requirements. In general, though, an R35 award is intended to provide the entirety of an investigator's support from a particular institute. In most cases, the grant is for a period exceeding that of a typical R01 award, the principal NIH funding vehicle.

Current NIH policy has made it somewhat easier for principal investigators launching independent careers to obtain their first R01s. The NIH has stated that success rates for early-stage investigators (those within 10 years of obtaining their terminal degrees) applying for their first R01s should equal approximately the rates for established investigators seeking new R01s (4). At the NINDS, we achieve this goal by funding most R01 applications from early-stage PIs that have scores within 10 percentage points of our funding pay line (5).

Although this policy makes it a little easier for new PIs to enter the system, it doesn't address the issue of funding stability over the duration of an investigator's career. In an attempt to assemble and maintain a continuous funding stream, PIs spend nearly half their time writing and administrating grants (6). Despite this, funding in most laboratories waxes and wanes; complete lapses in funding are not uncommon. PIs have less time to do research and interact with members of their laboratories, which adversely affects the quality of research and the training environment. In addition, to renew their NIH grants, which average about four years in length, PIs must generate data and publications quickly. This creates pressure that can lead to less rigorous research and discourage investigators from undertaking more long-term or high-risk projects. Finally, the present hypercompetitive environment takes a heavy toll on PI job satisfaction and discourages many of the best young scientists from pursuing careers in academic research.

The NINDS R35, called the Research Program Award, or RPA, is intended for outstanding investigators with track records of conducting high-impact, high-quality research in neuroscience for at least the past five years. An RPA is a single long-term grant for up to $750,000 direct costs per year for eight years and is designed to fund an investigator's research program rather than a specific research project. The award should represent the entirety of an investigator's funding from the NINDS and is intended to allow her or him to

spend more time engaging in creative, potentially longer-term projects. The RPA is not intended for new PIs who never have had an R01 grant because, as mentioned above, these PIs currently receive a significant advantage when applying for their first R01s. In exchange for the long-term stability and flexibility provided by the RPA, recipients must commit at least six calendar months of effort to the grant annually, relinquish their other sources of NINDS funding (with limited exceptions), and not apply for additional NINDS grants during the duration of the award (again, with a few exceptions). One important issue we considered when designing the RPA was the potential effect of this new program on the institute's funding pay line. Our internal modeling suggests that this effect will be relatively small, since the amount of a typical R35 grant is approximately equal to the PI's previous annual funding.

An RPA application is different from that required for other grants. For example, the research strategy section has no specific aims and is limited to six pages; presenting preliminary data is discouraged. The applicant is asked to describe the importance of his or her previous accomplishments and outline an eight-year vision for the research program. The RPA's reviewers focus primarily on the investigator's previous track record and the significance and long-term impact of the research proposed. Reviewers also consider whether the research program will benefit from the flexibility and long-term stability of the R35 award and whether the PI has a demonstrated record of conducting rigorous research.

In response to our July 2015 request for applications, the NINDS received 196 proposals spanning basic, translational and clinical neuroscience. We now have issued the first cohort of RPAs — 30 awards (funded in study-section score order) totaling approximately $25 million per year. The RPA recipients are diverse with respect to gender, career stage, lab size and other parameters. The award rate of the RPA of approximately 15 percent mirrored that of the 2016 NINDS R01 pay line (the 15th percentile). We are encouraged by the large number of exceptional, creative applications and look forward to the discoveries that will emerge from this more stable and flexible funding environment.

So far, the response by the neuroscience community to the RPA has been very positive. However, as mentioned above, the RPA is a pilot experiment. We actively will monitor its success compared to that of the traditional R01 and other funding mechanisms. In this regard, input from the research community is critical. We encourage you to share your thoughts about the program and how it can be improved. We anticipate that the reissued RFA with a few minor changes will be open for new applications this month.

We realize that the RPA cannot solve the problem of an increasing number of investigators competing for insufficient funds. We hope, however, that it will provide a subset of NINDS-funded investigators with increased stability and more freedom to pursue their research.

REFERENCES

1. http://www.braininitiative.org/achievements/
2. http://faseb.org/Science-Policy-and-Advocacy/Federal-Funding-Data/NIH-Research-Funding-Trends.aspx
3. https://report.nih.gov/NIHDatabook/Charts/Default.aspx?showm=Y&chartId=124&catId=13
4. https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-046.html
5. http://www.ninds.nih.gov/funding/2014-NINDS-Funding-Outcomes.htm
6. http://sites.nationalacademies.org/cs/groups/pgasite/documents/webpage/pga_087667.pdf

Anna Taylor (taylorann@mail.nih.gov) is a senior analyst in the division of extramural activities at the National Institute of Neurological Disorders and Stroke. Bob Finkelstein (FinkelsR@ninds.nih.gov) is the director of the division of extramural activities at the NINDS.

The myth of perfection

By Kaoru Sakabe

With the release of the imaging software Adobe Photoshop in the 1990s, "Photoshopping" entered the English lexicon. Like Google, Photoshop seamlessly has integrated itself into the scientific enterprise. Scientists use the software to tweak images and to generate publication-quality figures. It's just so easy to create a blemish-free image. But there are guidelines to what is and isn't acceptable to do with the software. There are a few simple rules to remember.

First, ask yourself whether any changes are needed. The best-case scenario is to be able to present your original, unaltered data in the figure. However, journal editors realize that sometimes the best case isn't possible — an overly dark H&E stain or an overly bright Coomassie stain of a gel are two examples.

Once you've decided it's appropriate and necessary to make changes, make sure your adjustments are linear. Most journals, including the journals published by the American Society for Biochemistry and Molecular Biology, require that adjustments be made uniformly to every pixel in the entire image. That means using the brightness and contrast functions in Photoshop is acceptable within reason,

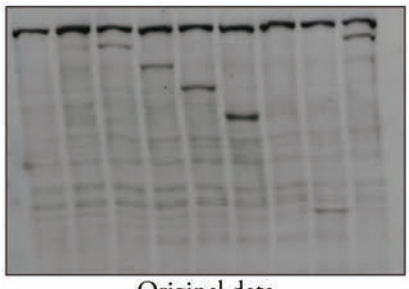
since these functions apply a linear adjustment to each pixel in the image. Also, go easy on moving the slider (see the figure). Overadjusting the brightness or contrast can hide background features, which is a misrepresentation of your data. Nonlinear adjustments include adjusting the gamma settings or using the "Curves" function in Photoshop. These actions are discouraged, since they do not apply changes equally to the pixels in the image. If these adjustments are used, then you must disclose their use in the figure legend.

Speaking of data misrepresentation, specifically enhancing, removing or obscuring features would fall into this category. Worried that a faint band won't support your conclusions? Bothered by the cell debris in the corner of your image? Concerned that the reviewers may say that the co-localization or the co-immunoprecipitation isn't strong enough? The temptation to enhance or remove these features is real, but this type of manipulation falls into the misconduct category and could have serious consequences.

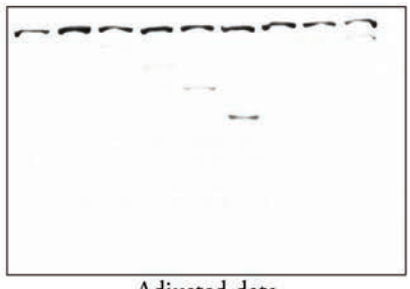
The final image should look like your original data, warts and all. You always should inspect your final figure and ask yourself if it is a true representation of the original capture or image. If your answer is no (or kind of), you should re-evaluate your figure.

Practically speaking, if any of these issues are discovered during the review of your paper or even after it is published, they could delay publication of your article, result in a correction, or even end in a retraction. More importantly, these issues go deeper and speak about the reproducibility of the work and your integrity as a scientist. Other researchers will not be able to replicate the results shown in your article if some of the data have been enhanced or hidden selectively. Presenting your data in a transparent manner ensures that you have done your due diligence.

Kaoru Sakabe (ksakabe@asbmb.org) is the data integrity manager at the ASBMB.



Original data



Adjusted data

Aggressively overadjusting the brightness and/or contrast misrepresents the actual data that were obtained and can mask potential biologically relevant results.

Funding undergraduate work

By Nadine Gombakomba

The American Society for Biochemistry and Molecular Biology Undergraduate Research Award funds students who are doing summer research projects. The undergraduate students are members of the ASBMB Student Chapters program and do research in the laboratory of an ASBMB member.

To apply, a student must submit a statement outlining the research project, his or her role in the project, and career goals. When they complete their research projects, the students are encouraged to present their work at the ASBMB Undergraduate Poster Competition during the ASBMB annual meeting. The application for the 2017 awards is open until March 6.

In 2016, the ASBMB gave 10 students this award. The students demonstrated a passion for research and intend to pursue careers in science and medicine. The following were some of the recipients:

Nicholas Braganca
(University of Tampa)

Nicholas Braganca is investigating the effects of Polyphenon E, a proprietary formulation of the polyphenols in green tea, on the gene expression of prostate cancer cells. Braganca also has been a lab mentor for analytical chemistry and biochemistry.

Braganca is the president of the University of Tampa's ASBMB Student Chapter, where he helps to lead the chapter's outreach events. After graduating, he plans to pursue an M.D./Ph.D. degree and become a cardiothoracic surgeon and researcher.

Zindzi Thompson
(Mary Baldwin College)

Last summer, Zindzi Thompson developed a method of detecting the molecule LL-37, a protein commonly found in the immune system. Thompson is now using the method to determine the effects of culturing cells with vitamin D on LL-37.

At the age of 13, Thompson was accepted into the Program for the Exceptionally Gifted at Mary Baldwin College and skipped high school to study for an undergraduate degree in chemistry. Currently a junior, Thompson plans to attend medical school after graduating and become a neurosurgeon.

Andrew Tobias
(Montclair State University)

Andrew Tobias first became interested in science in fourth grade when a teacher introduced him to rockets and meteorites. He is working on a project that involves cloning, expression and purification of a potential drug target, dihydrofolate reductase, which potentially can inhibit the growth of a filarial nematode that causes lymphatic filariasis.

Tobias intends to gain experience in the pharmaceutical industry before pursuing a doctoral degree. Tobias is the president of the chemistry club at Montclair State University. He is working with the club members to host a chemistry magic show for high school students.

Acacia Wimmer
(St. Mary's University of Minnesota)

Acacia Wimmer investigated the mechanistic role of an herbicide called atrazine. Wimmer studied atrazine's effects on fatty acid metabolism by quantifying acetyl CoA carboxylase levels in the livers of mice. After graduating, Wimmer plans to enroll in the physician assistant program at Concordia University Wisconsin. She would like to "take the talents and knowledge I have been given to help improve and support the lives of others." She advises undergraduates wanting to do research to be proactive, talk to professors and find opportunities through various organizations.

Yuyi Zhu
(Towson University)

Yuyi Zhu developed an interest in cellular biology after his seventh-grade teacher introduced images of cells to his class. Zhu's project focuses on repurposing drugs approved by the U.S. Food and Drug Administration by combining them with recombinant immunotoxins to improve some cancer treatments.

Zhu volunteers at the Greater Baltimore Center in the surgical intensive care unit and oncology unit and works with autistic adults at the Hussman Center for Adults with Autism. Once he graduates, he plans to pursue a Ph.D. in cancer biology.

Nadine Gombakomba (ngombakomba@asbmb.org) is the Student Chapters coordinator at the ASBMB.

The ASBMB Student Chapters welcomes its new chair!

By Ann Aguanno

On July 1, Quinn Vega will take on the role of Student Chapters chair at the American Society for Biochemistry and Molecular Biology. The ASBMB Student Chapters is devoted to building a national network of undergraduate students and faculty members for the advancement of research, education and science outreach. Its mission is to provide networking and career-development opportunities at regional and national conferences, access to research and science outreach, and funding and awards to facilitate these aims.

Quinn began with the ASBMB as the adviser for the student chapter on his home campus of Montclair State University. Quinn immediately became involved with ASBMB's educational efforts by serving as a mentor for students in a program sponsored by the Minority Affairs Committee and as a judge in the ASBMB Undergraduate Student Research Poster Competition held each year at the ASBMB annual meeting.

In 2009, he was brought on by the Student Chapters Steering Committee as the director of all student chapters in the northeast region of the U.S. Quinn continued to demonstrate his committment to undergraduate education as the Northeast director by leading efforts to provide professional development and networking opportunities to undergraduate faculty. For example, Quinn co-organized the highly successful Tranforming Undergraduate Education in the Life Sciences conference at Missouri Western State University.

PHOTO PROVIDED BY QUINN VEGA

Quinn Vega will become the chair of the ASBMB Student Chapters later this year.

A true Californian, Quinn received his B.S. in biology from the University of California, Irvine, and his Ph.D. in biology from the University of California, San Diego. He then moved on to the University of Michigan's department of biological chemistry for his postdoctoral fellowship and then to Montclair State University.

As a researcher, Quinn investigates the mechanism of cellular signal transduction. He has received funding from the National Science Foundation and the National Instututes of Health for both research and student training. He also serves as the chair of his department.

Quinn has been chair-elect of the ASBMB Student Chapters since last July. As the current chair, I cannot emphasize enough how valuable his advice and partnerhsip have been for me and for the Steering Committee. I am pleased to welcome Quinn as our new leader!

Ann Aguanno (aaguanno@mmm.edu) is a professor of biology at Marymount Manhattan College. She has been a member of the ASBMB Student Chapters Steering Committee since 2007 and its chair since 2014.

A note from the new Public Outreach Committee chair

By Susanna Greer

Over the past five years, the Public Outreach Committee at the American Society for Biochemistry and Molecular Biology has strived to fulfill its mission to increase the effectiveness of science outreach activities through the involvement of ASBMB members. As I take over for the previous chair, Tom Baldwin at the University of California, Riverside, my goal is to continue the fantastic work the committee has done and help to expand the reach and effects of our efforts. Ultimately, our aim is to establish the ASBMB as an organization that is known for promoting science outreach and makes it easy for its members to participate in programs and activities. In other words, we want you to get involved. Here's a sampling of how you can:

Skills training

The first step to being successful at outreach is being a good communicator. That's why the POC offers "The Art of Science Communication," an online course that provides scientists with fundamental training in science communication, focusing in particular on how to present science to a nonexpert audience. The course runs three times a year, February–March, June–July and October–November. Stay tuned to our website for announcements at www.asbmb.org/outreach.

For 2017, the committee is in the process of developing more courses aimed at helping participants communicate with certain types of audiences, such as policymakers and K–12 students. These courses will expand on the lessons taught in "The Art of Science Communication" to train attendees on how to engage effectively with different groups.

Resources

Communication skills honed? Ready to participate in outreach events but need ideas that work? The POC will sponsor a number of activities at the ASBMB annual meeting this year where you can improve your skills in outreach. Not going to the annual meeting? Not to worry: Check the "Resources" tab on our website. You'll find all kinds of great tools to get you started in outreach, from activity guides to how-to manuals. We constantly are adding new material to the website, so check often!

Opportunities

Too busy to plan an outreach event yourself? Want to find an outreach activity in your hometown? Just go to our website, type your zip code into the "Local Outreach Activities" tab, and you'll bring up a listing of outreach events close to home. Show up and bring your science to the masses: It doesn't get much easier than that. If a program doesn't exist where you live, reach out to us, and we'll help you start your own!

Member engagement

One area where the committee is looking to step up its game is greater engagement with the ASBMB membership, particularly with those of you who already have your own outreach activities. We are developing several outlets, including a regular outreach newsletter and social-media campaigns, to showcase the great outreach work that our members are doing (see "Share your ideas"). We also want to create more networking opportunities for people involved in outreach and help them share ideas and connect with one another. To do so, the committee is working to put on a career symposium at the University of Kentucky in 2017 focused on outreach and communication. The committee also hopes to arrange an in-depth outreach symposium in 2018.

Our long-term vision is that outreach becomes something that all scientists do as part of their jobs and get recognized and rewarded for doing. I often am amazed by the success stories I hear about scientists doing both outstanding science and outreach. But we all must do more. The POC hopes that each of you will introduce someone to science. If each of us is engaged in promoting science, we can be hopeful for the future of the enterprise that we hold so dear.

Share your ideas
Have an outreach program that you want to show off? Got a great outreach resource that you want others to use? Share them with us at outreach@asbmb.org.

Susanna Greer (susanna.greer@cancer.org) is the national director of the clinical cancer research, nutrition and immunology program at the American Cancer Society.

What is service?

By Matthew Cheung

My father always emphasized the importance of giving back to the community that has given so much to us. That thought has resonated with me. And it's how I find myself on this relentless pursuit to serve.

After an invitation from my dad, I began volunteering with the Lupus Foundation in high school. In college, I joined Alpha Phi Omega, the national service fraternity. Currently a senior at Saint Louis University, I have completed hundreds of service hours. Needless to say, service plays an integral part in my life. Through my experiences, I have explored the deeper meaning of what it truly means to serve but also have uncovered the darker side of service.

Volunteering at soup kitchens, hospitals and nonprofit organizations are just a few examples of the countless service opportunities that exist. Serving is made especially simple when surrounded by other motivated students at a university that places such a heavy emphasis on serving the greater community. In fact, SLU prides itself on completing more than one million service hours each year. But what does that really mean? After all, it's just a number.

We gather each October and April for universitywide day of service events in which upward of 4,000 students go out to spend five hours engaging in community service. Most of us find ourselves weeding, pulling roots, mulching and raking leaves. These mundane tasks are assigned to accommodate the mass quantity of students. We leave that day feeling great about ourselves because of the change we made that day and carry on with our merry lives. We never return to these sites. We never speak to these people again. So let's be honest. Did we actually make a difference? Sadly, I don't think so.

PHOTOS PROVIDED BY MATTHEW CHEUNG

Matthew Cheung and his friends volunteered at the Polycystic Kidney Disease Foundation annual walk in 2015.

Cheung and his brothers participated in a Lupus Foundation annual walk in 2012.

I know this because I've also fallen into this trap.

My point is not that days of service are terrible affairs that should be avoided. Rather, my point is that true service is more than just a one-day excursion. Service consists of continuous processes that develop into fruitful relationships. It's when genuine connections are built and strengthened over the course of time.

I've found these meaningful relationships personally while volunteering with disease-specific organizations, such as the Lupus Foundation, the Alzheimer's Association and the Polycystic Kidney Disease Foundation. I spend time helping out at their fundraising events including 5K races, walks and dinners. My dad and I volunteer together at many of these events. It's such a great experi-

Cheung and a group of Health Sciences Learning Community students volunteered with Randolph World Ministries in 2016.

ence because I get to interact with survivors and people struggling with these diseases. I get to hear about their stories and firsthand accounts of their struggles.

Additionally, I had the privilege of working with inspireSTL. Each Saturday, I provided free ACT prep for high school students from underprivileged areas. These students could not afford tutoring, so they were dependent on volunteers like me to help them.

One of my favorite service relationships I've built is with one of my professors who runs a small medical mission organization called Randolph World Ministries. I spend time at his house sorting medical supplies, creating sickle-cell kits and then shipping them off to clinics in Haiti.

Even better, I've had the opportunity to combine this with an on-campus position. I get the joy of working as a resident advisor for the Health Sciences Learning Community, where one of my goals is to develop programming that integrates a cocurricular experience for first-year college students. Once or twice a semester, I plan a service event that brings around 50 students to volunteer at Randolph World Ministries. Students love the events and are eager to return the next time. Not only do they get to see real-life applications of what they're learning in the classroom, but they have lots of fun as well. They get to spend time with each other while doing medically related work that benefits the people of Haiti.

I have developed strong, sustained relationships with the people I've served. It's satisfying knowing that others directly benefited from the work that I invested in. That's why I love doing service. I feel like I get more out of it than I put in. For that reason, one could argue service is inherently selfish. Maybe it is. But maybe it's meant to be a mutualistic relationship. Like humans and their gut bacteria, both parties work together, and each benefits.

As I reflect on what I've learned through my experiences, I constantly come across one larger question: Why does service even exist?

Raising money for disease, tutoring underprivileged students or packaging medical supplies for those in poverty all expose the underlying societal issues at hand. The greater problem in this picture is the fact that these inequalities exist in the first place. In an ideal world, none of our acts of service would be necessary to begin with.

After acknowledging these inequalities, I realize that my community service only offers a short-term solution. It does not solve the underlying problem. However, that does not mean that service isn't necessary; rather, we should be cognizant of these bigger concerns. As an aspiring physician-scientist, these current learning experiences will be key in shaping my future practice. It's a matter of using my privilege to maximize the service I can provide to those around me, striving to alleviate these greater issues.

Matthew Cheung (cheungmd1@gmail.com) is an undergraduate investigative and medical sciences major at Saint Louis University. He is one of the 2016 recipients of the Marion B. Sewer scholarship given out by the ASBMB.

Biochemist, ethicist, pastor, chaplain

By Craig Malbon

I sit at a patient's bedside. The patient is suffering and dying. I pause to reflect. From my earliest training in biochemistry at Case Western Reserve University through my postgraduate training at Brown University and Harvard University, I recall the phrase "from bench to bedside." The holy grail in biomedical research always has been to move a discovery made at the bench to a bedside therapeutic designed to alleviate suffering and disease. Although I have had no therapeutic derivative from my research approved by the U.S. Food and Drug Administration, I still travel from the bench to the bedside as a bivocational scientist, ordained minister and chaplain. So, in some deep way, I made the bench-to-bedside journey, just not the way I would have expected early in my career.

I began my research training in 1972, when I arrived at Case Western as a graduate student, keen to learn biochemistry at the place where the discovery of cyclic AMP and its role in cell signaling just was emerging. My training later at Brown was in fat-cell and hepatocyte isolation. Cell signaling was the hot topic of the time, I also spent nearly a year commuting to Harvard to study cholera toxin action with Michael Gill in the laboratory of Alwin "Pap" Pappenheimer. Those were halcyon days, a time of camaraderie and competitive efforts to hone research skills.

In 1977, I joined the faculty of a brand-new medical school built at Stony Brook on Long Island. The new 3-million nominal-square-foot Health Sciences Center had research labs on the same floor as acute and long-term clinical services. It was an experiment in research and health care design. It also was the site of my first independent laboratory.

Over the years, my laboratory was prosperous. We made discoveries in cell signaling, such as Wnt signaling, as well as in factors provoking breast cancer, such as the hyperphosphorylation of MAP kinases. We recently made some inroads into familial exudative vitreoretinopathy. When I was offered a position elsewhere, my institution made a competitive counteroffer that kept me on Long Island for 39 years. My colleagues and I have published more than 250 articles, book chapters and reviews and have garnered generous support from the National Institutes of Health, the American Cancer Society and the American Heart Association.

After getting a taste for research administration, I was appointed associate dean in the medical school by Jordan Cohen in 1988. Later, I was appointed founding vice president for research by the late John Marburger III. These two mentors shaped my administrative skills and were generous with their time. As a vice president of a research-intensive university, I was launched into discussions about science policy at the national level. I much enjoyed my years on the Science & Technology Steering Committee of Brookhaven National Laboratory, where I made many friends in the fields of physics and cosmology.

In 2000, I had created a new dimension to the competitive renewal of a national research service award program. It included efforts to offer training in bioethics for all program members as well as staff involved in institutional clinical trials. Perplexed by moral issues posed by clinical faculty who confronted suffering, death and end-of-life decisions, I reached out to professional ethicists. I assembled universitywide teaching faculty to offer a short course in bioethics. The course provided lectures and discussion followed by a meal. It was a great success, and I spent time more deeply thinking about ethics. Clinical faculty who attended the course continued to challenge the group with issues about early termination of pregnancy as well as palliative sedation. My inability adequately to plumb the depths of their issues about treatment outcomes and life-and-death decisions stimulated greater discernment.

In 2005, I left senior administration. I focused on my laboratory and an institutional postgraduate National Research Service Award program funded by the National Institute of Diabetes and Digestive and Kidney Diseases that I directed along with the Diabetes & Metabolic Diseases Research Program.

When I left senior administration, I grabbed the opportunity to spend time as a visiting scholar at Princeton Theological Seminary. There I had many conversations with formally trained ethicists. I entered a new world. There was a library with more than 2,000 periodicals and more than 1 million bound volumes (it's the

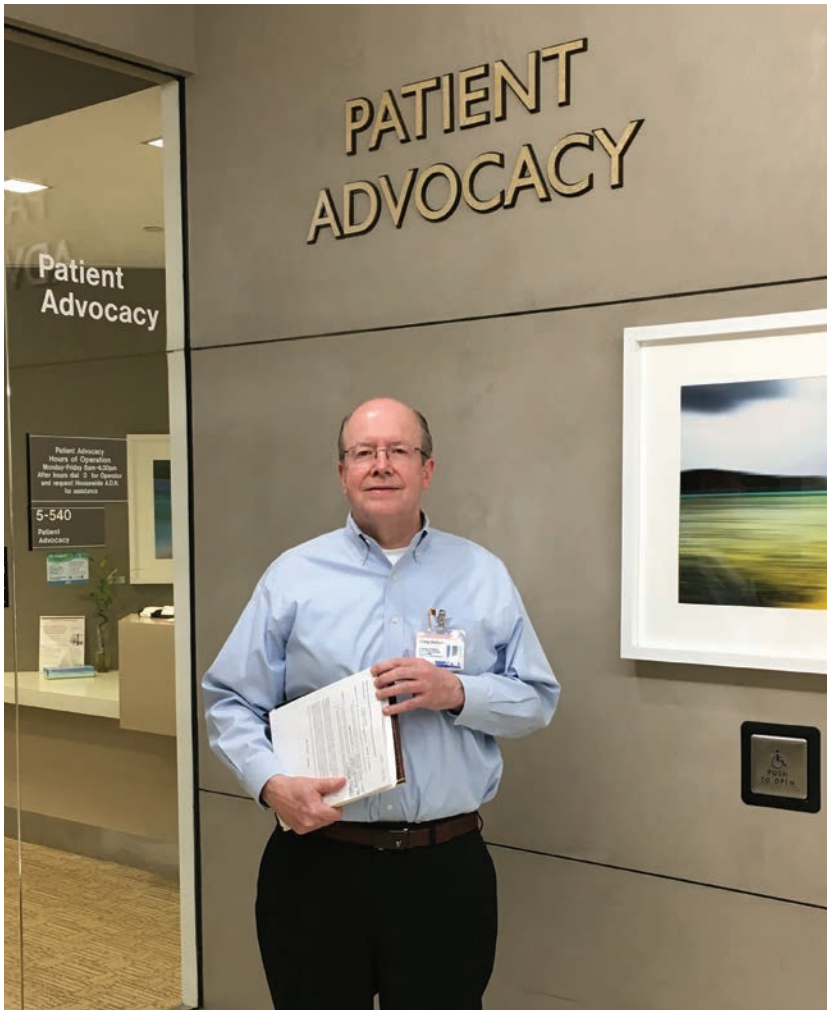


PHOTO PROVIDED BY CRAIG MALBON

A bench-to-bedside journey, but not in the conventional sense.

second-largest theological library in the world, surpassed only by the one at the Vatican). Most of the work was alien to me.

The weekends I spent at PTS were formative. I concluded that to do scholarship in ethics, I needed to train formally. I set my sights on Union Theological Seminary in New York City. Union has a 175-year history of wrestling with issues of social justice and human rights. Competition for placement in a very small entering class in the divinity master's degree program seemed like a long shot for a biomedical scientist in his mid-50s competing with the highest caliber of 20-somethings.

I negotiated two half-years free from teaching and committees at my home institution but still managed the lab work and grant writing. This was in lieu of the four full sabbatical years that I forewent while in administration. The institution was generous in its understanding of my goals. I applied for admission to Union fully aware that balancing the demands of my laboratory with seminary life would be a challenge. I surely was the last student admitted in my year, having been screened by faculty as well as Union President Joseph Hough.

Seminary work was the most demanding academic experience of my life. The reading assignments at first seemed crippling, but I was in wonder just to arrive at the seminary each day. I trained under Gary Dorrien, who was kind and supportive. During my training in ethics, I was co-opted by my classmates to give a sermon and reflection at the noontime chapel service that the entire school body attended. I suppose it was my senior status within this group of talented and committed students from all the great universities that prompted me to accept the task. In spite of being on the lecture and Gordon Conference circuit for several decades, I was challenged by the task of offering biblical exegesis and personal reflection in a seminary. It was not a lecture with PowerPoint slides!

After the sermon, Hough came and asked me again the goal of my studies. I replied, "Ethics." Hough said, "Malbon, I think it is more than that" and smiled. In the next three years, I graduated from Union, was ordained as a minister and trained as a chaplain!

My laboratory has downsized and continues to interrogate large scaffold proteins, such as AKAPs and Dishevelleds, which physically integrate complex intracellular signaling pathways. Just this month, we are using cryo-electron microscopy for the task of understanding AKAP structure! Additionally, I teach ethics in the medical and graduate schools. My chaplaincy focuses on end-of-life counseling of individuals and families. I pastor at a large 350-year-old church whose active congregation includes scientists, clinicians and other university faculty.

I am deeply thankful for the support that I've received from my family, community and institutions. Is my biomedical research concluded? I think not, as we are back to writing grant applications. The cosmology of my life, I have discerned, is a series of callings, first to science and then to chaplaincy. Who knows what comes next?

Craig Malbon (craig.malbon@stonybrook.edu) holds the title of leading professor and is affiliated with the departments of pharmacology and of preventive medicine in the school of medicine at Stony Brook University.

Wish I did my Ph.D. in the U.S.

By Biswapriya Misra

With an offer letter in my hand from one of the most prestigious education and research institutions in India, the Indian Institute of Technology Kharagpur, I was excited. But the prospect of getting a doctorate degree from India also gave me the feeling of settling for less. That feeling was bolstered further when I arrived in the U.S. as a postdoctoral researcher.

The offer from IIT Kharagpur was enviable, at least to my fellow botanists, friends and family. I had a master's degree from a top-notch university, but as it was a state institution, it didn't have the same clout as IIT Kharagpur. My admission interview went nearly perfectly. My written examination scores were nice and strong. I had secured fellowships to support my research in plant biotechnology for more than five years. But I had to work with limited laboratory resources. I now realize why I had the feeling of settling for less: I didn't do my Ph.D. in the most perfect place!

I'm comparing my experiences to what I see American students go through. I am startled by the amount of resources and technologies available to them. I feel that I did not get any of the things American graduate students get, such as access to resources, acquisition of skills, development of scientific street-smarts, opportunities to attend quality workshops and symposia, teaching experiences, and so on.

I feel I arrived late to many things they take for granted. I feel I have a lot to learn and assimilate.

For example, during class lectures in the U.S., I saw research manuscripts from journals, like Nature, the Journal of Biological Chemistry and Science, in the hands of undergraduate students. I did not have any access to any of those journals back in India. I hadn't even heard their names until toward the end of my master's degree! All I had were textbooks and the Machiavellian system of Indian education. In that system, I had to memorize passages prescribed in the syllabus, write a final exam at the end of one or two years, and come out with flying colors. I was completely unaware of the journals in which the research on which these textbooks were based was first reported! Seeing these undergraduates reading research articles, understanding them, summarizing the findings and writing reports astonished me. The college system was geared toward learning about research firsthand.

Another incident drove home how different my education was. During a postdoctoral stint at the University of Florida, Gainesville, my principal investigator got many applications from undergraduate students to do research for a few months. Much to my bewilderment, I was offered an undergraduate research assistant. I mentioned my confusion to my PI. I couldn't understand how an undergraduate could be allowed to work on a project funded by the National Science Foundation by my side. Back in India, I was not allowed to touch an autoclave until I started my master's degree, and I definitely was not allowed to touch a mass spectrometer at a core facility during my Ph.D.! I was surprised that an undergraduate student was getting the same opportunity on a project as me, who already had a Ph.D.

I realized two things. The first thing was that in the American academic system everyone has a right to learn. The second thing was that a Ph.D. isn't a prerequisite to do serious research. I looked at undergraduates and, for that matter, lab managers and technicians with fresh eyes. They were immensely talented, highly successful and contributing in significant ways to the progress of science.

I wish I had done my Ph.D. at a top-notch school in the U.S. or the European Union. I probably would have been way ahead of where I am now. But the one thing I don't regret about my Ph.D. is the mental and emotional strength I received by doing it. I survived my Ph.D. "catastrophe" because my PI was immensely supportive. I was strong to endure that five-year period of pain and train myself to secure an academic career in genomics and metabolomics. A faculty member at the university where I did my master's degree once suggested that I go for another "good" doctorate degree in Germany or the U.S. But I politely declined. A Ph.D. is not worth doing twice!

Biswapriya Misra (bbmisraccb@gmail.com) is a postdoctoral scientist at the Texas Biomedical Research Institute.

WHERE **DISCOVERERS** MEET

Scientific research and professional connections converge at the 2017 ASBMB Annual Meeting — and you should be a part of it. As the year's most important event for the biochemistry and molecular biology community, the ASBMB's annual meeting is the ideal forum at which to share your research, exchange ideas and explore potential collaborations with leading investigators. Join the conversation on this year's hot topics, including antibiotic resistance, organelle trafficking and signaling, genetic analysis and more.

EARLY BIRD REGISTRATION DEADLINE: FEB. 23.

Register early and save up to 48%!

NEW

Meet the speakers!
Join world-renowned biochemists and molecular biologists for informal networking and scientific discussion during midday poster sessions.

ASBMB '17
ANNUAL MEETING
CHICAGO | APRIL 22 – 26

SUBMIT YOUR ABSTRACT TODAY! | ASBMB.org/meeting2017

LATE-BREAKING ABSTRACT SUBMISSION DEADLINE: FEB. 8.

Take this opportunity to advance your work and discuss the molecular mechanisms of life. **Submit your poster session abstract today.**