Vol. 14 / No. 10 / November 2015

ASBMB TODAY

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

jbc the journal of biological chemistry

Search for Editor-in-Chief

The American Society for Biochemistry and Molecular Biology welcomes nominations and applications for the position of **editor-in-chief of the Journal of Biological Chemistry**. The JBC publishes original research that makes novel and important contributions to the study of the molecular and cellular bases of biological processes. The next editor-in-chief should be a public-facing thought leader, a committed advocate for authors and readers, a leader who listens and delegates, and an active researcher of significant accomplishment.

Candidates should possess:

- broad, general knowledge of biological chemistry;
- strategic planning experience;
- a commitment to publishing the very best science;
- an appreciation for data-driven decision making;
- the ability and desire to recruit outstanding scientists to serve as contributors, associate editors and editorial board members;
- a willingness to provide sustained and consistent editorial direction;
- proven interpersonal, communication, leadership and coalition–building skills;
- financial and business prowess; and
- scientific editorial experience.

The editor-in-chief will:

- provide visionary strategic direction,
- act as the steward of the journal's scientific content;
- report results and next steps to ASBMB executives and elected leadership;
- establish and refine journal policies and editorial guidelines;
- lead inclusive, productive meetings for board members and associate editors;
- respond to media requests;
- collaborate with staff members and vendors;
- represent the journal at meetings and other venues; and
- write quarterly (or more frequent) editorials.

The editor-in-chief will serve a five-year term, with the possibility of reappointment. The ASBMB will provide administrative support and a stipend.

A search committee appointed by the president of the ASBMB will review nominations and applications. An application package should include a cover letter, a one-page vision for the journal and a CV (of no more than four pages) highlighting relevant experience and achievements.

Send nominations and applications by Jan. 1, 2016, to the ASBMB Editor-in-Chief Search Committee

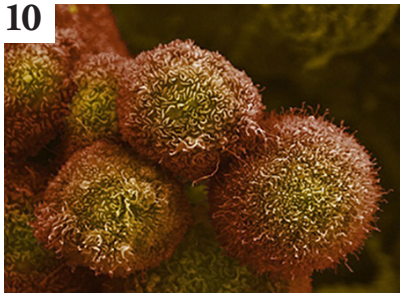
c/o ASBMB Senior Director of Publications and Content Development Nancy Rodnan (nrodnan@asbmb.org).

ASBMB
American Society for Biochemistry and Molecular Biology

CONTENTS

NEWS

10



FEATURES

16

Rajendrani Mukhopadhyay writes about the visa and immigration process facing foreign-born scientists.

26

PERSPECTIVES

28

31

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

ASSOCIATION MEDIA & PUBLISHING

Getting it right

By Steven McKnight

Somewhere around 30 years ago, a young scientist sent a grant application to the National Insitutes of Health. The scientist worked at an obscure research center in Smithville, Texas — an institution as far as imaginable from being elite. The grant proposal dealt with a series of antibodies made by the applicant to T cells of the immune system. The pattern of reactivity of the antibodies was weird, giving evidence that different T cells had surprisingly variable patterns of reactivity to the panel of antibodies. Irrespective of the weirdness of the science, the young age of the applicant, and the obscure nature of the institution to which the applicant was affiliated, a member of the review group recognized that the science might hold great promise.

The applicant was James Allison. His antibodies were recognizing the T-cell receptor — which, of course, varies from T cell to T cell in order to establish specificity for that arm of the immune-response pathway. The reviewer was Marian Koshland. The grant was funded. Koshland was so impressed with the application that she and her colleagues recruited Allison from Texas to the University of California, Berkeley. There, Allison studied the pathways controlling T-cell activation, helping him to co-discover that a T-cell protein called CTLA4 normally dampens the immune response pathway. While at

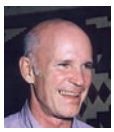
UC Berkeley, Allison also began his quest to discover therapeutic antibodies that might relieve the inhibitory activity of CTLA4 and thereby stimulate the immune-response pathway.

Fast-forward, and we see that Allison's science has led to one of the biggest breakthroughs in cancer treatment ever: the development of therapeutic antibodies that assist the immune systems of patients in clearing away tumor cells. Allison was the 2015 winner of the Lasker–DeBakey Clinical Medical Research Award. What a wonderful story!

What nuggets of information can we learn from this story? First and foremost — to me — is the fact that Allison's work dealt exclusively with basic science. He wanted no more than to understand the weird observation that different antibodies could distinguish variation on the surfaces of different T cells. He did not set out to find treatments for cancer; he was simply studying fundamental biology. Second, Allison's initial discovery of merit came while he was working at an obscure research institution. One does not have to be in the imperial halls of science to make discoveries of consequence. Third, the grant-review system was successful in sorting the wheat from the chaff in its evaluation of Allison's first grant application. Who knows, if not for Koshland's eagle eye for scientific merit, melanoma patients might not be benefiting from Allison's antibody to CTLA4.

Many members of the American Society for Biochemistry and Molecular Biology are basic scientists. We study in our small nooks and crannies at the outskirts of the huge biomedical industrial research complex. The complex is often loud in its promises to deliver breakthrough therapies to the most vexing of human diseases. Some of the most profound of advances can often be traced to cottage industry scientists working — when they hit it big — in obscurity.

How, I ask, can we communicate the need to preserve a culture that fosters individuality? How do we say to the people of power that the very best way forward has no plan or blueprint at all — other than the support of creative scientists willing to risk their careers on problems of unknown value? Without knowing what will make the biggest difference, how do we choose which projects to support? My wish is that more reviewers of grant applications would, as Koshland did, put more value in unique ideas and approaches than trendiness and predictability.



Steven McKnight (steven.mcknight@utsouthwestern.edu) is president of the American Society for Biochemistry and Molecular Biology and chairman of the biochemistry department at the University of Texas-Southwestern Medical Center at Dallas.

Next-generation researchers find allies on the Hill

By Sarah K. Martin

When National Institutes of Health Director Francis Collins testified before Congress in March, he highlighted challenges facing the next generation of researchers. "I try to contemplate the future of where biomedical research can go in the United States," Collins said. "(New investigators) are finding themselves in a situation that is the least supportive of that image in 50 years. They look ahead of them and see the more senior scientists struggling to keep their labs going and suffering rejection after rejection of grants that previously would have been supportive. And they wonder, 'Do we really want to sign up for that?' And many of them, regrettably, are making the decision to walk away."

In 1980, the average age of investigators receiving first R01-equivalent grants from the NIH was 35. By 2001, it was 42. Since then, the average age has continued to rise for M.D. and M.D./Ph.D. investigators and has stabilized for those with Ph.D.s. Facing a stagnant federal research budget and a reduction in the NIH's purchasing power, new investigators face great difficulties renewing grant funding. An average of only one in six investigators receive a second NIH grant.

U.S. Sens. Tammy Baldwin, D-Wisc., and Susan Collins, R-Maine, want this to change. They are introducing legislation to protect the future of research, science and innovation as sponsors of The Next Generation Researchers Act. Their act proposes creating an initiative within the NIH Office of the Director that will coordinate those NIH policies that promote opportunities for new researchers and earlier research independence.

The Next Generation of Researchers Initiative is designed to manage the Pathway to Independence Award, the NIH Director's New Innovator Award and the early-stage investigators grant-review procedures. It also seeks new policies to increase mentorship for early stage investigators, expand workforce diversity, improve workforce data collection and address the challenges of renewal funding.

Furthermore, the legislation directs the National Academy of Sciences to produce a comprehensive report on fostering the next generation of researchers. The report would evaluate barriers to entry into biomedical research, current NIH policies and the effect of the Budget Control Act on the biomedical workforce.

"In order for America to outinnovate the rest of the world and create an economy built to last, we must protect and strengthen our investments in research, science and innovation," said Baldwin in a statement. "We can't accomplish this without supporting and investing in the next generation of researchers."

New versus early-stage investigators

The National Institutes of Health define an investigator as new if he or she is an NIH research grant applicant who has not previously competed successfully for a substantial, NIH-independent research award other than grants for early-stage investigators; small research grants; or awards for training, infrastructure or career enhancement.

The NIH define an investigator as early stage if he or she is a new investigator who has completed his or her terminal research degree or medical residency within the past 10 years and has not yet won a substantial, competing NIH research grant.

Sarah K. Martin (smartin@asbmb.org) is the science policy fellow at the ASBMB.

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.

Four ASBMB members win Nobel prizes

By Angela Hopp

The Royal Swedish Academy of Sciences announced in October that four members of the American Society for Biochemistry and Molecular Biology won 2015 Nobel Prizes.


ŌMURA

ASBMB member Satoshi Ōmura of Kitasato University is one of three winners of the Nobel Prize for medicine or physiology for work on therapies for parasitic infections. Ōmura won half of the prize with William Campbell of Drew University for the discovery of avermectins, which "have radically lowered the incidence of river blindness and lymphatic filariasis," the academy said in a statement.

Ōmura was born in Japan and earned a master's degree from Tokyo Science University, a Ph.D. from the University of Tokyo and another Ph.D. from Tokyo University of Science. Today he is an emeritus professor at Kitasato University.

The other half of the prize went to Youyou Tu, the first China-based scientist to win the award, for her discovery of the antimalarial drug artemisinin.


LINDAHL

ASBMB members Tomas Lindahl at the Francis Crick Institute in London, Paul Modrich at Duke University School of Medicine, and Aziz Sancar at the University of North Carolina, Chapel Hill, won the Nobel in chemistry "for having mapped, at a molecular level, how cells repair damaged DNA and safeguard the genetic information," the academy said.


MODRICH

Lindahl was born in Sweden, earned his Ph.D. from the Karolinska Institute and worked at the University of Gothenburg. Today he is an emeritus group leader and director of Cancer Research UK at Clare Hall Laboratory. The prize announcement cited his work on base excision repair.

Modrich was born in the U.S. and earned his Ph.D. from Stanford University. He is a Howard Hughes Medical Institute investigator and a professor at Duke's medical school. The prize announcement cited his work on DNA mismatch repair.


SANCAR

Sancar was born in Turkey and earned his Ph.D. from the University of Texas at Dallas. He is a professor at UNC's medical school, a Howard Hughes Medical Institute investigator and an editorial board member for the ASBMB's Journal of Biological Chemistry. The prize announcement cited his work on the nucleotide excision repair pathway.

"How wonderful it is each fall to see the news from Stockholm on Nobel prize winners," ASBMB President Steven McKnight said. "This was a bonanza year for those of us who revere biochemists."

The JBC has featured the work of Modrich and Sancar in two articles known as "Classics": "Understanding DNA mismatch Repair: the work of Paul L. Modrich" and "DNA repair mechanisms: the work of Aziz Sancar." Lindahl also has published several papers in the JBC.

In addition, as Forbes writer David Kroll quipped, "to the contrary of the perennial basketball rivalry between Duke and UNC, the laboratories of Drs. Modrich and Sancar published a collaborative paper just last year, in the (JBC)." That paper was "Coupling of human DNA excision repair and the DNA damage checkpoint in a defined in vitro system."

F. Peter Guengerich, interim editor-in-chief of the JBC, commented: "The repair of DNA is an extremely important biochemical phenomenon. Humans have more than 100 genes devoted to this system. Many genetic diseases are due to deficiencies in this system … We are very happy to see their work recognized."

Angela Hopp (ahopp@asbmb.org) is executive editor of ASBMB Today and communications director for the ASBMB.
Rajendrani Mukhopadhyay (rmukhopadhyay@asbmb.org) contributed to this report.

Luger wins funding for genome institute


LUGER

Karolin Luger and an interdisciplinary team of investigators have been awarded a grant from Colorado State University to support the Institute for Genome Architecture and Function. Luger is on the board of directors of the institute, which operates as a multi-university hub for studying genome architecture and function in Colorado, combining interdisciplinary research approaches to develop novel technologies and foster innovation. The $200,000 award is sponsored by the Office of the Vice President for Research at CSU as part of its Catalyst for Innovative Partnerships program. The IGAF also provides support for investigators and training for students in a collaborative research environment. Luger recently moved her lab to the University of Colorado, Boulder, where she holds the Jenny Smoley Carruthers Endowed Chair for Chemistry and Biochemistry and studies chromatin architecture and dynamics though molecular and structural biology techniques. An investigator at the Howard Hughes Medical Institute, Luger has received the Searle Scholar Award, the Monfort Professor Award and the State Science Prize of Vorarlberg, Austria.


WALTER

Walter gets Vilcek Prize

Peter Walter is the 2015 recipient of the Vilcek Prize in Biomedical Science. The yearly $100,000 prize honors immigrant contributions to major American achievements. Recognized by the Vilcek Foundation for his seminal discoveries in cellular protein quality control, Walter is known for his contributions to describing the signal recognition particle, which targets newly synthesized proteins to the endoplasmic reticulum for processing and maturation. Walter's work also led to the discovery of the unfolded protein response, which is a major quality-control system used to regulate misfolded proteins in cells.

Professor in the biochemistry and biophysics department at the University of California, San Francisco, Walter is an investigator with the Howard Hughes Medical Institute. A National Academy of Sciences member, he has won the Shaw Prize and the Albert Lasker Basic Medical Research Award. He will give a plenary lecture at the 2016 ASBMB annual meeting in March in San Diego.

AAI award for Kanneganti


KANNEGANTI

Thirumala-Devi Kanneganti received the 2015 AAI-BD Biosciences Investigator Award for her outstanding early-career research contributions to the field of immunology. Kanneganti is a researcher in the department of immunology at the St. Jude Children's Research Hospital in Memphis, Tenn. Kanneganti was nominated for the prize by Nobel laureate Peter Doherty, who praised her as an extraordinary investigator with a broad view of her field. Kanneganti has been a member of the St. Jude faculty since 2007. Her laboratory focuses on how the innate immune system recognizes and responds to pathogens and how genetic mutations affect the development of inflammatory and autoimmune diseases.

Doudna wins 2015 Gruber Genetics Prize


DOUDNA

Jennifer Doudna, along with her collaborator Emmanuelle Charpentier, won the Gruber Genetics Prize. The international award carries an unrestricted prize of $500,000 for "groundbreaking work" that enables "fundamental shifts in knowledge and culture." Doudna and Charpentier were recognized for characterizing the CRISPR-Cas9 system. The CRISPR-Cas9 system is a bacterial defense mechanism that can cleave and edit foreign DNA. Their discovery marks a shift in the progress of scientific research, as the system can be utilized for targeted genome editing in a variety of model organisms. Doudna is a professor of biochemistry and molecular biology at the University of California, Berkeley. She is also an investigator at the Howard Hughes Medical Institute. Doudna was elected to the National Academy of Sciences in 2002 and the Institute of Medicine in 2010. Among her many accolades are the Eli Lilly Award in Biological Chemistry, the Alan T. Waterman Awar, the Lurie Prize in Biomedical Sciences, and the 2013 Mildred Cohn Award in Biological Chemistry from the ASBMB.

Written by Christine Lee

IN MEMORIAM: Richard Neil Armstrong (1948–2015)


CREDIT: VANDERBILT UNIVERSITY

Richard Neil Armstrong, professor of biochemistry and chemistry at Vanderbilt University, died in June. He was 66.

Armstrong was born in Boonville, Mo., on Dec. 14, 1948. After undergraduate studies in chemistry at Western Illinois University, he obtained a Ph.D. in organic chemistry from Marquette University. He was a postdoc at the University of Chicago and a staff fellow at the then National Institute of Arthritis, Metabolism and Digestive Disease (since renamed), before joining the chemistry department at the University of Maryland. In 1995, Armstrong became a profes-

sor of biochemistry and chemistry at Vanderbilt University.

Highly respected for his research into detoxification enzymes, which aid in an organism's ability to resist harmful chemicals, in 2004, Armstrong became editor-in-chief of the journal Biochemistry. He was elected a fellow of both the American Association for the Advancement of Science and the American Chemical Society. The ACS presented Armstrong with the Repligen Award for Chemistry of Biological Processes and named him an Arthur C. Cope Scholar in 2014. Additionally, Vanderbilt honored him with the Stanley Cohen Award for Outstanding Contributions to Research in 2005.

A ham radio aficionado and lone proprietor of "Uncle Ricky's Fishing School," Armstrong is survived by his wife of 31 years, Mary Frances Clark, and two children.

George Paul Hess (1924–2015)

George Paul Hess, professor emeritus of biochemistry at Cornell University, passed away in September. He was 92.

Hess was born in Vienna, Austria, and moved to the U.S. as a teenager. He completed his undergraduate and doctoral studies in biochemistry at the University of California, Berkeley, and did postdoctoral training in chemistry at the Massachusetts Institute of Technology. In 1955, Hess joined Cornell University's molecular biology and genetics department, where he would work for more than 50 years.

Hess' research focused on the structure and function of membrane-bound proteins that regulate communication between cells in the nervous system. He led a research group that developed new methods of exploring these proteins including a laser-pulse photolysis method and light-activated neurotransmitters.

Highly respected for his research acumen, Hess was a John S. Guggenheim fellow, a Fulbright senior research scholar and a recipient of the Alexander von Humboldt Award. A member of the National Academy of Sciences and the American Academy of Arts and Sciences, Hess was also a highly regarded professor recognized twice by the Cornell Merrill Presidential Scholars as an outstanding educator.

Hess is survived by his wife of 35 years, Susan Coombs, and four sons.

Written by Erik Chaulk

Gina Sosinsky (1955–2015)

Gina Sosinsky, professor-in-residence in the neurosciences department at the University of California, San Diego, died in September of complications from a bone marrow transplant. She was 60. A leader in the field of high-resolution microscopy, Sosinsky made significant contributions to the understanding of gap junctions.

By deciphering their molecular structures through electron microscopy, atomic force microscopy and other techniques, Sosinky's research led to the elucidation of submolecular structures of gap junctions composed of connexin 26. (Connexin 26 is the smallest of the family of proteins that make up gap junctions.) Her work extended to nodes of Ranvier and their relation to gap junction structure.

For her manifold contributions to science in general and to microscopy in particular, she was awarded the Morton D. Maser award in 2012 from the Microscopy Society of America.

Sosinsky's longtime collaborator, friend and fellow UCSD professor Susan S. Taylor called her "A gifted scientist, a special friend and … a special mentor to each of us in so many ways … With her magical tools she taught us to see the world of biology in ways that we had not imagined." Sosinsky was born on April 15, 1955, in New York City. The daughter of a bookkeeper and a college chemistry lecturer, she developed an early interest in science and medicine. The family left New York for the Chicago suburbs, where Sosinsky finished high school. She received her undergraduate degree in biology from the University of Chicago and a Ph.D. in biophysics from the University of California, Berkeley, graduating in 1983. According to her husband, Berkeley is where she first began to work as an electron microscopist interested in visualizing macromolecular specimens.

Sosinsky's postdoc research at Brandeis University, on gap junctions and their imaging, took place in the laboratory of Don Caspar and David DeRosier and involved a collaboration with Dan Goodenough at Harvard University. Sosinsky met her husband, John Badger, when he too joined Caspar's lab as a postdoc. The couple married while still at Brandeis and moved together to San Diego. Sosinsky became an assistant professor at UCSD in 1995.

Sosinsky served as the assistant director of the National Center for Microscopy and Imaging Research at UCSD, was biological director of the Microscopy Society of America from 2010 to 2012 and was an advocate for women in science and engineering, spending seven years as co-chair of the UCSD Women in Science Committee. She also served on the editorial board for the Journal of Biological Chemistry.

Sosinsky was a movie buff who enjoyed old-time musicals and science fiction movies. She also loved to swim, hike, ski and snorkel. In the last decade of her life, she had overcome several recurrences of ovarian cancer and in her last weeks made efforts to ensure members of her lab would be OK. She left behind her husband and three teenage sons.

Written by Samarpita Sengupta

John A. Glomset (1928 – 2015)

By Henry N. Higgs

"Nature is trying to tell us something. In fact, she's screaming in our ears. If we would only listen."

I've long forgotten the topic of the seminar in which John Glomset offered these remarkable words. But I jotted them down and am sharing them here because they so succinctly describe his approach to science. John's career was large in scope: from the biophysics of lipid–lipid interactions to medical aspects of cholesterol transport. All along, his consideration of natural processes was at the fore of his work. I keep this in mind as I attempt to summarize his long and eventful life in the sciences.

John was born in Des Moines, Iowa, on Nov. 2, 1928. Following something of a family tradition, he attended the University of Chicago as an undergraduate. He went on to medical school at the University of Uppsala in Uppsala, Sweden, where he met his future wife, Britt. They were together happily for the rest of his life.

Having completed both a medical degree and a Ph.D. in medical chemistry at Uppsala, John obtained a faculty position at the University of Washington in 1960 and would stay there for the rest of his career. His early work focused on cholesterol metabolism and transport, with his major contribution being the discovery of lecithin-cholesterol acyl transferase, or LCAT, a central enzyme in the packaging of cholesterol into lipoproteins. This was a heady time in cholesterol research, and John's work contributed significantly to the field.

While following this research path, John always was listening to nature. That's how he did science. Instead of forcing information out of natural processes, he designed scenarios in which nature could provide information in its own time. This approach paid off at least twice for him. The first time was his discovery of platelet-derived growth factor with Russell Ross in the 1970s. The finding came out of their serum preparations for cell-culture experiments. Changing the centrifuge used in the preparation significantly altered the cell growth activity of the resulting serum. Many might have discounted this as an irritation. But John felt that nature was screaming in his ear. He and Ross determined that the difference was in the degree of platelet contamination, which led them to purify this important growth factor.

The second discovery was protein prenylation. At the time, John was tracking cholesterol metabolism by treating cells with a radioactive synthetic intermediate. While isolating cholesterol fractions from the cells, he continually found that a portion of the radioactivity ended up in a non-lipid fraction. He could have ignored this fraction, but again he listened to nature. He teamed up with Mike Gelb in a very fruitful collaboration, and together they identified a protein (lamin B) that was covalently modified by a farnesyl moiety.

In 1991, I joined John's lab as a graduate student and was captivated by his research passion at the time — phospholipid heterogeneity in mammalian cells. Why do cells have hundreds of different phospholipids, varying in headgroup and fatty acyl chains in a dizzying array of combinations? John's idea was that their specific chemical properties would cause subtly different packing properties, resulting in membrane domains. These domains would be small and highly transient entities that could reorganize dramatically at the slightest change (e.g., phospholipase activity). In this way, membrane signaling could induce much more than the simple modification of an individual lipid or protein, instead creating larger-scale changes in membrane organization.

John Glomset

The idea of lipid domains now is generally accepted, thanks to the work of many labs. As was typical with John, most of his work remained unpublished and would have been difficult to interpret as work on lipid domains even if published. John took two approaches: the examination of biosynthetic pathways and molecular modeling. In the first approach, John would force cells to synthesize certain phospholipid species that they did not ordinarily possess. The cells would rapidly remodel these lipids to very specific combinations of fatty acyl chains through transacylation and acyltransferase reactions, with distinct

fingerprints of fatty acyl combinations for each headgroup. John was fascinated by both the intricacy and the robustness of these responses. Nature was most definitely trying to tell us something. John's hypothesis was that these precise combinations of lipids were essential for appropriate membrane domains.

John's molecular modeling approach was a collaboration with Howard Brockman.. The two found that phospholipids containing one saturated and one polyunsaturated chain could pack more tightly than lipids containing one saturated and one monounsaturated chain. These findings ran counter to the prevailing simplistic idea that more unsaturation causes looser bilayer packing. The key here, again, was John listening to nature by modeling phospholipids that actually exist in mammalian membranes. These late works rarely got published, which is a shame, because the findings were profound and somewhat ahead of their time.

John referred to his life as charmed. He knew how lucky he was to be able to follow his scientific passions. While not universally known, he was a Howard Hughes Medical Institute investigator for many years, was elected to the National Academy of Sciences in 1990 and was well regarded by those who did know him. Nobelists Michael Brown and Joe Goldstein would say, "Read Glomset's papers. They will seem odd now, but they will be crucial in 10 years."

Outside of science, John and Britt raised two sons, Peter and Nils, who have successfully pursued their own paths. Carpentry was John's passion, and he built much of the family home near Seattle as well as their vacation home on the Olympic Peninsula.

One final word on John's somewhat unusual scientific philosophy. I have been told many times, "Do not fall in love with your models; they compromise objectivity." John's philosophy was almost diametrically opposed: Fall in love with your models, nurture them and turn them over lovingly in your hands. All the while, however, test them critically. The instant you get clear evidence that your model is wrong, change it. You must have the sense to balance the love of your model with what the data tell you. The benefit of this love affair is that even if it is ill-fated, it will take you on a wonderful journey, and you will learn something. John would engage others in these love affairs through long conversations. Unbeknownst to him, the lab defined the John Unit, or JU, as one hour spent "discussing" science, which took the form of listening to John. I logged many JUs in all sorts of places.

Through these conversations, one could understand John's ideas, which were deep if not always testable. They painted a picture, a beautiful one. I think John would allow me to modify his original lines: Nature is painting a picture for us. It is right before our eyes. If we would only open them and see it.

Henry N. Higgs (Henry.N.Higgs@dartmouth.edu) is professor of biochemistry at the Geisel School of Medicine at Dartmouth College.

Classifying pancreatic tumors

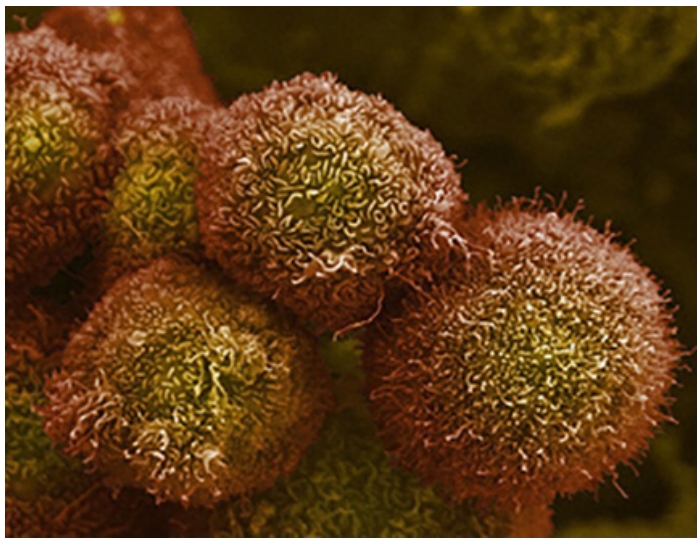
By Indumathi Sridharan

Pancreatic cancer is like a killer lurking in the shadows. The disease spreads aggressively during early stages without causing specific symptoms.

Every year in the U.S., about 50,000 people are diagnosed with pancreatic cancer. Most are diagnosed at advanced stages when even surgical removal of the cancer may prove to be ineffective.

About 80 percent of patients will die within a year after diagnosis, and only 6 percent will survive beyond five years.

November is pancreatic awareness month, highlighting the urgent need for better diagnosis and treatment methods for the disease.



ANNE WESTON, LONDON RESEARCH INSTITUTE, CANCER RESEARCH UK
(IMAGE AVAILABLE UNDER A CREATIVE COMMONS ATTRIBUTION, NONCOMMERCIAL, NO DERIVATIVES LICENSE)
Pancreatic cancer cells grown in culture.

How does pancreatic cancer develop?

The most common form of pancreatic cancer affects the exocrine tissue, which produces digestive enzymes. These exocrine tumors are called pancreatic adenocarcinoma, or PDA. PDA develops either from precancerous microscopic lesions or from larger, fluid-filled pancreatic cysts that can be seen on abdominal imaging studies. In most cases, the lesions are not detected, because they do not cause any symptoms. If detected early, the lesions can be cured.

What are the risk factors and symptoms?

Risk factors for pancreatic cancer include family history, smoking and certain occupational exposures to dyes and pesticides. Common symptoms include profound weight loss, jaundice (which can also cause itching), nausea, appetite loss, abdominal pain and back pain.

What are the latest research developments?

Identifying heterogeneity in PDA tumors is an important step toward developing more targeted treatments. Jen Jen Yeh and colleagues at the University of North Carolina are working on classifying PDA into subtypes based on the molecular characteristics of the stroma, the dense tissue surrounding the cancerous tissue (1). Using mathematical approaches and gene-expression analysis, the researchers identified two distinct stromal types among PDA tumor samples — normal and activated. The activated stromal type had higher expression of tumor-promoting genes and was linked to poor survival outcomes in patients with PDA.

Other researchers are looking at whole genomes to classify PDA. Sean Grimmond and colleagues at the University of Queensland, Australia, performed whole-genome sequencing in PDA tumor samples to assess variations in chromosomal structure that disrupt gene function. They classified the tumors into four subtypes: stable, locally rearranged, scattered and unstable. Notably, the unstable tumors consisted of more than 200 structural variations, which primarily disrupted genes related to DNA repair. As these unstable tumors lack proper DNA-repair mechanisms, they respond better to treatments like platinum-based chemotherapy, which kills cancer cells by causing excessive DNA damage (2).

Indumathi Sridharan (sridharan.indumathi@gmail.com) earned her bachelor's degree in bioinformatics in India. She holds a Ph.D. in molecular biochemistry from Illinois Institute of Technology, Chicago. She did her postdoctoral work in bionanotechnology at Northwestern University.

REFERENCES

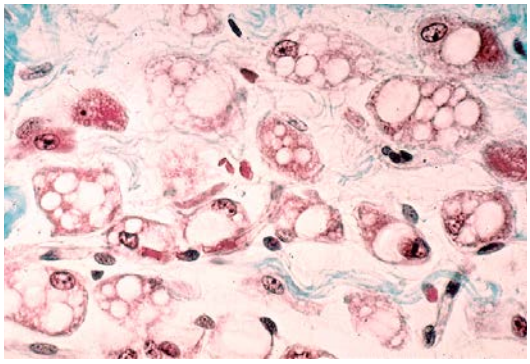
1.Moffitt, R.A. *et al., Nat Gen,* **47**, 1168 – 1178 (2015).

2. Waddell, *N. et al., Nature*, **518**, 495 – 501 (2015).

Regulating fatty tissue

By Adam Cornish

Many of us have gone on diets to decrease body fat. But what if you needed to put on fat? People born with Berardinelli-Seip Congenital Lipodystrophy would do anything to gain just a few pounds. Patients suffering from the disease have mutations in their BSCL2 gene that result in a lack of fatty tissue in the body and a lack of functioning adipoctyes for lipid storage. They develop insulin resistance, accumulate fat in both muscle and the liver, and are prone to type 2 diabetes. Recently, the role of Bscl2 regulation in mature adipocyte maintenance was investigated and the results described in the **Journal of Lipid Research**.



Bscl2 plays a role in browning adipose tissue.

Two primary forms of adipose tissue are present in the body: white and brown. White adipose tissue, or WAT, mainly functions as energy storage, releasing fatty acids into the bloodstream to feed the body, while brown adipose tissue, or BAT, acts to generate heat by consuming fat stores and is predominant in infants, who cannot shiver in response to cold temperatures. Interestingly, studies have found that WAT can brown, forming beige tissue with increased lipolysis and subsequently lowered lipid content.

Previously, global knockdown of Bscl2 in mice resulted in widespread ablation of WAT, while the remaining white fat demonstrated substantial browning effects. These findings compelled Hongyi Zhou and Weiqin Chen at Georgia Regents University to examine the role that Bscl2 plays in adipose development.

To investigate the effects of Bscl2 on mature adipocyte maintenance, mouse models were generated to knockout Bscl2 specifically in adipose tissues after the mice reached adulthood, thus avoiding complicating factors that would arise in global knockouts during infancy. The body weight, food intake and energy expenditures of the mice (versus a control group) were monitored for twelve weeks after inducing Bscl2 knockout, and the mice also were tested for resistance to insulin and glucose tolerance. Intriguingly, the knockout mice showed decreased body fat, reduced food intake and slightly increased energy expenditure, overall leading to leaner mice, even when placed on a high-fat diet. Insulin resistance was noted as observed in human subjects with BSCL2 mutations, but there was not a decrease in glucose tolerance, presenting incomplete symptoms for type 2 diabetes. Importantly, body WAT mass decreased sharply, and browning was noted in the remaining tissues.

The impact of knocking out Bscl2 on gene expression in BAT and WAT was measured using next-generation RNA sequencing. As expected, genes involved in browning, lipolysis and fatty acid oxidation all were upregulated, establishing a basis for reconnecting Bscl2 with beige cell formation and decreased lipid stores. The RNA sequencing also revealed that ADRB3, a G-protein-coupled adrenergic receptor known to stimulate lipolysis, was downregulated in the knockout mice despite the lean phenotype observed. Based on these findings, Bscl2 and ADRB3 have a complex relationship in maintaining whole-body homeostasis, but Bscl2 has a definitive role in lipolysis and browning of WAT in adult tissues.

This discovery immediately conjures ideas of treatments that could regulate Bscl2 to induce the lean phenotype in obese individuals, but much remains to be discovered regarding the role(s) of Bscl2. Knockout mice fed a high-fat diet showed an increase in liver mass of 130 percent. This likely was due to heightened fatty acid synthesis and could act as a precursor to fatty liver disease, a condition often observed in individuals with mutations in the gene. This emphasizes that selective knockout or knockdown of the gene is unlikely to serve as an effective weight-loss treatment.

Further research is needed to tease apart the detailed mechanism by which Bscl2 regulates WAT formation, browning and lipolysis and how these effects intersect with ADRB3 signaling pathways to regulate energy homeostasis. In particular, the structure of Bscl2 needs to be resolved, as there are no known homologs of the protein, limiting predictions of binding targets or effectors. The key to understanding WAT development and browning lies in elucidating Bscl2 signaling pathways and its interaction partners, which could provide essential information for the future treatment of obesity.

Adam Cornish (acornis3@jhu.edu) teaches advanced placement chemistry, blogs about science and pays too much attention to national politics.

Actions of iron-dependent dioxygenases

By Christine C. Lee

Essential cellular processes including protein modification, DNA damage repair and epigenetic regulation require the activity of α-ketoglutarate (2-oxoglutarate or 2OG) and other iron-dependent oxygenases. The eighth of the **Journal of Biological Chemistry**'s thematic series on metals in biology features key topics related to this class of oxygenases. The editor of the series, F. Peter Guengerich from Vanderbilt University, highlights recent advances in four key areas of Fe(II)- and 2OG-dependent oxygenase biology: the chemical mechanisms of catalysis; posttranslational protein modifications; epigenetic regulation by the activity of the ten-eleven translocation, or Tet, dioxygenases; and the role of the AlkB family of oxygenases in damaged DNA and RNA repair.

The Fe(II)- and 2OG-dependent enzymes aid in overcoming kinetic barriers involved in biochemical reactions. The first review by Salette Martinez and Robert P. Hausinger at Michigan State University details mechanisms that require Fe(II)- and 2OG-dependent oxygenases to catalyze hydroxylation, halogenation, ring formation and desaturation reactions. Each of these four catalytic reactions is discussed in detail, with examples from human biology and commentary on key enzymatic intermediates. This first minireview is central to understanding the fundamental mechanisms underlying the posttranslational modifications, epigenetic regulations, and DNA and RNA repair processes covered in the subsequent minireviews.

The roles of Fe(II)- and 2OG-dependent oxygenases in posttranslational modifications are presented in the second minireview from Suzana Markolovic, Sarah E. Wilkins, and Christopher J. Schofield at the University of Oxford. Structural studies and reaction mechanisms featured in this review pointedly illustrate the contributions of Fe(II)- and 2OG-dependent oxygenases on enzymatic activity and changes to macromolecular structure. In particular, posttranslational hydroxylation of macromolecules, such as pro-collagen and hypoxia-inducible factors, are regulated by Fe(II)- and 2OG-dependent oxygenases. In addition, N-demethylation of histones catalyzed by these oxygenases affects transcription and posttranscriptional events. This review covers the importance of Fe(II)- and 2OG-dependent oxygenases in regulating protein–protein interactions in addition to regulatory roles in gene expression via histone methylation and demethylation reactions.

The epigenetic roles of 2OG-dependent oxygenases are detailed further in the third minireview from Hideharu Hashimoto, Xing Zhang, Paula Vertino and Xiaodong Cheng at Emory University. Iterative oxidations of the DNA base cytosine are performed by DNA methyltransferases, which convert cytosine to 5-methylcytosisine, or 5meC; 5-hydroxymethylcytosine, or 5hmC; 5-formylcytosine, or 5fmC; and 5-carboxylcytosine, or 5caC. Cytosine modifications do not affect base pairing but may affect epigenetic functions by changing macromolecular interactions and controlling gene expression. A subset of 5meC further is oxidized into 5hmC, 5fmC and 5caC by the activity of Tet dioxygenases, a type of 2OG-dependent oxygenase. This review discusses the downstream implications of Tet enzyme activity on transcription factor binding and base excision repair by DNA glycosylases.

In the fourth minireview, Bogdan

Fedeles and colleagues at the Massachusetts Institute of Technology focus on nucleic acid damage repair, highlighting the AlkB family of oxygenases. Studies have shown that the bacterial AlkB oxygenases remove methyl groups and lesions from DNA as a protective mechanism for maintaining genome integrity. While precise functions remain unknown, humans have nine AlkB homologs, two of which repair damaged DNA while the remaining homologs demethylate RNA and proteins. This comprehensive review provides details on AlkB structure, mechanism, substrate specificity and methodologies for studying AlkB activity in vitro and in vivo.

Significant achievements in understanding the Fe(II)- and 2OG-dependent oxygenases featured in this minireview demonstrate the exciting potential in developing diagnostic tools to identify, investigate and treat human diseases.

Christine C. Lee (clee217@jhu.edu) is a doctoral candidate in the Department of Biochemistry and Molecular Biology at the Johns Hopkins Bloomberg School of Public Health.

Digging into grass sickness

Rare horse disease resembles human neurodegenerative disorders

By Rajendrani Mukhophadhyay

Each year in the U.K., about 2 percent of horses die from grass sickness. No one knows what causes the disease, but it does occur almost exclusively in grass-fed animals including ponies and donkeys. A similar disease is thought to afflict dogs, cats, rabbits, hares, llamas and possibly sheep.

Researchers recently reported their analysis of tissue samples taken from horses stricken with the disease in the journal **Molecular & Cellular Proteomics**. In their attempt to understand what happens at the molecular level of equine grass sickness, the researchers found misfolded and dysregulated proteins in the tissues that resembled those found in human neurodegenerative conditions, such as Alzheimer's disease, Parkinson's disease and Huntington's disease.

BRUCE MCGORUM

A horse suffering from grass sickness.

Animals with grass sickness usually suffer gut paralysis. The animals roll, sweat, drool and have trouble swallowing. Animals acutely afflicted with the disease usually have to be euthanized.

The disease is known to attack the neurons, but the causative agent is not known. To get a look at what goes on at the molecular level, Thomas Wishart at The Roslin Institute in Scotland teamed up with Bruce McGorum at the University of Edinburgh's veterinary school. The investigators applied proteomic techniques to samples taken from horses that came down with grass sickness.

Wishart says they do know which tissues are affected most consistently: "We considered that a proteomic analysis would provide a snapshot of the molecular processes in play within those samples at that point in time."

He points out that the work described in the MCP paper "is the first application of modern proteomic tools and in-silico analytical techniques to equine neuronal tissues and to an inherent neurodegenerative disease of large animals that is not a model of human disease."

The investigators found that the expression levels of 506 proteins were changed in the ganglia taken from horses felled by grass sickness. Moreover, some of the proteins were misfolded, aggregated or in the wrong places. The proteins included amyloid precursor protein, the microtubule-associated protein tau and several components of the ubiquitin proteasome system. These proteins have been implicated in human neurodegenerative disorders.

Finding this similarity between human and horse neurodegenerative diseases, says Wishart, suggests the aggregated or misregulated proteins are "more likely to be end-stage regulators or late consequences rather than initiators of the degenerative cascades."

As equine grass sickness can be hard to diagnose in some horses, a next step for the investigators is to see if they can come up with a noninvasive diagnostic test.

Rajendrani Mukhopadhyay (rmukhopadhyay@asbmb.org) is the chief science correspondent for the American Society for Biochemistry and Molecular Biology. Follow her on Twitter at twitter.com/rajmukhop.

Reproductive assist

Finding sheds light on infertility puzzle

By Tracey Bryant

We don't know if a sperm actually experiences joy when it finally finds the egg, but it does wiggle excitedly. Patricia A. Martin–DeLeon, a reproductive biologist at the University of Delaware, has witnessed this behavior many times in her studies of fertility in mice, the closest genetic model to humans (and with a much faster reproductive cycle).

In a recent issue of the **Journal of Biological Chemistry**, Martin–DeLeon and her team revealed for the first time what happens next in the fertilization process. They said the finding could one day help couples struggling with infertility.

Once an egg exits an ovary and enters the fallopian tube, the hairlike cilia that line this tiny tube sweep the egg toward the uterus. While in the tube, the egg either meets the sperm and gets fertilized, which must happen within a 12- to 24-hour window, or dissolves.

In 2013, Martin–DeLeon and her team reported the discovery of special vesicles in fallopian tubes. They named these cargo-filled sacs oviductosomes. Inside these vesicles, they found a calcium-clearance pump, plasma membrane $Ca2^{+}$-ATPase 4, among other things.

In their recent JBC paper, Martin–DeLeon and her team report that oviductosomes help the sperm get ready for its all-important drive into the end zone. The tiny, cargo-filled sacs attach to the sperm like decorations on a Christmas tree before the sperm fuses with the egg. Once these sacs are in place, they transfer proteins, including the calcium-clearance pump, to the sperm.

"This calcium pump is required by the sperm just prior to fertilization, as well as in the early embryo," Martin–DeLeon says. "The sperm pumps out calcium and takes in hydrogen ions, which seems to give it that last push into the egg and also is critical to starting the zygote's life."

Martin–DeLeon and her team labeled oviductosomes from a female mouse with a fluorescent dye and incubated them together with the sperm. Within an hour, the oviductosomes fused to the sperm's surface. After two to three hours, the oviductosomes continued to accumulate, primarily on the sperm's head and the midpiece of its tail. Integrins, membrane receptors on both the sperm and the oviductosomes, helped to facilitate their bonding, along with fusion stalks on the sperm's surface.

"Discovery of these oviductosomes provides us with a window into the cargo being delivered by the female to the sperm," Martin–DeLeon says. "We've shown that these oviductosomes are carrying critical molecules that include not only proteins, but also nucleic acids such as RNA and also lipids. That gives us hope they can be used as vehicles for improving fertility and the chances of producing healthy embryos and offspring."

Martin–DeLeon and her team now are analyzing the protein-rich cargo to find out exactly what gives the sperm what it needs for its last push to penetrate the egg — always head first, tail out — to fertilize it. "We may identify proteins required to improve the efficiency of (in vitro fertilization), and improve the outcome and health of the offspring," she said. "It's really another step in the direction of personalized medicine, since individuals carrying mutations of one of a variety of genes account for the largest group of infertile couples."

Tracey Bryant (tbryant@udel.edu) is director of research communications at the University of Delaware.

Pulling apart the cytoskeleton

By Alexandra Pantos

Maintaining the shape of the cell, creating proper internal structure, guiding organelles and pulling chromosomes apart during mitosis are some of the important functions of the cytoskeleton. The cytoskeleton is composed of three main structural components: actin filaments, microtubules and intermediate filaments. In a series of thematic minireviews, the **Journal of Biological Chemistry** highlights what we know so far about the cytoskeleton.

The editors of "The state of the cytoskeleton in 2015," Robert Fischer of the National Heart, Lung and Blood Institute and Velia Fowler at The Scripps Research institute,

describe how cytoskeletal polymers have been a topic of interest for more than 70 years. However, many questions about the polymers are just now beginning to be answered. The more specific topics discussed in these minireviews include actin mechanics and fragmentation, vimentin intermediate filament networks and the microtubule cytoskeleton.

Actin filaments determine the shape of the cell surface and are involved in cellular locomotion. In the minireview titled "Actin mechanics and fragmentation," Enrique De La Cruz of Yale University and Margaret Gardel at the University of Chicago discuss recent advances in understanding the mechanical properties and stability of actin filaments. This includes how forces can influence local biochemical interactions leading to formation of mechanically sensitive and dynamic states of actin filaments. The research could provide crucial information on how the actin cytoskeleton helps cells respond to mechanical forces.

Intermediate filaments are composed of various intermediate filament proteins, one of which is called vimentin. Vimentin helps to keep the organelles in their proper places within the cell. Organelles anchored by vimentin include the nucleus, endoplasmic reticulum and mitochondria. In their minireview titled "Properties of vimentin intermediate filament networks," Robert Goldman at Northwestern University and colleagues discuss the role of intermediate filaments in regulating cell architecture and function. More specifically, the authors note that mutations in the genes encoding intermediate filament proteins lead to a number of human diseases, including cataracts, myopathies, and a progressive and fatal neurodegenerative disorder called Alexander disease.

Microtubules are long, hollow and more rigid than actin filaments. In "Writing and reading the tubulin code," Antonina Roll–Mecak at the National Institutes of Health and colleagues discuss tubulin, which forms the heterodimers that make up microtubules. Specifically discussed is the tubulin code, which consists of post-translational marks that are then interpreted by two categories of cellular effectors. The first category of effectors is those that are bound to the microtubule and alter its properties noncovalently; this includes motors and microtubule-associated proteins. The second category consists of those that actually modify the tubulin subunits at a chemical level; these effectors are tubulin post-translational modification enzymes.

In the minireview titled "Building the microtubule cytoskeleton piece by piece," Ray Alfaro–Aco and Sabine Petry of Princeton University note the importance of the microtubule cytoskeleton within the cell. They explain that these important functions rely on the precise arrangements of microtubules, which is achieved by the teamwork of a class of proteins called microtubule-associated proteins. They highlight how these MAPs work together to create a whole that is greater than the sum of the microtubule-network parts.

Septins, though not one of the main three components of the cytoskeleton, play an important role in the cytoskeleton. In "Septin form and function at the cell cortex," Andrew Bridges and Amy Gladfelter of Dartmouth College review septins, which are GTP-binding proteins that form structures on the cell cortex. The cell cortex is a layer of cytoplasm on the inside of the plasma membrane that helps support the membrane and connects with actin and microtubule cytoskeletal systems. The focus of the review is on gaining an understanding of how septins and the plasma membrane interact.

Along with the discovery that bacterial cells are spatially organized despite their lack of membrane-enclosed organelles came the revelation that bacteria contained structural homologs of eukaryotic actin and tubulin. This discovery led investigators to wonder if homologous polymers present in bacteria may have roles in organization and structure that are similar to those of their eukaryotic counterparts. Research on these homologs is reviewed in "Bacterial filament systems: toward understanding their emergent behavior and cellular functions" by Ethan Garner at Harvard University and colleagues. This minireview summarizes the current understanding of how the homologs are assembled in addition to their dynamic behavior within the bacterial cells.

These minireviews provide insight into the variety of important roles of the cytoskeleton. The more knowledge researchers continue to gain about the form and function of the cytoskeleton, the bigger the impact on preventing or curing diseases that involve cytoskeletal dysfunction, such as Alzheimer's, Parkinson's and Amyotrophic lateral sclerosis (ALS).

Alexandra Pantos (apantos@asbmb.org) is an editorial assistant and former intern for ASBMB Today.

SCIENCE ON A VISA

The U.S. biomedical research enterprise heavily depends on scientists who were born overseas. But the legal pathway to work and live in this country is different for each skilled worker, and navigating the complex visa and immigration system can be daunting.

By Rajendrani Mukhopadhyay

Prologue

It was February 2014, and the sky was a chilled blue. My eyes watered from a vicious cold, but I had to go out. I pulled on a vibrant red jacket. I wanted to be photographed later in the day, and I wanted the jacket color to be symbolic.

In the car with my husband, I tapped on our GPS, entering the address I had received in the mail a few weeks before from U.S. Citizenship and Immigration Services. Neither of us recognized the address, which was somewhere near Baltimore. We soon found ourselves driving through nondescript, sparse suburbia, winding down a road that was surrounded by flat greens and woods.

The GPS directed us to the back of a single-level, gray building that squatted on an asphalt parking lot. A dark glass door with a black steel frame marked the entrance to the building. There was a giant flagpole on the sidewalk in front of the door. An enormous Stars and Stripes, designed to inspire awe, draped from the top of the pole.

Later that February day, I uploaded a photo of myself clutching a small version of the Stars and Stripes against my red jacket. It was official, I told my Facebook friends. I now was an American citizen, 16 years after I first rolled into the U.S. from Canada as a biochemistry graduate student on a Greyhound bus.

The complexity of the visa and immigration process makes those of us who are in it, or who have been through it, skittish. I consider myself to be very lucky to have gotten through the system with a few hiccups. Even with my citizenship and a U.S. passport in hand, I can't help but feel uneasy revealing how I became a citizen. I don't want others scrutinizing the steps I took through the visa and immigration maze. I still have flashbacks to sleepless nights spent worrying that an innocent error on my paperwork would get me kicked out of the country.

Back when I was wading through the paperwork, I, like a number of my fellow foreigners, was especially hesitant to voice my concerns about the confusing system. After all, I had decided to stay in the country, so I couldn't very well complain about what I had to do to stay.

Because most people are hesitant to talk about the issues they face while holding temporary visas or trying to get green cards, I have decided to share parts of my story here. The decisions I made while going through this process were based on my personal circumstances, and every person coming into the U.S. has his or her own unique situation. There is no one-size-fits-all approach to these matters. For this reason, this article should in no way be considered legal advice.

The system and the numbers

From the 1920s to the mid-1960s, admission to the U.S. largely depended upon an immigrant's country of birth. The quota system during that time favored immigrants from Europe (70 percent of the slots were reserved for the British, Irish and Germans). In 1965, the Hart–Celler Act did away with the national origins quotas and set forth new immigration priorities: facilitating family reunification and bringing in skilled workers from any country.

Since the act passed, according to a recent Pew Research Center report, about 59 million immigrants have arrived in the U.S. "For the past half-century, these modern-era immigrants and their descendants have accounted for just over half the nation's population growth and have reshaped its racial and ethnic composition," the report said.

Another report, this one released by the National Academies in September and titled "The Integration of

CONTINUED ON PAGE 18

CONTINUED FROM PAGE 17

Immigrants into American Society," noted: "One difference from earlier waves of immigration is the large percentage of highly skilled immigrants now coming to the United States. Over a quarter of the foreign-born now have a college education or more, and they contribute a great deal to the U.S. scientific and technical workforce."

According to the National Science Foundation, 18 percent of the scientists and engineers residing in the United States in 2013 were immigrants. In addition, the NSF found that the life sciences had the highest employment growth among immigrant scientists and engineers from 2003 and 2013, followed by computer and mathematical sciences and social sciences.

To work in the U.S., immigrants must go through the U.S. visa and immigration system. But this is a daunting task. The system "is second in complexity only to the tax code," said Michael Teitelbaum in his book "Falling Behind: Boom, Bust & the Global Race for Scientific Talent."

Immigration lawyer Frances Taylor of Baltimore's Taylor & Ryan law firm wholeheartedly agrees. "It's absolutely Byzantine. I've been working in this field for close to 30 years, and there are still days where I'm learning something new," says Taylor. "It would be shocking if anybody who is trying to navigate the system could do it easily, without a lot of stress, bother and pain."

The J-1 visa

Biomedical research relies heavily on non-U.S. citizen postdoctoral fellows. Nearly 60 percent of postdocs in the life sciences in 2008 were temporary residents of the U.S., according to Paula Stephan's book, "How Economics Shape Science."

Fellows who earn their Ph.D.s abroad come into the U.S. on the J-1 visa. The J-1 visa program is designed to give citizens of other countries an experience of American life that they can take back to their home countries. Overseen by the U.S. Department of State, the J-1 visa, with its various categories, allows foreigners to come to the U.S. to "teach, study, conduct research, demonstrate special skills or receive on-the-job training for periods ranging from a few weeks to several years," according to the department's website.

Last year, the State Department issued nearly 32,000 J-1 visas, which can be valid for as long as five years, for professors and research scholars. "It's a status that's easy to obtain," says Taylor. "But it brings with it burdens that many people find difficult."

The greatest burden is the J-1 visa's home-residency requirement. Once a J-1 status expires, the visa holder has to return to his or her country of origin for at least two years.

This stipulation applies to medical trainees, people funded by the U.S. or their home countries' governments, and people trained in certain subject areas, such as biology, mathematics and physical sciences. For the latter category, the State Department draws up a list of fields requiring specialized knowledge and skills that are considered to be crucial for the development of an exchange visitor's home country. For example, Indian citizens trained in any area of science, engineering technology or math must return to India for at least two years when their J-1 statuses end.

"Very often, we find that people come in and are doing their work or getting their education and doing some fruitful work with the right kind of support. But then their J (status) comes to an end, and they've got to leave," says Taylor.

Amita Bansal is a postdoctoral fellow at the University of Pennsylvania on a J-1 visa. Bansal, who earned her Ph.D. in New Zealand, says the home-residency requirement "is chal-


Bansal

lenging because that limits a lot of postdocs from thinking of longer-term career plans in the United States."

A J-1 holder can apply for a waiver from the home-residency requirement. The waiver request requires dealing with the home-country government as well as the U.S. government. If an applicant is successful, he or she will get a different visa to stay in the country.

Bansal points out another J-1 drawback: J-1 visas are not always given out for the full five years for which they can be issued. The duration of a J-1 may depend on the amount of available funding from, for instance, a research grant.

A postdoctoral fellow can apply for an extension on an initial J-1 visa. If successful, the fellow gets a revised DS-2019 document, which is a certificate of eligibility for J-1 status, with new dates. The document allows the J-1 holder to stay legally in the U.S.

But even the revised DS-2019 can cause headaches, particularly when it comes to international travel for scientific conferences and going back home to visit family, says Bansal. If a postdoctoral fellow needs to go abroad, he or she must make arrangements during the journey to get a new J-1 visa stamp to re-enter the U.S.

Bansal points out that much of the complexity of the visa system isn't apparent when a person is still outside of the U.S. It's only when the person accepts a postdoctoral fellowship and enters the visa process that the complexities of the system become obvious.

Bansal says people like her persevere because they are in the U.S. for the science. "Do you turn down a position because of the mayhem the visa process may create in your life later on? Or do you take that position because you are passionate about doing your research?" she asks. "For most of us, we're passionate about research. It's the complicated visa system which makes the postdoctoral life difficult."


Kooijman

Love presents problems too, as Edgar Kooijman found out when he was a Ph.D. student at Kent State University in the late 1990s. A citizen of the Netherlands, Kooijman then held an F-1 student visa. But shortly after he began his studies, "I met this wonderful Filipino lady who was working here as a researcher," says Kooijman. His future wife was working on her Ph.D. at an institution in the Philippines and was in the U.S. on a J-1 visa as a visiting research scholar. The visa had a home-residency requirement, which meant Kooijman's future wife would have to return to the Philippines. "We got married and then it was 'Oh, shoot! Now what are we going to do?'" Kooijman recalls.

They both quit their graduate programs and left the U.S. for the Netherlands. Back in his home country, Kooijman went on to get his Ph.D. at Utrecht University, and he and his wife started a family. (There's more to this story below.)

The H-1B work visa

By the time I had completed my Ph.D. in 2004, I long had decided to devote myself to science writing. I didn't apply for a postdoctoral position. Instead, I aimed to land a job straight out of graduate school. To do that, I had to move away from my F-1 student visa and get a temporary work visa, known as the H-1B.

First introduced in the 1990 Immi-

CONTINUED ON PAGE 20

CONTINUED FROM PAGE 19

gration Act, the H-1B status usually is granted for a three-year period with the possibility of renewal. An American employer must sponsor the H-1B worker. The employer has to attest to the Department of Labor that the foreign worker will be treated like other employees, given appropriate working conditions, and get paid the prevailing wage or the same wage the employer pays to other employees, whichever is higher. The employer also must pay the costs of the process (including the filing fees) and submit paperwork on the behalf of the foreign worker.

I was fortunate to have a generous employer willing to sponsor my visa, so after wading through the paperwork with my employer and my immigration lawyer, Vivian Wang, I managed to get one.

But the setup could lead to abuse. "Your ability to stay in the country is dependent on whether you're employed by that specific employer. That puts you in a vulnerable position. You don't want to talk back to your boss, because if you get terminated, you have the leave the country," says Ronil Hira, an associate professor of public policy at Howard University. "That puts a lot of bargaining power in the employer's hands."


Muia

Joshua Muia, a Kenyan citizen on an H-1B visa at Washington University School of Medicine in St. Louis, is an instructor of medicine. When he was job hunting, he worried about being discriminated against because of his need for H-1B sponsorship. "You don't know how employers will think," he says. "If you tell them you need an H-1B, you don't know if they will say, 'That's a lot of work,' even if you have qualifications that are unique."

At academic and nonprofit institutions, there is no limit on the number of H-1Bs available. But Jennifer Kerilla at Johns Hopkins University and Ilana Smith at the California Institute of Technology, both international office directors, emphasize that their institutions are very careful with applying for H-1B visas so as not to abuse their privilege.

For the private sector, where I worked, there is a congressionally mandated limit on the number of H-1B visas issued every year. The cap is 65,000. Up to 20,000 additional applications from people who have obtained master's degrees or Ph.D.s from U.S. institutions are exempt from this limit. (I qualified for that category.)

For the 85,000 available H-1B visas for fiscal year 2016, there were more than 230,000 applications in April 2015, the month when the application process opened. Wang says the overwhelming number of applications forced USCIS "to run a computer-generated lottery to decide which applications get in and which don't get in." As with any lottery, there are many disappointed people.

"The need is grossly disproportionate to the supply," says immigration lawyer Taylor. Pointing out that the process isn't cheap and painless for employers, Taylor adds, "No one does this for fun. If they are doing it, they are doing it because the person they are sponsoring is really good or they can't find a U.S. worker who is going to do this job. Congress has created an artificially limited system and made it very difficult for people in industry." (In some circumstances, there are other options. See the sidebar "O-1 and L-1 options.")

It's important to note that not everyone agrees with Taylor on the supply and demand for H-1B visas in the private sector. There is much debate about what types of workers should be allowed into the U.S. and

O-1 and L-1 options

There are two other nonimmigrant visa options open to members of the highly skilled foreign workforce. Both the L-1 visa and the O-1 visa can be "a backup option if the person doesn't get in on the H-1B lottery," says immigration lawyer Vivian Wang.

"To qualify for an O-1 visa, the beneficiary must demonstrate extraordinary ability by sustained national or international acclaim and must be coming temporarily to the United States to continue work in the area of extraordinary ability," says the U.S. Citizenship and Immigration Services website. "Extraordinary ability in the fields of science, education, business or athletics means a level of expertise indicating that the person is one of the small percentage who has risen to the very top of the field of endeavor."

The O-1 visa certainly applies to scientists who've earned awards for their work, have a notable publication record and have been invited to give talks at conferences, Wang explains. Jennifer Kerilla and Ilana Smith, both directors of international offices at top-tier institutions, emphasize that the bar for the O-1 visa is high, so the foreign student or scholar has to strive for excellence.

"All of the things that (principal investigators) encourage postdocs to do, the postdocs should be doing them. Ultimately, it helps create a dimension to one's accomplishments that fit into the criteria that USCIS will look at in a standardized way," says Smith. Whenever she hears someone turn down the opportunity to present at a conference or to review a paper, she is disappointed: "One has to take advantage of all of the opportunities offered."

The L-1A visa allows an American employer to bring an executive or manager from one of its affiliated international offices to one of its U.S. offices. The visa also lets a foreign company that does not yet have an affiliated U.S. office send an executive or manager to the United States to establish a U.S. presence.

"In recent years, because of the H-1B quota problem, some large companies consider sending the person to the overseas office to work one year so the person can become qualified to transfer back into the U.S. office on an L visa that way," says Wang.

about what they contribute to the country's economy.

Going for the green card

With my H-1B paperwork complete in 2005, I immediately began to look into getting a green card. After living in the country for seven years, I badly wanted to become a part of it. A tornado of paperwork, fees and a medical exam (to make sure I wasn't ridden with tuberculosis and other transmittable diseases) ate up about a year.

For those who want to transition from temporary skilled workers to permanent residents (and it's important to note that not everyone does), there are various ways of getting a green card. Self-petition or employer sponsorship are the two options for highly skilled workers. Self-petition works for people with impressive résumés; for example, the EB-1A category, known as the "alien of extraordinary ability," can accept people who have excelled in their careers.

The EB-3 employer-sponsored route, which I took, requires the employer to prove that the company is not passing over an equally qualified American worker by hiring the foreign worker. The proof takes the form of a certification issued by the Department of Labor. The company posts the job and sees if any qualified American workers apply. "If a single qualified U.S. worker is found, the application fails," says Wang.

However, if the employer doesn't find an American worker equally qualified as the foreign worker, the Labor Department issues a certification for the foreign worker. With the certificate in hand, the employer submits an immigration petition for the foreign-born worker to USCIS. "It's very time-consuming and very expensive," says Wang of the process. "For example, the current processing time from the time of filing is eight to 12 months without audit." The employer

CONTINUED ON PAGE 22

CONTINUED FROM PAGE 21

and the candidate have to pay for, among other things, the job postings, the Labor Department certification step and the medical exam.

The U.S. can issue at least 140,000 employment-based green cards each year. The distribution of those permits is based on the applicants' countries of origin. For applicants from countries like China, India and the Philippines, waiting for the backlog can take years. Indian immigrants can expect to wait 11 or more years for some employment-based green cards.

Furthermore, the immigrant has to hold the same job as covered by the Labor Department's certification. "While they wait several years for their green card application to go through, if something happens at their company — for example, the company has layoffs — the labor certification application will fail," says Wang. "Nothing can go wrong while your application is pending!"

Muia, the Kenyan instructor of medicine on an H-1B visa, points out that a foreign scientist's aspirations to pursue a career as an independent researcher can be uncertain until that green card shows up. Many grants and fellowships require applicants to be permanent residents or U.S. citizens. "It may take you a while to petition for a green card and get started," he says, adding it may take up to 10 years for a Kenyan like him to get a green card.

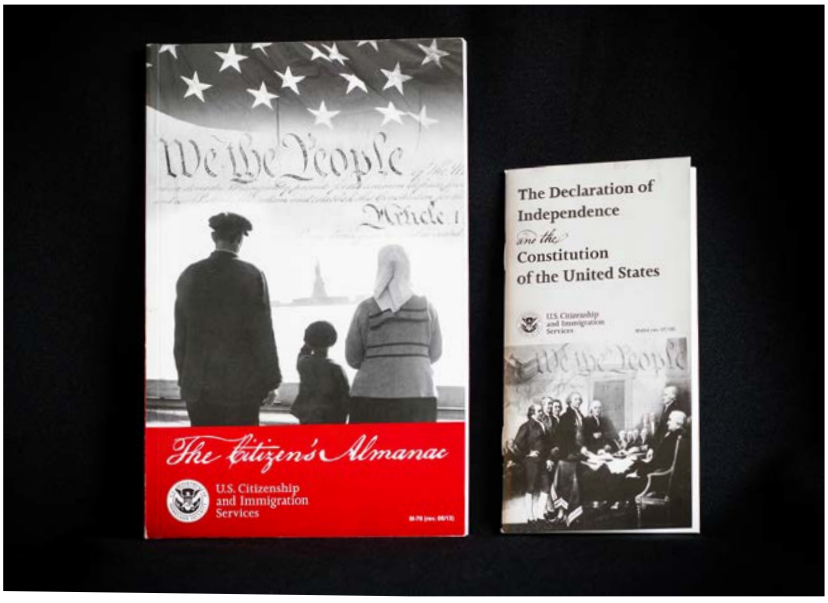
But the system can have unexpected surprises. The Kooijmans' case is an example of what happens when someone is from a country that doesn't have a backlog of green card applications. After spending several years in the Netherlands (during which time his wife became a Dutch citizen), they returned to the U.S. so that Kooijman's wife could finish her Ph.D. They went back to Kent State, where Kooijman eventually became a tenure-track faculty member on an H-1B visa. He became eligible to apply for green cards for himself, his wife and their two children.

"I guess U.S. government doesn't expect any Dutch people to want to ever move to the U.S.," he says. "We submitted the paperwork. We had to go to Cleveland for biometric processing. I thought they were going to give us a full-blown interview, but all they did was took our fingerprints and our picture and we were done. Three months later, our green cards rolled into the mailbox. Unbelievable."

He counts himself and his family very lucky, because, he says, "I have colleagues who are from India and China who having been waiting five years for green cards, and they haven't gotten anything yet."

The green card application process also held an unanticipated surprise for me. I knew of the backlog in processing green card paperwork for Indian-born nationals like me, so I was desperate to submit the paperwork as quickly as possible.

On the day I was about to submit the green card paperwork, I caught a mistake. My country of birth was recorded as India, which was correct — but so was my husband's. That wasn't correct: He was born in



EMILY HUFF

Study guides given to would-be citizens of the U.S.

Canada.

I mentioned the mistake to Wang. The relief in Wang's voice over the phone was palpable. She told me that this would mean the application would go into the smaller queue — the Canadian one. This was an out-of-the-blue welcome twist. But there still was an anxious wait with an unsettling silence from the USCIS.

In early 2008, a nondescript white envelope arrived in the mailbox. In it were instructions to visit an unmarked office in a strip mall in a suburb of Washington, D.C., on a particular day. When we showed up, it turned out to be a white-walled office with regulation-gray chairs with red numbers flashing on a screen. When my number came up, an employee from the Department of Homeland Security who didn't indulge in conversational pleasantries took my photo and my fingerprints.

The author on the day she became a U.S. citizen.

In May 2008, another nondescript envelope turned up in the mailbox. In it nestled a card in a deep green color. (That's when it dawned on me that it is a green card in the most literal sense.) The overwhelming sense of relief at getting my green card, which was the same size as a credit card, left me feeling weak in the knees for days. I was free to switch jobs if I desired. I could seriously contemplate becoming a citizen.

Epilogue

When the fifth year of holding a green card was complete, I was eligible to apply for citizenship. I welcomed the paperwork as an old friend and gave myself a crash course in American history, civics and law.

On that cold February day in 2014, I passed the citizenship test. After assuring the government that, among other things, I didn't belong to the Communist Party or have syphilis, I took the oath to become a U.S. citizen. I accepted my naturalization certificate from smiling DHS officials and momentarily panicked when I was asked to hand over my green card. I had carried that green card in my wallet for more than five years with the same fervor a toddler reserves for a lovie.

I pledged allegiance to the flag and sang "The Star-Spangled Banner" as best as I could with a sore throat. With tears in my eyes, brought on by the relief of ending a long, nerve-wracking journey, I watched a video of President Barack Obama welcoming me and my fellow freshly minted U.S. citizens.

Rajendrani Mukhopadhyay (rmukhopadhyay@asbmb.org) is the chief science correspondent for the American Society for Biochemistry and Molecular Biology. Follow her on Twitter at twitter.com/rajmukhop.

Meet Kathryn J. Moore

Associate editor of the Journal of Lipid Research

By Angela Hopp

Kathryn J. Moore at New York University Medical Center has been an associate editor for the Journal of Lipid Research since 2014. Moore's lab studies the innate immune system and microRNAs in the regulation of lipoprotein metabolism and atherosclerosis. ASBMB Today's executive editor, Angela Hopp, interviewed Moore to learn more about her scientific interests, academic path, and thoughts on balancing work and home life. The interview has been edited for length and clarity.

Briefly explain what your research group is studying.

My research team investigates the mechanisms underlying chronic sterile inflammation and metabolic dysregulation in atherosclerosis and diet-induced obesity. Our current projects focus on three main areas: noncoding RNA regulation of cholesterol metabolism and inflammation, mechanisms of sterile innate immune activation, and neuronal guidance cue regulation of immune cell trafficking and inflammation.

Using animal models combined with cellular and molecular biology techniques, we aim to understand better how imbalances in metabolism and noncoding RNAs promote disease.

Tell us about your academic background and research training.

I grew up in Montreal, Canada, where I attended McGill University for both my undergraduate and graduate studies. My early interests were in infectious disease, and I obtained a bachelor's degree in microbiology and a Ph.D. in parasitology/immunology.

While studying the host immune response to the trypanosome Leishmania donovani, I became fascinated with macrophages and their front-line role in innate immunity. This became

an enduring passion. I moved to Boston to pursue postdoctoral training at Harvard Medical School, focusing on the role of macrophage-driven inflammation in lupus nephritis and atherosclerosis. I was intrigued by the mechanisms underlying chronic sterile inflammation in these conditions and how the macrophage, despite its good intentions, could wreak such havoc.

One of the things that I love most about science is the freedom to explore. My lab continues to study macrophages and their various roles in innate immunity, lipid metabolism and inflammation, which continually takes us into new directions – non-coding RNA, cellular metabolism, immune cell migration. Every day presents a new puzzle, and I enjoy being continuously challenged.

What does it mean to you, on a personal level, to be an associate editor for the JLR?

Joe Witztum, one of the editors-in-chief, called to ask me personally to consider becoming an associate editor, and despite my busy schedule, I couldn't say no. Joe and Ed Dennis, the other editor-in-chief, work incredibly hard to keep JLR one of the top lipid journals in our field, and they inspire me to try do the same.

Do you have any advice for balancing life inside and outside of the lab?

Achieving work-life balance is a daily challenge! I have two small kids and commute for three hours a day. I've learned that everyone has advice on how to balance the demands of an academic research career and family, but you need figure out what works for you personally.

I am constantly making to-do lists and prioritizing items so that I have a clear picture of everything that is pending. One side of my list has work items and the other side family and home items so that I am aware of all of my responsibilities and can think about how to divide my time. It helps to be honest with those around you about your responsibilities and their expectations.

It helps to be honest with those around you about your responsibilities and their expectations.

Times are changing for both men and women, and topics like scheduling meetings to avoid conflicts with daycare or school drop-off or pickup are no longer frowned upon. Although an academic research career is very demanding, it also comes with a degree of flexibility that is not present in an industry setting. That means that I can still chaperone a school trip or work from home on a day when I need to attend a soccer game at 3 p.m. But, inevitably, there is not enough time in the day to get everything done, and I find myself returning emails after midnight!

What do you do outside of the lab? Hobbies?

I love home improvement projects. I get some of my best scientific ideas with a paintbrush in hand.

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

Develop a circle of mentors and peers that you can go to for feedback and advice. No one person can fulfill all of your mentoring needs, and it is important to build a network of people to help guide you on your road to success. Finally, never give up!

Angela Hopp (ahopp@asbmb.org) is the communications director for the ASBMB and executive editor for ASBMB Today.

PHOTO COURTESY OF KATHRYN J. MOORE

Kathryn J. Moore spends time with her husband, Robert Blaustein of Merck, and two children, 9-year-old Jake and 7-year-old Emma.

Klari Reis' Petri dish paintings evoke cellular processes.

The Petri painter

By Nicole C. Woitowich

To scientists, Petri dishes may be just another lab consumable. To artist Klari Reis, they are containers for vivid, mesmerizing creations.

In her early 20s, Reis was diagnosed with the chronic immune disorder Crohn's disease. Reis was in London for art school at the time and eager to learn all she could about the disease and its treatments. Her doctor also happened to be a researcher at King's College London, and, noting Reis' determined interest, he invited her into the lab to view her blood cells reacting to immune suppressants and additives. Fascinated by the cellular structures and the bright nuclear stains she saw, Reis decided then and there to translate what was under the microscope into art.

Reis' Petri dish installation at Clemson University.

Reis, who is now 38, already had been creating unique works by painting with epoxy polymer, a material similar to resin that commonly is used in the production of surfboards, high-gloss floors and cars and which gave her paintings a shiny, plastic appearance. As she considered fusing her novel method with explicitly biological subject matter, using Petri dishes to encapsulate the paintings seemed like a natural next step.

"When I started to paint biological images, I immediately thought that Petri dishes would be an excellent substrate or container for the paintings. It just took about four years of practicing and trial and error to get the composition of epoxy to work correctly within the Petri dishes," she says.

Reis resembles a lab virologist when at work in her San Francisco-based studio. She dons an airtight coverall suit, gloves, a respirator and goggles before breaking out the epoxy. As she fills the Petri dishes with a combination of epoxy and a choice of paints, powders or dyes, the various chemicals react in a pushing, dividing, stretching and bubbling of bright hues that resembles mitosis or cell motility. The process is never quite the same, and taken together, her finished dishes reflect the expansive variety of life that can be viewed under the microscope.

Reis describes her dishes as "colorful and personal, yet approachable." Initially she thought the collection would be small, maybe no more than 150 pieces. But she says, "I just realized that I loved making them and I kept going, and I am still making them today!"

In 2009, Reis began the project "A Daily Dish," for which she unveils a new Petri dish painting each day on her blog of the same name (www.adailydish.com). The project

initially was conceived to run for a year but Reis continued making the dishes and restarted the blog in 2013. She makes the dishes she posts in batches and prices them to sell individually or in groups. "I work on five to 15 at a time, and it takes about a week to complete," she says. All of this productivity allows Reis to exhibit the dishes together as larger installations. They've been hung in patterns of circles inside larger circles, as dancing waves, and as rising walls of color in public and private settings around the world.

In addition to her Petri dish collection, her portfolio includes pieces that seem to derive from a similar molecular starting point but are more systemic in nature. They resemble cells in a network communicating with other cells, highlighting the interconnectedness of living systems. In the collection "Street Anatomy," Reis recreated topographical maps of major cities. But instead of mimicking the grey grids cities appear to be from the air, "Each block ended up looking like a cellular form and the city looking like a bodily system," she says.

Over the past several years, Reis' ability to create works that represent the dynamic nature of living systems has garnered the attention of the scientific community. One of her paintings graced the cover of the journal Nature Chemical Biology, and biotech and pharmaceutical companies alike have requested custom works. In 2014, Reis was commissioned to create an expansive installation for the Life Sciences Building at Clemson University in Clemson, S.C., which features 600 Petri dish paintings and spans three floors.

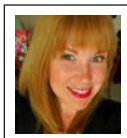
Clemson art professor David Detrich is impressed with the science-meets-art intersectionality of Reis' work. "The fact that the installation embodies attributes of both disciplines is a thing of beauty in and of itself … There is an inherent beauty in the way the piece functions visually, but also conceptually and intellectually when we ponder the seeming disparities between art and science," he says.

THOMAS KUOH PHOTOGRAPHY

The artist in her San Francisco studio.

Detrich imagines viewers of Reis' work will be challenged to step outside the comfort zones of academic divisions and begin to ask questions about the relationship of art to science. "The end run suggests that there is perhaps a seamless, coexistent connection between the two," he says.

Although Reis' art may challenge its viewers to explore a melding of these worlds, the artist herself is humble about the implications of her work. When asked why she thinks it is so appealing to researchers, she says, "(The paintings are) creative experimentation and hopefully give off that expression."



Nicole C. Woitowich (nicole.woitowich@gmail.com) is a member of the public outreach committee and a Ph.D. candidate at Rosalind Franklin University of Medicine and Science.

A mix of paint and epoxy settle in a Petri dish.

ALL PHOTOS OF ARTWORK COURTESY OF KLARI ART

A topographical map from Reis' "Street Anatomy" collection.

Messages on bottles

A scientist celebrates winemaking creativity through artfully designed labels

By Indumathi Sridharan

Silvery grapevines under purple skies wrap around the label of a 2012 bottle of cabernet sauvignon. The label on a 2013 blend of sauvignon blanc and sémillon reads, "Rain or shine, I'm on your side," in bright hues of gold, pink and blue.

Both wines are produced by Bare Bottle, a California-based wine company that believes what's on the bottle can matter as much to today's wine drinker as what's in it. The company teams winemakers with graphic designers to produce the visually arresting labels.

ALL IMAGES COURTESY OF COREY MILLER

Given the emphasis on label artistry, it's surprising to discover that Bare Bottle is the brainchild of a medically trained scientist. Corey Miller is a self-proclaimed wine geek who set out to become a physician-scientist. But a stint in San Francisco that cemented Miller's commitment to research, also triggered an unexpected foray into the wine industry.

Unexpected perks of doing science

Miller says his father, who also was a physician-scientist, handed down a love for science and medicine. "He showed me that the two paths could influence each other. He laid out a great example," Miller says.

Miller started his research career as a summer student examining chemical mechanisms in an organic chemistry lab. But he soon found doing science for science's sake was not enough. More interested in thinking about biology from the perspective of disease, he completed a bachelor's degree in biochemistry at the University of Michigan and then pursued an M.D./Ph.D. in the immunology department at the University of California, San Francisco.

Time at UCSF brought revelations. After the first two years of medical school, he started doctoral work on T-cell biology and found that, unlike clinical practice, academic research offered him a greater degree of creative freedom. The relaxed pace of research also afforded him the time and opportunity to reignite one of his longtime interests — wine.

The San Francisco Bay Area is the epicenter of American wine culture. It contains two major wine regions, Napa Valley and Sonoma Valley, both located a short driving distance from San Francisco in the region's North Bay. It is also home to a deep market of local wine connoisseurs and hobbyists that extends throughout Northern California. Miller tapped into this community and found some professionals in the area's East Bay. "There are a number of wineries in Berkeley that operate as cooperatives," says Miller. "It is a collaborative environment with a mix of hobby winemak-

ers and professionals."

Miller approached the cooperatives to learn about the basics of winemaking. And that's when things fell into place. "I realized that all the biochemistry and microbiology courses I took as an undergraduate and during medical school prepared me equally well for a career as a winemaker. That realization gave me the hubris to believe I could make good wine," says Miller.

But, as he learned from his first winemaking attempt, there's more to great wine than just mixing and waiting. Reminiscing about that not-so-stellar first vintage, Miller says, "It was a disaster. The wine turned out thin, flavorless and horribly undrinkable."

Like any seasoned scientist, Miller sought to understand the disaster by analyzing the variables. He found that a large batch volume and greater quantities of yeast were necessary to keep the temperature high enough to extract maximum flavor from the grapes. Soon, he became proficient enough to sell his own wines to retail stores and restaurants in the Bay Area. The venture was not commercially successful, but he gained insight into the craft of winemaking and the industry and became even more intent on making a mark in the world of wine.

Corey Miller is a medically trained scientist and the founder of Bare Bottle.

'Wine meets design'

The general perception of wine is that it's highly technical and requires focused study and special knowledge to fully appreciate. But Miller saw winemaking as a creative endeavor that could be accessible to all. While winemakers may adhere to techniques and parameters, they also push boundaries of the craft through experimentation, analysis and imagination. In the wine label, Miller saw a bridge that could showcase that creativity while also providing a visual story.

It was this idea of pairing design with wine that provided the foundation for Bare Bottle, which Miller first began working on in 2012 during his graduate school years. "I want to bring the winemaker out from behind the winery and tell a story about their creative process through an equally original label," he says.

Finding financial backers was no easy task. Early on, Miller's biggest hurdle was convincing potential investors that he had what it takes to run a wine company, especially given his professional background. "It was challenging to adequately articulate Bare Bottle's concept to investors and prove that I, a scientist, am the right person to take this concept to market," he says.

Miller says he was lucky that San Francisco has a large startup culture and many investors looking for the next big idea. After finishing his M.D./Ph.D. in 2014, Miller raised the seed capital he needed to launch Bare Bottle.

For each release, Miller works with his team to pair a winemaker with a designer. The winemaker creates a custom blend, and the designer tastes and draws inspiration from the wine. The

CONTINUED ON PAGE 30

CONTINUED FROM PAGE 29

result is an evocative piece of original art that shares a visual interpretation of a tasting experience.

Bare Bottle released its first two wines in the summer of 2015. True to Miller's original vision, Bare Bottle's website also features audio interviews and photo essays of the winemaker and designer that offer glimpses into each maker's unique creative process.

Looking to the future

Miller is now a postdoctoral scholar at UCSF, where he studies T cell development and the thymic stromal cells that are responsible for negative selection and immune self-tolerance. Juggling a research career with the responsibilities of a startup is daunting. Despite the challenges, Miller believes that young scientists should be open to entrepreneurship, which can be an equally fulfilling way to use their training.

"In my view, scientific training helps you identify interesting questions and problems that other people don't see. That is also the foundation of entrepreneurship," says Miller. And considering the precarious nature of academic funding, Miller says entrepreneurial success also can provide a certain degree of financial buffer and independence.

With science and winemaking eating up most of his days, Miller has little time to unwind. But he says he doesn't need to because he finds catharsis in working on completely different projects. "For me, balance comes from the fact that, on average, one of the two things I'm focused on will be going well at any given time," he says. "In the end, if you are doing what excites you, you shouldn't be so unhappy as to need mental recharging and escape."

So what does Miller's 10-year plan look like? He laughs out loud and says, "I don't have one. There may come a time when I have to grow up and pick either science or Bare Bottle. But, for now, I am excited about working on both."

Indumathi Sridharan (sridharan.indumathi@gmail.com) earned her bachelor's degree in bioinformatics in India. She holds a Ph.D. in molecular biochemistry from Illinois Institute of Technology, Chicago. She did her postdoctoral work in bionanotechnology at Northwestern University.

Science and spices

Rajini Rao unleashes her creative spirit in her recipes and cooking blog

By Alexandra Pantos

When she goes on vacation, Rajini Rao at Johns Hopkins University carries small amounts of spices with her in 15-milliliter screw-cap tubes. Rao says she enjoys trying local produce and uses the spices to cook one vegetarian meal a day when she and her family are traveling. The biochemist loves to cook so much she has an entire kitchen cabinet at home brimming with spices from around the world.

Rao grew up in India, in particular in Kolkata in the state of West Bengal and in Dehradun in the northern state of Uttarkhand. After graduating from college in Bangalore, in south India, she moved to the U.S. for a graduate program in biochemistry at the University of Rochester in Rochester, N.Y. Though she made the move in the 1980s because biochemistry programs and research were more advanced in the U.S. than in India, it was a bold step for her to take. It was "practically unheard of for young, unmarried females to travel so far from home," says Rao. It took a bit of persuasion and compromise with her parents and grandparents before she was allowed to go.

The compromise was that she agreed to have tea with a young bachelor before she left India. That bachelor eventually moved to the U.S. as well and became her husband. Like a well-balanced dish, their pairing has been a great match. Her husband "has been a huge supporter of my research career and an enthusiastic partner in raising our kids," she says. "We've been drinking tea together for 30 years."

As a child, Rao initially wanted to be a physician, but she realized that she was "too squeamish to be a doctor." She heard about biochemistry while she was still very young and says "the term charmed and intrigued me. So the next time I was pinched on the cheek by a relative or family friend and asked what I wanted to be when I grew up, I replied, 'biochemist.'"

PHOTOS COURTESY OF RAJINI RAO

A young Rajini Rao and her husband.

The fascination with biochemistry only grew stronger as time went on. ATP synthase, which she worked on in graduate school, was a topic Rao fell in love with during college while reading her pirated copy of Albert Lehninger's "Principles of Biochemistry."

Today, Rao's research is on ion transport proteins, including proton pumps, calcium ATPases and sodium-hydrogen exchangers. Her lab is currently "focused on linking transporter defects to autism, cancer and neurodegenerative diseases," she says.

Although she is immersed in her work in the U.S., cooking has helped Rao to maintain her connection to India. Her mother got her started with cooking when she was a child and still teaches her recipes. There are some mixtures of spices that her mother uses but that Rao hasn't learned to make yet. (Her mother

Rao, right, with her children and parents in Bangalore, India.

Rao's falafels are tinted with tumeric.

graciously packs small batches of spice mixes for Rao to take back to the U.S.)

To set up her kitchen for success, she stocks her pantry with the basics: "flours, grains, lentils and plenty of aromatics like fresh lemons, ginger, cilantro and onions." When asked what she considers the most important ingredients always to have on hand, Rao without hesitation mentions her spices. There are many she uses routinely, but Rao says her go-to spices are coriander, cumin, fennel, cloves and mustard seeds, all of which she stocks whole, not ground. Rao says she enjoys adding her own twist to recipes, sometimes leading to "everything tasting Indian, much to my chagrin!" (See page 34 for one of Rao's recipes.)

Rao has a blog titled "Madame Scientist's Not-So-Mad Musings" where she occasionally pairs her recipes with stories. The stories sometimes bring in her scientific expertise, like a recent post on falafel. In "Falafel Faves and Favism," Rao explains that falafel originally was made from fava beans, but the beans can set off life-threatening anemia known as favism in a few people of Mediterranean descent who inherit particular variants of glucose-6-phosphate dehydrogenase. For that reason, people stopped using fava beans in their falafel and switched to chickpeas.

Her interest in blogging has an additional facet: She enjoys writing. As a head of a busy research laboratory, Rao says, her blog has become "an outlet for my joy of storytelling, an expression of my sense of humor, and a document of my experiments at the bench — which are now more in the kitchen than in the lab."

Rao's mattar paneer with chappatis and yogurt.

Alexandra Pantos (apantos@asbmb.org) is an editorial assistant and former intern for ASBMB Today.

Rajini Rao's Practically Perfect Pilaf

• Measure out basmati rice: I use 2 cups to serve four generously (with leftovers for lunch the next day). Rinse a few times under cold running water. To drain, cover with a plate and let the water dribble out or simply tilt as much as you dare. Season the wet rice with coarse salt, a pinch of sugar and some red chili powder. Toss together and let sit for about 20 minutes while you prep the rest of the pilaf. This step further elongates the already long grain and makes it as delicate as a flower.

• Measure out twice as much water as rice (by volume) into a pot and heat on the back burner. I use 4 cups.

• Grate 2 carrots coarsely. Do you peel carrots? Why?

• Wash and roughly chop a bag of spinach. I use baby spinach, so I leave it alone.

• Thinly slice one sweet onion.

• Gather your spices: 2 – 3 cardamom pods, split (you ought to save the shells for tea, but I leave them in); 2 bay leaves; cinnamon sticks; some cloves; and about a tablespoon of fennel seed.

• Heat some oil in a heavy-bottomed pan. I like to use the broad, shallow type so that the rice is not crushed by its own weight at the bottom. A broad base also allows some golden crunchiness to develop at the bottom, Persian style.

• Add whole spices and let sizzle for a few seconds.

• Add sliced onions and toss around on high first. Then reduce heat to allow partial caramelization. You want the onions to turn partly brown so that they impart their rich color and sweetness to the pilaf.

• Add the grated carrots and spinach and mix. At this point, I add a handful of dry fruits and nuts (cranberries, golden raisins, almonds or whatever you have on hand).

• Add the pre-soaked basmati rice and toss together gently. Take care not to break the delicate grain. My mother told me so.

• Add the premeasured hot water and stir. I like to dot the surface with some clarified butter to infuse the rice with a heavenly, buttery flavor. Cover and let steam on low heat for about 10 more minutes.

• The rice is done when the water is absorbed. I add a handful of unsalted, roasted cashews at this point. Gently toss to mix.

Excerpted from Rao's blog, "Madame Scientist's Not-So-Mad Musings"

What you need to know about the HOPES program

The American Society for Biochemistry and Molecular Biology established the Hands-on Opportunities to Promote Engagement in Science grant program in 2011 to incentivize and support the development of outreach programs and partnerships by teachers and researchers.

About the grants

Each year, the ASBMB awards grants of up to $2,000 for partnerships between K – 12 teacher(s) and academic researchers to bring hands-on, inquiry-based learning to K – 12 students. Applications are judged based upon the diversity of the target audience, the nature of the project/activity and the plan for sharing responsibilities. As of 2015, the grants became renewable for up to one more year.

About the workshop

The annual workshops include: presentations from previous grant recipients, hands-on outreach demos and networking opportunities.

The past five years — by the numbers

Competition

131 applications
41 winners

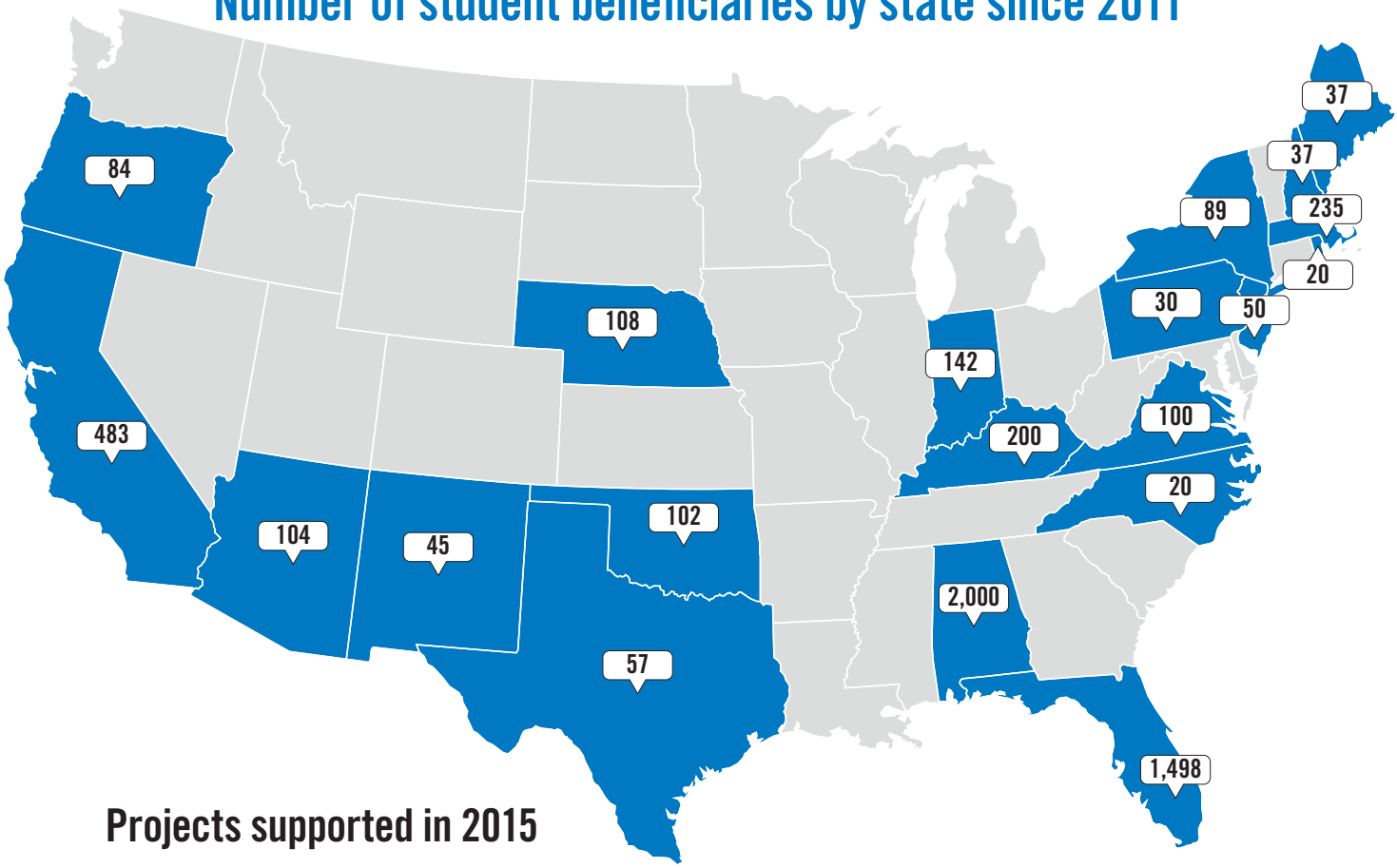
Participants

67 teachers
50 scientists
175 undergraduates

Impact

5,741 K – 12 students
2,264 underrepresented students
2,572 low-income students

Number of student beneficiaries by state since 2011



Projects supported in 2015

1. Supporting Science Instruction for Deaf Students: Sara Raven, Kent State University

2. Introducing Kinesiology STEM Activities in Clarkston School District: Robert Catena, Washington State University

3. Collaboration between a Community College and a Local High School to Engage Students in Authentic Microbiology Research: Joan Petersen, Queensborough Community College

4. Collaborative Development and Implementation of Problem-basedBiomedical Laboratory Projects into the Curricula of Regional High School Biology Classes: Darren Stoub, Dordt College

5. Drosophila Microbiome: Using Microbiology and Molecular Techniques to Identify Microbiome Diversity: Neal Silverman, University of Massachusetts Medical School

6. From Atoms to Biomolecules: Increasing Appreciation of Central Dogma and Biomolecule Evolution with Eighth-Grade Students: Daniel Dowling, University of Massachusetts Boston

7. CSI: Choosing Science and Innovation: Authentic Science Experiences for Fifth-Grade Students: Bethany Melroe Lehrman, Dakota Wesleyan University

8. Student Explorations of Synthetic Biology: Todd Eckdahl, Missouri Western University

9. "Hands-on, Minds-on" Biology Laboratory Outreach: Susan Stull, North Central Missouri College

Organizing committee

Regina Stevens-Truss, Kalamazoo College

Peter Kennelly, Virginia Tech University

Ray Sweet, formerly of Janssen R&D

Geoff Hunt, American Society for Biochemistry and Molecular Biology

Learn more www.asbmb.org/outreach

Community, suds and science

By Caitlin Fritz

It is another late night at Landmark Americana Tap and Grill, a popular sports bar in the Wynnefield neighborhood of Philadelphia. Gathered among the bartenders and patrons are teachers and students, parents and teenagers, a librarian, a motorcycle enthusiast, a postal worker and a microbiologist. Amid talk of who is ordering the next round of beer and cheese fries is a lively discussion about the differences between a bacterium and a virus. This is Science on the Hill, and the bar is abuzz with chatter about the science of everyday phenomena.

A bimonthly public science education program funded by the American Society for Biochemistry and Molecular Biology's Outreach Seed Grant Program, Science on the Hill is the brainchild of co-organizers Edwin Li, an assistant professor of biology at Saint Joseph's University, and Caitlin Fritz, who manages GeoKids LINKS, a program that places SJU fellows in local elementary school classrooms. Modeled after science cafés, which bring scientists out of the lab to engage community audiences in informal discussions, Science on the Hill cuts through the pressures of a formal classroom or lecture hall, replacing quizzes with quesadillas, study notes with nachos and lab reports with lagers.

Now in its second year, Science on the Hill has featured experts covering a variety of topics, including climate change, epigenetics, urban landscapes and a scandalous version of Darwin's voyage on the HMS Beagle. Many of the events get attendees off of their bar stools and out of their seats. Participants have swabbed for bacteria, popped water balloons to demonstrate Neosporin's effect on a bacterial cell and caught Wiffle® balls as they acted

PHOTO COURTESY OF CAITLYN FRITZ

Botanist Karen Snetselaar shows how vacant city lots can become biodiverse landscapes.

out the role of cell receptors. No one has spilled a glass or knocked over a table … yet.

Discussions are open and casual, and participants are empowered to contribute their own insights. One avid soccer fan found a discussion so engaging he missed watching the World Cup to stay late and challenge the Darwin speaker on the basis of evolution.

Audience members tell the organizers they come back to Science on the Hill events because the topics are interesting, current and provide opportunities to learn. After the recent measles outbreak in the U.S., Paul Offit of the Children's Hospital of Philadelphia shared firsthand insights from a similar outbreak in 1991. Cynell Scott, who regularly attends Science on the Hill, said talks like Offit's put "a microscope on it and make you look at everyday things with a different view."

Li, the co-organizer said, "Science cafés welcome everyone, especially those who are interested in the topic but who may not typically have the chance to get involved." For instance, many families attend Science on the Hill.

Scott, who regularly brings her two teenage children to the Landmark for the events, enjoys "the interactive, fun and informative atmosphere" and the opportunity to "engage her children outside of a school setting with people of all different ages. Science is part of everyone, and Science on the Hill allows us to find common ground regardless of other barriers."

Scott's children say the events have deepened their interest in science by helping them look at it in a different way and gain a better understanding of what scientists do.

Posters designed by the author for Science on the Hill events.

While the idea of mixing science with drinks is not novel, the events have been transformative for this local neighborhood. Neighbors share ideas for new gardening techniques, librarians exchange contact information with new patrons, and teachers interact with students and parents outside of school walls.

The events frequently go well past their scheduled times, with the waitstaff chiming in on the lingering conversations as they clean tables. Some bartenders request to be scheduled for science nights so they too can participate.

Regular attendees bring so many friends and family that the talks have had to move to a larger room. As the program growss, the goal is to hold a science night in the community once a month and expand to include scientists from a wider range of disciplines.

More information on Science on the Hill can be found at http://scienceonthehill.weebly.com.

Caitlin Fritz (cfritz@sju.edu) is the GeoKids LINKS Program Manager at Saint Joseph's University. She holds degrees in environmental science and community development and planning.

Re: President's Message, October issue

Dr. McKnight,

Why do you continue to use this forum to beat up and demonize (National Institutes of Health) reviewers, especially those who have not been in the system for decades or are not what you consider real scientists? This elitist idea you keep pushing of study sections infested with vermin (what you so eloquently called riffraff in previous articles) is highly insulting to the hundreds of us who volunteer our precious time and effort to provide thoughtful and stringent review of grants for the NIH and is simply wrong.

You seem to have a personal vendetta toward younger investigators, who you seem to feel are not worthy to be working scientists because they do not necessarily hold your view that flitting between shiny objects (what you term "vertically ascending science") is their preferred approach to science and that those pursuing this course of carefully building the body of knowledge through solid, unflashy science are taking NIH funds that rightfully belong to persons like yourself.

Your preferred approach of expelling reviewers from study sections that do not perform to some undefined and nebulous standard that only you seem to be aware of is simply a thinly veiled way to make sure that junior investigators (who lack study section experience) are not able to be involved in a process that is essential to their survival in academic science.

As someone in a position of authority and influence, you should be promoting solutions to help all scientists, not just those who you deem worthy. You should be using your position to promote increased funding levels for all of us, not beating up on those of us who have been struggling to establish our careers in the harshest funding environment in modern times, and trying to make it even harder for us to succeed.

You should be ashamed of yourself, Dr. McKnight, for trying to make biomedical science an even more competitive and difficult career path to follow.

— *Philapodia*

P.S. By the way, the NIH process is by no means hands-off as you imply. The Scientific Review Officers, or SROs, that actually organize the study sections already monitor reviewers for quality. If a reviewer isn't up to snuff, then he or she simply won't be invited back. Having an IC director come and babysit the SROs (many of whom have been doing their jobs effectively for years) is simply micromanagement and is a waste of everyone's time. The IC directors' time would be much better spent trying to secure new streams of funds for their investigators.

Upcoming ASBMB events and deadlines

NOV.

Nov. 5: Abstract-submission deadline for the ASBMB 2016 Annual Meeting, San Diego
Nov. 12: Travel-award application deadline for the ASBMB 2016 Annual Meeting, San Diego
Nov. 11 – 14: Annual Biomedical Research Conference for Minority Students (ABRCMS), Booth #900, Seattle
Nov. 21: ASBMB workshop Developing and Sharing Best Practices: From Concept to Classroom, San Diego

DEC.

Dec. 1: Deadline for 2017 Special Symposia proposals
Dec. 5 – 8: ASBMB Special Symposium Kinases and Pseudokinases: Spines, Scaffolds and Molecular Switches, San Diego

JAN.

Jan. 9: ASBMB workshop Developing and Sharing Best Practices: From Concept to Classroom, Melbourne, Fla.
Jan. 23: ASBMB workshop Developing and Sharing Best Practices: From Concept to Classroom, Hattiesburg, Miss.
Jan. 23: ASBMB workshop Developing and Sharing Best Practices: From Concept to Classroom, New York City
Jan. 28: Late-breaking abstract deadline for the ASBMB 2016 Annual Meeting, San Diego

ASBMB
American Society for Biochemistry and Molecular Biology

REMINDER: Renew your 2016 ASBMB Dues!

ASBMB Member Benefits:

- Career resources, including an online job board, blog and free workshops for graduate students and postdocs
- Reduced publication fees and FREE color in all ASBMB journals*
- Free online access to all ASBMB journals:
    - Journal of Biological Chemistry
    - Molecular & Cellular Proteomics
    - Journal of Lipid Research
- Free print and online subscription to ASBMB Today, the member magazine
- Travel awards
- Discounts on registration for ASBMB meetings
- A voice on Capitol Hill

*Must be a regular member publishing as the corresponding author.

www.asbmb.org/renew

ASBMB
American Society for Biochemistry and Molecular Biology

Sample ASBMB Abstract Topic Category Titles (#2000-2697)

- Bioinorganic Catalysis
- Cell Signaling, Kinase and Chemotheraphy
- Chemical Biology and Drug Discovery
- Chromatin Organization and Gene Regulation
- DNA Replication, Repair and Recombination
- Education and Professional Development
- Glycoscience in Biology
- Lipids and Lipid Signaling
- Metabolism, Disease and Drug Design
- Non-Alcoholic Fatty Liver Disease
- Post-translational Modifications
- Protein Synthesis and Degradation
- Recent Advances in Protein Engineering
- Systems Biology and Proteomics

Abstract-submission deadline: Nov. 5

Travel-award application deadline: Nov. 12

ASBMB members can save up to 56% on MEETING COSTS!

Late-breaking poster abstracts welcome!

www.asbmb.org/meeting2016