

Vol. 17 / No. 3 / March 2018

ASBMB TODAY

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



MYALGIC ENCEPHALOMYELITIS

Unknown cause. No cure. New hope.

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to advocate for science,
connect researchers around the world
and build a bright future
for biochemists
and molecular biologists everywhere.

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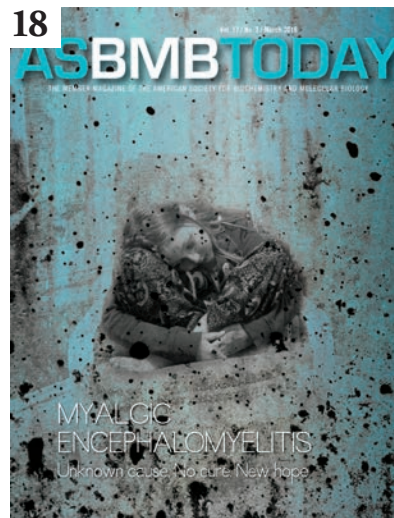
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WHEN SCIENCE MEETS SICKNESS



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PRINT ISSN 2372-0409

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EDITOR'S NOTE

Not crying wolf

By Comfort Dorn

Have you ever felt sick enough that you thought you should see a doctor — made an appointment, took time off work, hired a babysitter, spent an hour thumbing through ancient magazines in the waiting room — only to be told (implicitly or explicitly) that you're exaggerating, that it's all in your mind? Or the result of your bad, sloppy living habits? Or not really a big deal and it will go away soon?

If you're nodding along, chances are you're female.

There's plenty of evidence — enough that all those doctors should be pretty embarrassed by now — that women are at greater risk for certain conditions that cause pain (migraines, for starters) and that they are treated less aggressively for pain than men.

For the medical profession, I'm sure it's complicated. With insurance companies breathing down their necks, doctors feel pressure to move patients in and out quickly. Like the mechanic who can't find the source of that funny noise your car makes, a doctor might get impatient with someone who doesn't have a clear-cut, diagnosable and treatable problem. So they put it back on the patient or imply that if they can't find it, it's probably no big thing.

Part of this is undoubtedly plain old garden-variety sexism. We've made some progress in gender equity, but men's bodies are still regarded as the norm in many aspects of life, including health. Much about women, including their pain, remains a side note. In addition, the diseases that are difficult or impossible to diagnose — those for which telltale markers have yet to be found — seem largely to afflict women. Fibromyalgia, autoimmune disorders, polycystic

ovary syndrome — and the subject of this month's cover story: the almost unpronounceable myalgic encephalomyelitis.

As Lily Williams reminds us in her feature story on page 18, ME used to go by the less accurate “chronic fatigue syndrome.” For years, it has languished, with research that went nowhere and patients disrespected. It mostly strikes women (though plenty of children and some men get it), and it's difficult to diagnose and almost impossible to treat. It's finally getting a bit of attention from the National Institutes of Health, with \$7 million in targeted funding for four research centers.

I first heard of chronic fatigue in an interview with the author Lauren Hillenbrand, who described researching and writing her bestseller “Seabiscuit” while lying flat on her back. That stuck in my mind because, although words are my job, even on my best day I have trouble stringing them together. And Hillenbrand is no outlier. A quick internet search shows that famous sufferers range from Florence Nightingale to musicians Randy Newman and Cher to U.S. soccer star Michelle Akers.

When I think of Lizzie Mooney, the 12-year-old Illinois girl in Williams' story who has been terribly sick with ME for a quarter of her life, it makes me wish doctors were more willing to listen to and believe their patients — and to admit they still don't have all the answers.



Comfort Dorn
(cdorn@asbmb.org) is managing
editor of ASBMB Today. Follow her
on Twitter @cdorn56.

Appropriations season — what we want and how to help

By Benjamin Corb

As the calendar turns to March, appropriations season begins on Capitol Hill and advocates from every constituency kick their efforts into high gear. The American Society for Biochemistry and Molecular Biology is no different, and we enter this spring with an invigorated interest in increasing the research budgets at the National Institutes of Health, the National Science Foundation and the Department of Energy's Office of Science. For fiscal year 2019, we are calling on Congress to increase federal investments in the life sciences by 8 percent at all agencies. Particularly of interest to the ASBMB community is that this would mean an increase of \$2.6 billion to the NIH, \$600 million to the NSF and \$430 million to the DOE's Office of Science.

The increases we are looking for extend beyond the annual biomedical research and development price index inflationary rate of 2.2 percent. This accounts for inflation and also provides new dollars to increase funding rates across all three agencies. These increases are critical not only to ongoing research efforts but also to create funding opportunities for new scientists beginning their careers, a constituency of the research community the NIH has been looking to support since the introduction of its Next Generation Researcher Initiative

last year.

Funding increases at this level are not easy to come by. First, legislators responsible for determining budget levels must account for mandated caps to federal spending that have been in place since 2011. These caps limit the total amount of federal spending authorized in a particular year for all discretionary funding. The ASBMB has long been a proud supporter and leader of Nondefense Discretionary United, a coalition of federal, state and local organizations that have called for the raising of caps on nondefense discretionary federal spending, where the overwhelming majority of federal funds for science come from. The ASBMB, NDD United and thousands of other groups have been working for years with congressional leaders on both sides of the aisle to #RaiseTheCaps successfully three times, most recently in the current budget deal, which has raised spending caps into fiscal year 2019 — and we must continue to do so to ensure there is room in the federal budget for increases in science investments.

Legislators also must understand that an increased investment in science is vital to their constituents and to the nation. This is where we need your help. We hope you will participate in the Public Affairs Advisory

Committee's March 9 training webinar on how to write an op-ed piece (check the policy blog for details). Legislators and their staffs read local papers to stay in touch with the issues important to their constituents back home. There is no better way to build support for investments in your work than telling the people and politicians in your community about the impact your research might have on their lives. We urge ASBMB members across the country to draft and publish opinion pieces in local newspapers during the month of March.

Writing an op-ed letter too much work? Visit asbmb.org/advocacy for sample tweets and letters that you can personalize and share to tell your representatives about the support you need. Share your experiences with us at publicaffairs@asbmb.org. We'll feature your tweets, letters and op-eds on our blog and spread the word about the important role you play in helping us to secure these much-needed funding increases this year. We look forward to working with you.



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



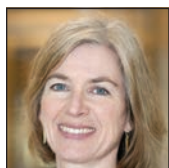
Check in every other week for a new Pipettes & Politics podcast episode to hear candid conversations about topics like new legislation in Congress, policies at federal agencies and policy issues within the research community.



Member update

By Erik Chaulk

NAS honors Doudna for CRISPR work



DOUDNA

Jennifer Doudna has received the 2018 Award in Chemical Sciences from the National Academy of Sciences for co-

inventing the gene-editing technology CRISPR-Cas9.

CRISPR-Cas9 allows scientists efficiently to alter specific parts of the genome. It has revolutionized the field of genetics through its simplicity, versatility and precision compared to other gene-editing tools, demonstrating the potential for a wide range of applications.

Established in 1978, the NAS Award in Chemical Sciences recognizes innovative research in the chemical sciences. The award carries a \$15,000 prize.

Doudna is a professor of chemistry and of biochemistry and molecular biology at the University of California at Berkeley.

Medina-Bolivar article in Altmetric top 100



MEDINA-BOLIVAR

Arkansas State University professor Fabricio Medina-Bolivar's research has been recognized in Altmetric's top 100 articles of 2017.

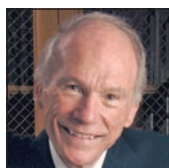
Medina-Bolivar is among the authors of a paper on plant tissue scaffolding titled "Crossing kingdoms: Using decellularized plants as perfusable tissue engineering scaffolds." The paper, published in *Biomaterials*,

placed at No. 53 on Altmetric's list of the most influential scientific papers of the year.

Medina-Bolivar's research focus lies in plant metabolic engineering for the production and discovery of pharmaceuticals.

Altmetric is a digital science company that collects and tracks data on scholarly content complementary to traditional citation metrics, including mentions on social media and in mainstream media coverage.

In memoriam: Daniel W. Foster



FOSTER

Daniel W. Foster, former chairman of the department of internal medicine at the University of Texas Southwestern

Medical Center, passed away Jan. 18. He was 87.

Foster received his bachelor's degree from the University of Texas at El Paso in 1951 and obtained his medical degree from UT Southwestern in 1955, graduating first in his class.

After completing his residency at Parkland Memorial Hospital in Dallas and a research fellowship at the National Institutes of Health, Foster returned to UT Southwestern, joining the faculty in 1962. He became a full professor in 1969 and was appointed chairman of internal medicine in 1987, a position he held until 2003.

Foster contributed significant research that led to greater understanding of obesity and diseases of the heart and liver.

In 1974, he began hosting the

nationally televised program "Daniel Foster, M.D.," a weekly program that focused on medical topics. He also served on the President's Council on Bioethics.

Foster is survived by his wife, Dorothy; three sons, Christopher, Daniel and Michael; and one grandchild.

Cech named STORM science adviser



CECH

STORM Therapeutics has named Thomas Cech as a science adviser.

Founded in 2015, STORM Therapeutics is a

British-based developer of small-molecule inhibitors of RNA-modifying enzymes for the treatment of cancer.

A leading figure in the field of RNA research, Cech shared the 1989 Nobel Prize in chemistry for discovering the catalytic properties of RNA. He also received the Albert Lasker Basic Medical Research Award and the National Medal of Science.

Cech is a distinguished professor of chemistry and biochemistry at the University of Colorado, Boulder, and director of the BioFrontiers Institute, an interdisciplinary bioscience research and education hub with a focus on improving human health.

In memoriam: Aloys L. Tappel

Aloys L. Tappel, a professor emeritus at the University of California, Davis, passed away Nov. 25 from pneumonia. He was 91.

Born Nov. 21, 1926, in St. Louis, Tappel studied chemical engineering

American Academy of Microbiology names new fellows

Eight members of the American Society for Biochemistry and Molecular Biology are among the 96 new fellows elected to the American Academy of Microbiology.

The American Academy of Microbiology is an honorary leadership group within the American Society for Microbiology, which recognizes significant research toward and promotion of microbiology.

Over the past 50 years, more than 2,400 distinguished scientists have been elected as fellows in recognition of their original contributions toward advancement in the microbial sciences.

Congratulations to the following ASBMB members:

- Thomas Dever, National Institutes of Health
- Borden D. Lacy, Vanderbilt University Medical Center
- Shan-Lu Liu, M.D., Ohio State University
- Beronda Montgomery, Michigan State University
- Jean Patterson, Texas Biomedical Research Institute
- Holger Sondermann, Cornell University
- Michael Surette, McMaster University
- Hung Ton-That, University of Texas at Houston

at Iowa State University, where he earned his undergraduate degree. He then earned his Ph.D. in biochemistry at the University of Minnesota, where he met his future wife, Ardelle Amber Fish.

Tappel came to UC Davis in 1951 as a member of the department of food science and technology. He remained on the faculty for 50 years, focusing on teaching food biochemistry and nutrition.

Among his many accolades, Tappel received the 1965 Guggenheim Fellowship, the 1973 Borden Award from the American Institute of Nutrition, and the 1991 Award for the Advancement of Application of Agricultural and Food Chemistry from the American Chemical Society.

He is survived by his wife, Amber; daughters, Susan, Mary, Cath and Liz;

sons, Steve and Paul; and 13 grandchildren.

In memoriam: Eldon Carl Nelson



NELSON

Oklahoma State University professor Eldon Carl Nelson passed away at his home Dec. 27. He was 82.

Nelson was born Dec. 13, 1935, in Dola, Ohio. He attended the Ohio State University, graduating in 1957 with a degree in animal science and agricultural education. After teaching at Belle Center High School for a year, he returned to Ohio State, receiving his master's in 1960 and Ph.D. in 1963.

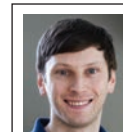
Nelson then joined the depart-

ment of biochemistry and molecular biology at Oklahoma State University, where he stayed for more than 40 years.

His research centered on the isolation and identification of metabolites of vitamin A, synthetic analogs and related retinoids.

A decorated faculty member, Nelson was recognized by the university with the outstanding professor, outstanding adviser and outstanding mentor awards.

He is survived by his wife, Jo; daughters, Laura and Julie; and four grandchildren.



Erik Chaulk (echaulk@asbmb.org) is a peer-review coordinator and digital publications web specialist at the ASBMB.

Send us your news

Have you recently been promoted or honored? Do you have good news to share with your fellow ASBMB members? Email it to us at asbmbtoday@asbmb.org — and don't forget to include a photo!



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Camilla Stejskal, Boston University

Brittney Stevens, Vanguard University

Edward Stites, Salk Institute for Biological Studies

Omar Stocks, Rhodes College

Brandon Strong, California Polytechnic State University, San Luis Obispo

Edward Stuenkel, University of Michigan

Dawoud Sulaiman, University of California, Los Angeles

Ewa Swiezewska, Polish Academy of Sciences

Julianna Szuwalski, Rhodes College

Tiffany Tadros, Vanguard University

Danyal Tahseen, Trinity University

Tari Tan, Harvard Medical School

Kaare Teilum, University of Copenhagen

Conor Templeton, Medical University of South Carolina

Kaleb Tenhagen, University of Wisconsin–Stevens Point

Jeffery Tessem, Brigham Young University

Kourtland Thompson, University of Wisconsin–Stout

Yee Mon Thu, Grinnell College

Gemma Topaz, Roxbury Community College

Zally Torres, University of Puerto Rico, Rio Piedras

Dwight Towler, University of Texas Southwestern Medical Center

Sydney Townsend, University of Nebraska–Lincoln

Tran Doan Ngoc Tran, Texas A & M University

Samuel Trenner, Rhodes College

Lata Udari, Eastern Illinois University

Haruna Ueda, University of Tsukuba

Yuri Ueda, National Cancer Center East Japan

Shalom Umunnakwe

Taylor Underwood, Vanguard University

Selena Vanapruks, Colgate University

Sonika Vatsa, Boston University

Carlos Vera, University of Colorado Boulder

Astrid Viera, Vanguard University

James Villanueva, International American University College of Medicine

Catherine Vrentas, United States Department of Agriculture

Isha Walawalkar, Boston University

Jian–Hua Wang, Institute Pasteur of Shanghai, Chinese Academy of Sciences

Colin Welsh, Rhodes College

Kathleen Wendover, Hendrix College

Joshua Weseli, University of Wisconsin–La Crosse

Connor West, Medical University of South Carolina

H. Steven Wiley, Pacific Northwest National Lab

Lauren Wilson, University of Arizona

Christopher Winski, University of the Incarnate Word

Tiffany Wong, University of Maryland

Jie Xiao, Johns Hopkins School of Medicine

Wuhan Xiao, Institute of Hydrobiology, Chinese Academy of Sciences

Xuebiao Yao, University of Science and Technology of China

Victor Yu, University of Arizona

Jin Zhang, University of California, San Diego

Feng Zhao, Puer University

Miaoyun Zhao, University of Nebraska–Lincoln

The state of the lipid research community — improving grant review

By *Binks Wattenberg*

I have just returned from Washington, D.C., where I was on a National Institutes of Health study section. I am happy to report that the state of the lipid research community is excellent. But it always can be better, particularly when getting our grants reviewed, and that is a prime focus of the American Society for Biochemistry and Molecular Biology's Lipid Research Division, or LRD.

The underlying premise of a new LRD initiative is that grants with a lipid focus suffer when study sections do not have sufficient lipid-centric reviewers. Although the scientific review officers, or SROs, work to get relevant expertise on the panels, several have told me they sometimes struggle to find lipid reviewers. We need individuals on these panels who can put the lipid work into context for the other study section members. Toward this end, we have an ongoing effort to improve the review of lipid-related grants by identifying qualified reviewers with lipid expertise. This has been a three-phase effort.

First, early last year we reached out to the ASBMB membership to encourage members involved in lipid research to join the LRD if they had not done so already. This has swelled the ranks of the division, and we are now 640 members strong.

The second phase was a survey



NIH PHOTO

National Institutes of Health study sessions meet at the main NIH campus in Bethesda, Maryland, shown in this aerial photo.

sent out to the LRD membership to capture the review experience and research expertise of each member. The response? Not bad, but could be better. Out of the total membership, 348 received the survey. (Why not all? Explanation below.) Of those, we received 143 responses — an outstanding response rate for this kind of survey request. The survey identified 46 individuals who have NIH reviewing experience, which is the strong preference of the SROs, and an additional eight U.S.-based researchers with non-NIH reviewing experience. Those individuals might be recruited by SROs to increase the ranks of reviewers.

In the third phase, the results of the survey, in spreadsheet form, are now being distributed to SROs of study sections that historically have handled grants from the LRD mem-

bership. The SROs' responses have been very enthusiastic. Finding qualified reviewers with the right expertise is one of their most time-consuming challenges. They definitely will use our results.

We know there are more qualified reviewers out there, and the SROs would love to have them serve on their panels. So rather than the usual kvetching around the bar about the terrible review your lipid grant received, here is how you can help. First, if you do lipid research and are not an LRD member, join us. Go to the

Lipid Corner under the "About Us" tab at asbmb.org and click the red "Join the Lipid Research Division" button. Second, only a little more than half of the LRD membership received the survey, because many of you have asked not to receive e-mails from the ASBMB. We have no way to reach you. Please consider changing this in your profile so we can get in touch.

While the state of our community is strong in many ways, the fate of lipid grants is in your hands, in more ways than one. Help us to help you.



Binks Wattenberg (brian.wattenberg@vcuhealth.org) is an associate professor in the department of biochemistry and molecular biology at Virginia Commonwealth University.

miRNAs take the wrecking ball to colorectal cancer

By Rachel Evans

Analogies for cancer abound, from a military-style battle against villainous cells that mutate and harm the peaceful host to a garden where doctors pluck out the weedy cancer and nourish the helpful immune cells. A laboratory in the molecular oncology group at the Madrid Institute of Advanced Studies, or IMDEA, Research Institute on Food and Health Sciences in Spain sometimes views cancer as an illegal construction project. Researchers who focus on the role of lipid metabolism in cancer describe the disease as an unauthorized building that requires delivery of construction materials (nutrients) as the structure (tumor) grows. Their goal is to understand how to block delivery and use of these materials.

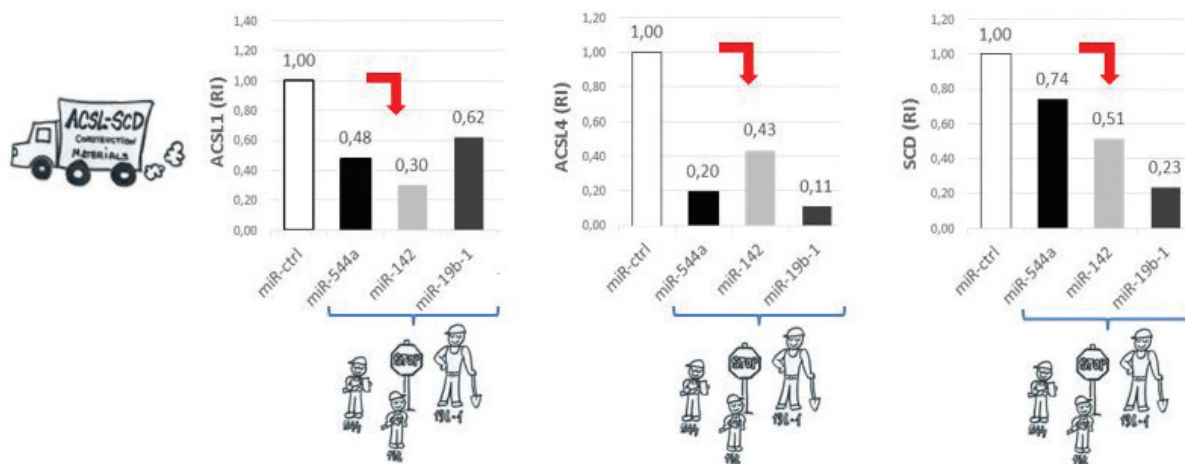
In a paper in the **Journal of Lipid Research**, these researchers describe how they identified unique microRNA networks that may limit delivery of these resources to cancerous cells and help combat the disease.

The “construction materials” in cancer are often lipids that provide energy for ever-growing cancer cells. Many of these cells have altered lipid metabolism to enable rapid growth and carcinogenesis in a harsh tumor microenvironment. IMDEA researcher Ana Ramirez de Molina and her Ph.D. student, Silvia Cruz Gil, explain that the group previously identified a key pathway in altered lipid metabolism, known as the abnormal acyl-CoA synthetase/ stearoyl-CoA desaturase, or ACSL/SCD, lipid network, which promotes invasion and migration of colorectal cancer cells. Inhibitors of the ACSL/SCD network actually reduce cancer cell viability. This network could present a novel colorectal cancer therapy target, so the group wanted to identify inhibitory miRNAs, as these have emerged as “potent epigenetic modulators of cellular homeostasis,” Ramirez de Molina said. In the cancer-as-construction metaphor,

these miRNAs are the city workers that come in to block shipments and stop work on the illegal building.

In their latest project, the group sought to identify miRNAs specific to the ACSL/SCD network that combat cancer cells. In extensive bioinformatics assays using miRNA-detecting algorithms, they identified 31 miRNAs that may bind a region of mRNA, leading to reduced expression of the ACSL/SCD network. The researchers then confirmed the roles of miRNAs with RNA and protein detection techniques. They identified three main miRNAs that reduced both RNA and protein expression: miR-544a, miR-142 and miR-19b.

The expression of miRNA-19b corresponded to disease outcome: low levels of expression were correlated with increased symptoms and disease progression. The group used cell invasion assays and biochemical techniques to show that miRNA-19b expression reduces adhesion and inva-



COURTESY OF ANA RAMIREZ DE MOLINA/IMDEA RESEARCH INSTITUTE ON FOOD AND HEALTH SCIENCES

In colorectal cancer patients, higher expression of miR-19b is associated with better survival. This can be thought of as having more city workers (miRNAs) to prevent delivery of construction materials for cancer via the ACSL/SCD network.

sion through direct targeting of the ACSL/SCD network. They also found that miRNA-19b expression reduced lipid storage and respiratory capacity — curtailing metaphorical resources for the ever-growing building. Treating patients with miRNAs like 19b potentially would provide targeted, tailored reduction of oncogene expression to reduce cancer progression.

miRNA levels also may indicate disease severity and give physicians a clearer understanding of individual patients' cases. Ramirez de Molina encourages health systems to use miRNA detection especially for colorectal cancer, because it often shows minimal symptoms until the disease has spread extensively. She is excited about tools like miRNAs. "The possibility to detect them as early detection biomarkers and to modulate their action would represent a promising and very advantageous tool against cancer progression," she said.

Further research on therapeutic use of miRNAs is needed, and these findings provide excellent fuel for such studies. The lab now is studying the ACSL/SCD network in complex tumor organoids of colorectal cancer as well as tumors in other types of cancer. Their discovery of these networks and their respective miRNAs could help identify more city workers in the body that will block progress of this illegal construction; future work likely will shed more light on the networks delivering fuel and supplies to harmful cancer cells.



Rachel Evans (revans46@jhmi.edu) is a Ph.D. candidate at the Johns Hopkins Bloomberg School of Public Health. When she is not in the lab studying malaria development and antimalarial resistance, she is baking up a storm in her apartment.

Upcoming ASBMB events and deadlines

- MAR** 6–9: ASBMB–Deuel Conference on Lipids
 9: Public Affairs Advisory Committee training webinar on how to write an op-ed
 15: Accreditation application deadline
- APR** 12: Capital Hill Day
 13: IMAGE grant-writing workshop nominations deadline
 16: Outreach Student Chapters grants deadline
 21–25: ASBMB annual meeting
 30: Art of Science Communication Course applications open
- MAY** 2: ASBMB award nominations deadline
- JUN** 1: Marion B. Sewer Distinguished Scholarship for Undergraduates deadline
 14–16: IMAGE grant-writing workshop



When HIV drugs don't cooperate

By *Sasha Mushegian*

The term “synergy” has gained a reputation as an overused buzzword, but it has a quantifiable definition in pharmacology. Two drugs are considered synergistic if their effectiveness when used together is greater than the sum of their effects alone. That is, a drug that is synergistic with another doesn't just perform a beneficial function itself but makes the second drug perform its function better.

Researchers at Thomas Jefferson University studying combinations of drugs against HIV have discovered why some drugs sometimes act synergistically but sometimes do not. The paper describing their research was published in the **Journal of Biological Chemistry**.

Second-line HIV drugs, used after first-line treatments have failed, target several steps in the process by which the virus enters human T cells. Because of the particular steps and proteins they target, two types of these drugs, called co-receptor antagonists and fusion inhibitors, are expected to be synergistic. But multiple previous studies have yielded contradictory results: sometimes these drug classes were indeed strongly synergistic, but sometimes they displayed no synergy at all.

Co-receptor antagonists like maraviroc (marketed under the brand name Selzentry) bind to receptors on host cells known as co-receptors. Fusion inhibitors like enfuvirtide (marketed as Fuzeon) bind to a viral protein called gp41 when it's in a particular transitional phase. To understand why these drugs don't always synergize as expected — and to gain a better understanding of the steps of the HIV infection process — associate professor of biochemistry and molecular biology Michael Root and his then-graduate student



Koree Ahn applied various doses of maraviroc and enfuvirtide to cells and viruses with slightly different genetic sequences.

“We found that many different factors are important for (determining) whether there's a synergistic interaction between these two classes of inhibitors or not,” Ahn said.

The first factor was the strength of the binding between enfuvirtide and gp41, which could vary depending on mutations in the viral gene that encodes gp41. If the sequence of the gp41 protein was such that enfuvirtide bound to it very tightly, then enfuvirtide and maraviroc acted synergistically. But the weaker the binding, the weaker the synergy between the two drugs.

This finding implies that when virus proteins evolve to avoid binding drugs, it doesn't affect only the efficacy of the drug in question; it also affects how much its effects are boosted by other drugs. This is bad news for patients, because adding synergistic drugs to a treatment regimen is thought to be a way to combat loss of drug efficacy.

The second factor affecting synergy was the density of co-receptors on

host cells, which can vary significantly among patients. “Some (patients) might have very high levels of (co-receptors) on their T-lymphocytes, and those patients would see robust synergy between these two classes of drugs,” Root said. “Another individual might have lower levels of co-receptors on the cell surface, and therefore not have as robust synergy, or none at all.”

Together, these results suggest that variations in viruses and in patients need to be considered when predicting the efficacy of drug combinations, including newly developed co-receptor antagonists and fusion inhibitors. The paper by Ahn and Root suggests mathematical models for doing just that.

“You need to use these (drugs) with care,” Root said. “Drug resistance can emerge with either one, and when resistance emerges you lose that extra benefit of synergy.”



Sasha Mushegian (amushegian@asmb.org) is scientific communicator for the Journal of Biological Chemistry.

A rare blood disease can teach us about blood clotting

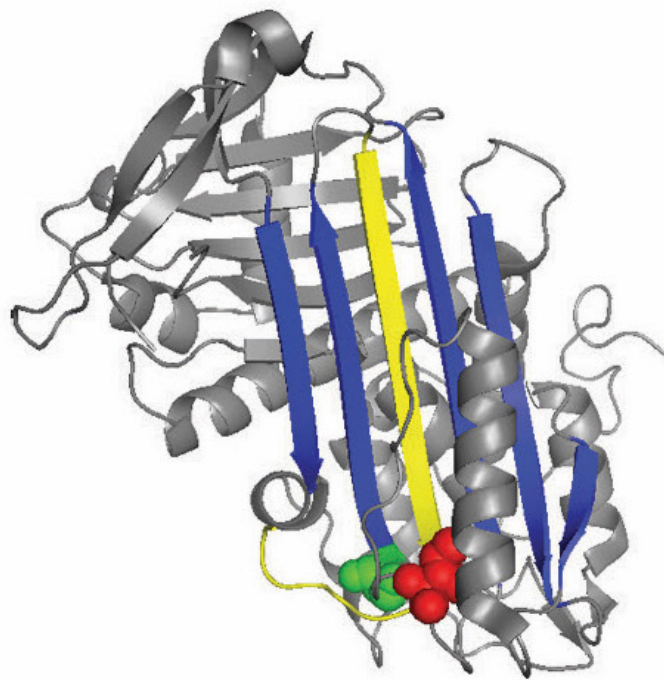
By Sasha Mushegian

When a person is injured, blood clotting is essential. However, once the danger has passed, it is equally essential to stop the clotting response in order to prevent thrombosis, or the obstruction of blood flow by clots. A protein called antithrombin is responsible for stopping coagulation, but about one in 2,000 people have a hereditary deficiency in antithrombin that puts them at much higher risk of life-threatening blood clots.

Researchers in Spain have analyzed the mutations in the antithrombin proteins of these patients and discovered that a section of the protein plays an unexpected role in its function. This insight into how antithrombin works could lead not only to treatments for patients with antithrombin deficiency, but also to better-designed drugs for other blood disorders. The research was published in the **Journal of Biological Chemistry**.

The Centro Regional de Hemodonacion and Hospital Universitario Morales Meseguer of the Universidad de Murcia in Spain is a reference center for the diagnosis of antithrombin deficiency. For more than 15 years, researchers at the laboratory have been receiving samples from patients with diverse mutations that affect how their antithrombin works.

Antithrombin normally inhibits



COURTESY OF IRENE MARTÍNEZ-MARTÍNEZ/UNIVERSIDAD DE MURCIA

A ribbon diagram of antithrombin highlights locations of functionally important mutations.

thrombin by inserting a loop-shaped region, called the reactive center loop, into the active site of the thrombin protein, preventing thrombin from catalyzing clot formation by distorting the shape of the thrombin's active site. Many antithrombin mutations that cause clotting diseases directly or indirectly affect the reactive center loop. However, biochemical studies led by Irene Martínez-Martínez discovered that mutations in a completely different part of the antithrombin also contributed to its dysfunction.

"We saw that we (had) mutants that were affecting the function of the protein even though they were very far from the main part of the protein that is in charge of the inhibition," Martínez-Martínez said. "People

thought that the anti-thrombin function was mainly focused on one domain of the protein. With this work, we have realized that is not true."

The researchers' analyses of the new mutations suggested that the domain of the antithrombin at the opposite end of the reactive center loop helps keep the thrombin trapped in its final, distorted form. When there were specific mutations in this region, the thrombin was more often able to return to its active form and degrade and release the antithrombin.

Martínez-Martínez hopes that understanding the importance of

this region of the antithrombin could lead to better drugs for preventing blood clotting by activating antithrombin or preventing bleeding by inhibiting it. She also emphasizes that the essential nature of this domain of the protein could not have been predicted from simply studying the sequences of healthy antithrombins.

"This work has been possible thanks to the characterization of mutations identified in patients," Martínez-Martínez said.



Sasha Mushegian (amushegian@asmb.org) is scientific communicator for the Journal of Biological Chemistry.

Charting the mitochondrial interactome

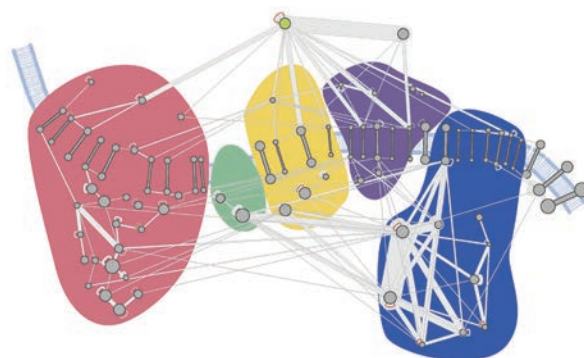
By *Saddiq Zahari*

As the powerhouses of the cell, mitochondria host various supramolecular protein complexes. Delineating the structural basis of these protein complexes is essential to improve our understanding of how mitochondria function and generate energy. In a study published in **Molecular & Cellular Proteomics**, Albert Heck and a team of investigators at Utrecht University in the Netherlands, in collaboration with the National Institutes of Health, aimed to discover the organization and interactions of proteins in the mitochondria of mouse hearts.

“We were most curious about the organization of protein molecules within mitochondria, because proteins are the molecular building blocks that make the mitochondrial energy factory work,” Heck said. “It was already known which proteins are involved in energy generation, but it is still not fully understood how these building blocks come together within intact mitochondria.”

To chart the organization of proteins within mitochondria, the researchers used a kind of molecular glue, or cross-linker, small enough to enter intact mitochondria and form stable links between any proteins within close proximity of one another. The mitochondria then were broken apart, and the proteins were digested and run on a mass spectrometer to identify especially the cross-linked peptides.

The researchers catalogued the largest set of mitochondrial protein interactions thus far, with 3,322 unique cross-links. This unprecedented depth was achieved using optimized mass spectrometry fragmentation schemes



A molecular map of the oxidative phosphorylation supercomplexes.

COURTESY OF PHILIP LÖSSL/UTRECHT UNIVERSITY.

and data analysis strategies. “In contrast to earlier work based on similar strategies, our approach is much more sensitive, allowing us to present a more complete molecular interaction map of all proteins within mitochondria,” Heck said.

This molecular interaction map, or interactome, revealed a dense and interconnected network of proteins. The researchers used the map to study the higher-order organization of proteins and the architecture of protein complexes in mitochondria. Among these are the oxidative phosphorylation supercomplexes, a series of five protein complexes cumulatively responsible for generating energy. In addition to confirming known interactions, the researchers found novel cross-links between individual complexes, leading them to suggest that all five complexes coexist in close proximity.

Going a step further to validate their map, the investigators soaked the mitochondria in a high-salt solution to disrupt the protein supercomplexes. They showed, using the same cross-linking technique, that these “dysfunctional” mitochondria displayed a very different protein interaction network. “These data show that protein organization and

mitochondria function are two sides of the same coin,” said co-author Philip Lössl. “We believe that our protein maps will help us understand the organization principles that allow mitochondria to work as molecular powerhouses.”

Chemical cross-linking and mass spectrometry allowed the researchers to probe native architecture of protein assemblies in mitochondria that are still intact and functioning. Most traditional biochemical methods for studying protein–protein interactions involve solubilizing the membrane using a detergent, which can introduce artifacts. “In such studies, the forceful breaking of the mitochondria can have dramatic effects on the protein organization and important information may be lost,” Lössl said. With the extensive comparative analyses and structural validation performed in their study, the researchers believe that the supercomplex interactions detected in intact mitochondria should be considered genuine.

The researchers believe their approach can be used to compare mitochondrial organization in diseases related to mitochondrial dysfunction, such as Parkinson’s and autism spectrum disorders. “Our approach can be used to elucidate how the molecular landscape of mitochondria is reprogrammed during disease development,” Heck said, “ultimately providing targets for future therapies.”



Saddiq Zahari (szahari@asmb.org) is the editor for manuscript integrity at *Molecular & Cellular Proteomics*.

From the journals

By *Sasha Mushagian, Laurel Oldach & Saddiq Zahari*

We offer a selection of recent papers on a variety of topics from the **Journal of Biological Chemistry**, the **Journal of Lipid Research** and **Molecular & Cellular Proteomics**.

'Minibrains' mimic childhood disease

Sandhoff disease is a lysosomal storage disease, one of a group of rare but severe disorders caused by accumulation of macromolecules that cannot be broken down. The genetic mutations that cause Sandhoff disease affect an enzyme that breaks down the sphingolipid GM2 ganglioside. When the enzyme cannot function, GM2 ganglioside accumulates in neurons, causing seizures and cognitive and motor decline that begin at about six months of age. Most patients die before age 5. Much of what is known about the course of the disease before symptoms appear is based on animal models. In the **Journal of Lipid Research**, researchers at the National Institute of Diabetes and Digestive and Kidney Diseases write about using patient-derived stem cells to grow simple miniaturized brains,

called cerebral organoids, which more closely model fetal brains affected by Sandhoff disease. The researchers, led by Richard Proia, compared the affected organoids with tissue from a deceased patient and with organoids with the disease mutation corrected by genome editing. As in the patient's brain tissue taken after death, Sandhoff disease organoids showed GM2 accumulation and overgrowth; they also had delays in gene expression. The research establishes a new model for studying lysosomal storage disorders and suggests that GM2 accumulation not only causes neurodegeneration but also may disrupt neurodevelopment prior to birth.

DOI: 10.1194/jlr.M081323

Colon cancer and glycosylation

Cancer can develop not just because of changes in the types and amounts of proteins present in a cell but also due to changes in how those proteins are modified — for example, by attachment of sugars (glycosylation). Kirstine Lavrsen and colleagues at the University of

Copenhagen discovered that GalNAc-transferase 6, known as GalNAc-T6, one of 20 polypeptides that initiate GalNAc-type O-glycosylation of proteins, was absent in healthy colon tissue but abundant in colon cancer tissue. Editing GalNAc-T6 out of a colon cancer cell line changed its growth form to one more closely resembling healthy colon tissue. Based on the glycosylation targets of GalNAc-T6 in the cancer cell lines, the authors hypothesized that expression of the enzyme disrupts epithelial development in the colon by affecting cell-cell adhesion. The study was published in the **Journal of Biological Chemistry**.

DOI: 10.1074/jbc.M117.812826

Comparing protein lives across species

Some proteins in the cell live longer than others. While it is established that the turnover rates of different proteins are highly variable, it is not known how conserved the turnover rates of the same proteins across species are. Researchers led by Sina Ghaemmaghami at the University of

Biochemical steps toward accessible vaccines

Glycoconjugate vaccines consist of a carrier protein attached to a capsular polysaccharide from the pathogen of interest. Production of glycoconjugate vaccines, for example against the bacterial meningitis agent *Neisseria meningitidis*, is challenging in resource-limited settings due to the biohazards and industrial-scale processes involved in purifying bacterial capsular polysaccharides. Timm Fiebig and colleagues at Hannover Medical School developed chemoenzymatic methods to produce *N. meningitidis* capsular polysaccharides from recombinant capsule polymerases. The streamlined protocols and optimized enzymes described in the study, published in the **Journal of Biological Chemistry**, were used to produce targeted carbohydrate antigens in two hours with standard laboratory equipment.

DOI: 10.1074/jbc.RA117.000488



Babies' skin inspires eczema lotion

Babies are soft and adorable and, as parents know, very delicate. Their skin must be moisturized frequently, because it is still slightly water-permeable. Newborns emerge from the womb covered with a waxy substance called the vernix, which protects their skin from drying. Recently, researchers have begun to realize that the vernix also helps babies adapt to life outside the womb by stimulating cells in the skin to make water-resistant lipid molecules. Scientists at Leiden University in the Netherlands, led by Joke Bouwstra, thought it might be possible to harness the vernix to treat adults with skin problems. They formulated a lotion based on lipids found in the vernix and tested it on the skin of healthy volunteers. In a recent paper in the **Journal of Lipid Research**, the researchers showed that disrupting the water barrier on healthy volunteers' arms using tape caused a change in the lipids that make up the barrier. With the new, shorter-chain lipids, more water could escape through the damaged skin. Applying the lotion sped up recovery by returning the lipid profile to



normal. The researchers found changes to the synthesis of lipids that were not included in the lotion, suggesting that the lotion could mimic the vernix by changing how the skin makes lipids. The researchers have not yet determined which ingredient drives the changes. The lotion, or one similar to it, might someday help treat itchy skin rashes like eczema that are driven by irritants crossing a broken skin barrier.

DOI: 10.1194/jlr.M079186

Rochester attempted to answer this question by systematically measuring the proteome turnover kinetics in primary fibroblasts from eight different rodent species, from mouse to naked mole rat. The researchers used stable isotope labeling and mass spectrometry to quantify the rate of incorporation of heavy amino acid isotopes in order to calculate protein degradation rates and half-lives. The researchers observed two striking trends. First, more closely related species have higher correlations of proteome turnover kinetics. Second, the higher the maximum lifespan of the species, the lower the global protein turnover rates. To explain the latter unexpected trend, the investigators hypothesized that long-lived species may have evolved to reduce the energetic demands of continuous protein turnover, which would lessen the generation of reactive oxygen species and the subsequent oxidative damage. This study was published in **Molecular & Cellular Proteomics**.

DOI: 10.1074/mcp.RA117.000574

RAGE in the brain after infection

Patients recovering from sepsis often have long-term damage to the central nervous system, including cognitive impairment and neurodegeneration. Juciano Gasparotto from the Universidade Federal do Rio Grande do Sul in Brazil and colleagues at the University of Texas examined the role of receptor for advanced glycation end products, or RAGE, a signaling protein involved in both inflammation and amyloid protein function, in brain dysfunction following sepsis in rats. They found that RAGE-mediated signaling increased in brains after sepsis and appeared to increase phosphorylation of Tau protein, a hallmark of neurodegeneration. Thus, RAGE may be a key factor in the progression of long-term brain disorders after sepsis. The study was published in the **Journal of Biological Chemistry**.

DOI: 10.1074/jbc.M117.786756

How to IsoTaG a T cell

Post-translational modifications of proteins are important for activation of T cells during an immune response. One of these modifications, O-GlcNAc, is known to be involved in the activation of T cells; however, its function on most glycoproteins remains unknown due to difficulty in characterizing and mapping O-GlcNAc sites. In a study published in **Molecular & Cellular Proteomics**, investigators at Harvard and Stanford universities led by Christina Woo employed a method called IsoTaG to catalogue and quantify the O-GlcNAc sites in resting and activated human T cells. IsoTaG works by metabolically labeling O-GlcNAc residues and tagging them via click chemistry with a probe to enable enrichment and subsequent identification using mass spectrometry. The investigators identified 2,219 O-GlcNAcylated peptides from 1,045 glycoproteins, the most comprehensive characterization of O-GlcNAc modification sites so far. Using gel shift assays, they further confirmed

the quantitative findings of a number of proteins that showed significant changes during T cell activation. The results provide a valuable resource for future studies aimed at a mechanistic understanding of the function of O-GlcNAc on specific proteins during T cell activation.

DOI: 10.1074/mcp.RA117.000261

How a kinase binds the membrane

Sphingosine-1-phosphate is a phospholipid linked to cancer and inflammatory diseases including multiple sclerosis. The phospholipid is generated when sphingosine kinase 1, called SK1 for short, translocates to the plasma membrane and phosphorylates sphingosine, but the membrane recruitment step is not well-understood. In a new paper in the **Journal of Lipid Research**, Michael Pulkoski-Gross and colleagues at Stony Brook University in New York identify a novel cationic patch near a known hydrophobic site on the enzyme, explaining its preference for anionic membrane lipids. Both the cationic and hydrophobic features, which form a single membrane-binding surface, are required for SK1 to bind to membranes and drive a cellular invasion phenotype that may be linked to cancer metastasis. The finding may offer a new target for drugs that disrupt the interface rather than the kinase active site.

DOI: 10.1194/jlr.M081307

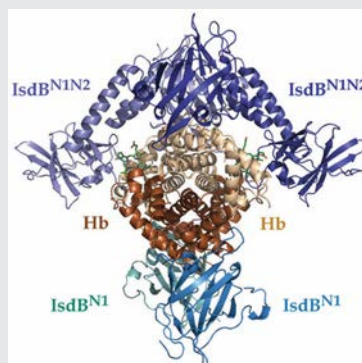
When collagen is lost

Dystrophic epidermolysis bullosa, or DEB, is an inherited skin fragility disorder characterized by skin blistering, abnormal wound healing and excessive scarring, which often leads to aggressive skin cancer. It is caused by biallelic loss-of-function mutations in the gene COL7A1, which codes for the extracellular protein collagen VII. How the loss of collagen VII in epithelial cells contributes to

How staph bacteria steal our iron

Staphylococcus aureus, a widespread opportunistic pathogen, is able to “steal” heme from the hemoglobin in human blood as its preferred iron source for growth. In the **Journal of Biological Chemistry**, Catherine F.M. Bowden and colleagues at the University of British Columbia published a crystal structure of IsdB, a critical membrane protein in the *S. aureus* iron-scavenging pathway. By crystallizing an intermediate state in which heme is being transferred between hemoglobin and IsdB, the authors were able to propose a model by which IsdB unfolds hemoglobin’s heme-binding pocket to transfer heme to the bacterium.

DOI: 10.1074/jbc.M117.806562



COURTESY OF THE UNIVERSITY OF BRITISH COLUMBIA

The crystal structure of the overall IsdB^{N1N2}-Hb complex. IsdB molecules are colored in shades of blue, alpha Hb molecules are beige and beta Hb molecules are dark orange. Heme moieties in the alpha Hb chains are shown as green sticks.

DEB disease progression remains ill-understood. In a study published in **Molecular & Cellular Proteomics**, researchers at the University of Freiburg led by Jorn Dengjel performed a global transcriptome and proteome profiling comparing primary DEB keratinocytes to normal human keratinocytes. The researchers found that loss of collagen VII not only affected the composition of the cellular microenvironment but also led to global changes in cell homeostasis on mRNA and on protein level. They showed that TGF-beta-dependent inflammatory and proteolytic processes were perturbed in DEB cells both in vitro and in vivo. The study provides a global yet detailed picture of dysregulated molecular consequences of collagen VII deficiency.

DOI: 10.1074/mcp.RA117.000437

Statins could help with wound healing in diabetes

Statins, drugs commonly used to lower cholesterol, have additional beneficial effects, including improv-

ing wound healing. Andrew P. Sawaya and colleagues at the University of Miami published a study in the **Journal of Biological Chemistry** examining the mechanism by which a topically applied statin improves healing of diabetic foot ulcers, a debilitating complication of diabetes. The mevastatin treatment induced expression of a long noncoding RNA that blocked c-Myc, a transcription factor associated with nonhealing wounds. The results suggest that statins could be repurposed as part of a diabetes management regimen.

DOI: 10.1074/jbc.M117.811240



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Saddiq Zahari (szahari@asbmb.org) is the editor for manuscript integrity at Molecular & Cellular Proteomics.

FEATURE

MYALGIC ENCEPHALOMYELITIS

Unknown cause. No cure. New hope.

By Lily Williams



Research on a condition that has befuddled scientists for eight decades receives fresh funding, and more than a million Americans, many confined to dark bedrooms, wait for answers

Lizzie Mooney is 12 years old. She is tall for her age with long blonde hair. She likes to wear Chicago Bears pajama bottoms and a hoodie. She's funny, making up games and teasing her siblings.

Lizzie excels in reading and math. She spends time crafting and watches science shows with her parents at night. But it's hard for her to make it downstairs to the TV room. She can't go to school. In fact, she might only leave her house once a week.

For the past three years, Lizzie has been sick.

The government estimates that as many as 1 million to 2.5 million Americans have the same disease as Lizzie: myalgic encephalomyelitis, or ME. Despite these numbers, you probably haven't heard of ME. What you might have heard of instead is chronic fatigue syndrome, or CFS. This euphemism for ME conjures an image of someone who just doesn't feel like getting out of bed.

For many ME patients, getting out of bed would be the highlight of their week or month. About 25 percent of patients are housebound, in rooms with the blinds drawn and noises muffled. Patients' bodies are sensitive to all kinds of stimulation; they suffer from gastrointestinal problems, inability to sleep, chronic pain and the disease's trademarks: cognitive dysfunction and post-exertional malaise, or PEM. Many patients describe PEM as a crash. Something as simple as a short walk can severely worsen a patient's symptoms, leaving them bedridden, unable to recover, for weeks or months. There's no telling how long the crash will last. Imagine having to decide between taking a shower and making yourself lunch. It could be your only activity for the week. Patients with ME have reported lower quality-of-life scores than patients with terminal cancer and heart disease.

Yet federal funding for ME research remains at a fraction of what



LILY WILLIAMS

Lizzie Mooney has myalgic encephalomyelitis. Her health has decreased over the past three years to the point where she can barely leave her house or even eat meals at the table with her family.

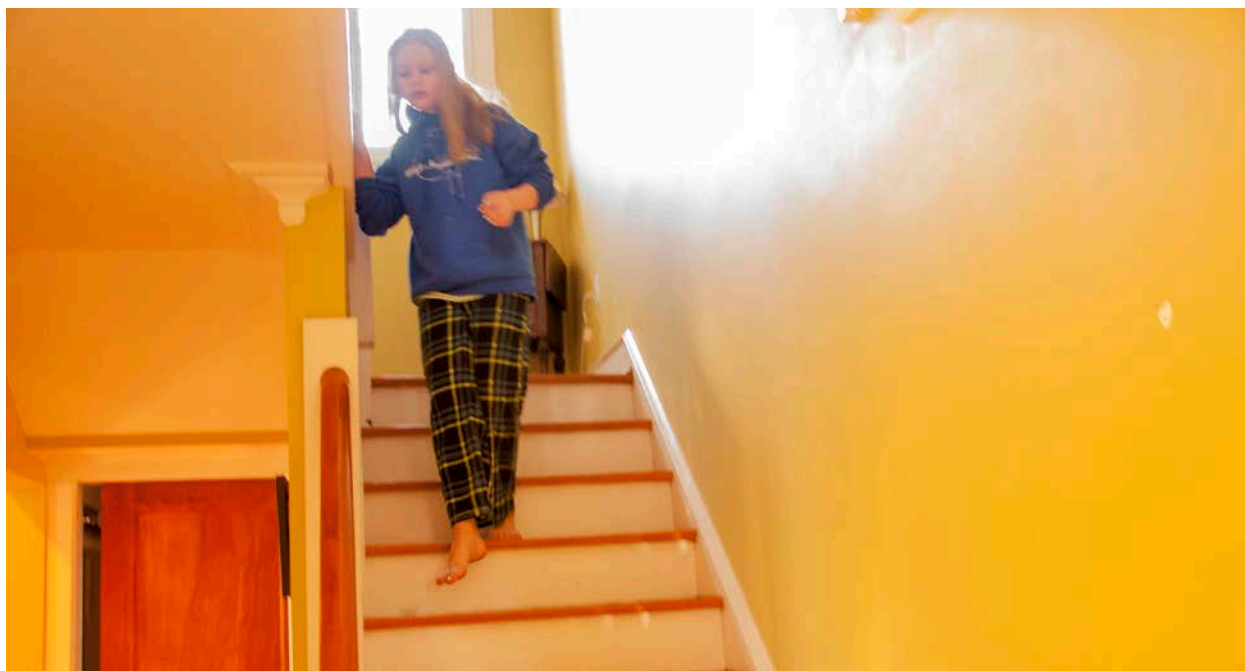
is spent on each of these. In fact, research funding for ME remains less than what the government spends on headaches or hay fever. Multiple sclerosis funding is 12 times the funding for ME, but an estimated 400,000 patients in the U.S. have MS, fewer than half the number who have ME even according to the most conservative estimate.

When Lizzie got sick, her mother, Amy Mooney, took her to their primary care physician, who diagnosed Lizzie with a mononucleosis-like illness. Lizzie spent the next four months in bed. Mooney took her to infectious disease doctors, rheumatologists, neurologists and gastroenterologists, but no one could make a diagnosis.

"The most painful moment was when an infectious disease doctor took me into the hallway," Amy Mooney said. "He said, 'Congratulations. Her blood work is completely normal. Nothing is wrong with her.' In the patient room, they were asking Lizzie if we have a healthy family life: Do we have abusive family situations?

LILY WILLIAMS

Left: Lizzie Mooney sits just outside the kitchen of her family's home in Illinois. Myalgic encephalomyelitis saps her energy, but she was still curious about the lady with the camera who hung out in her house for a week.



LILY WILLIAMS

Lizzie makes her way down the stairs for a morning tutoring session. Immediately after these sessions, and sometimes halfway through, she retreats to her dark bedroom, where she sometimes shakes in pain for hours.

Are we going through a divorce?

“The physician at the pediatric hospital wrote a note to the school saying it was safe for her to go to school,” Mooney said. “Get her back to school. Kids with cancer go to school.”

Lizzie hasn’t been to school since she was nine. She works at home with a private tutor when she can.

For decades, the search for pathogenic underpinnings for ME came up empty, and the disease was attributed to psychological causes. Stigma, skepticism and limited funding have fueled what advocates characterize as a vicious cycle that’s left a big hole in ME research. But advances in our understanding of the gut microbiome, cell-mediated immunity, mitochondrial dysfunction and dozens of other variables may open the door to new approaches to understanding and treating the disease.

While ME’s existence is no longer controversial, within the ME community, federal funding for ME research is. In recent years, the National Institutes of Health has spent between

\$5 million and \$8 million a year on ME research. In 2017, the NIH earmarked \$7 million for a first-time ME research collaboration of four centers. But some advocates say the government should be dedicating more than 50 times that amount.

Steps in the right direction?

Among those advocates is journalist Hillary Johnson, who says billions of dollars would be an appropriate figure.

Johnson spent almost a decade during the 1980s and 1990s researching the befuddling lack of interest in ME by government entities such as the Centers for Disease Control and Prevention and the NIH. She compiled her findings into a book, “Osler’s Web.”

In her book, Johnson chronicles the ’80s as a time when the CDC actively buried ME research and funding. She also casts Stephen Straus, a senior investigator in the Laboratory of Clinical Investigation at the NIH’s



COURTESY OF LINDSAY FRANCE/CORNELL UNIVERSITY

Professors Maureen Hanson and Andrew Grimson examine a cartridge containing DNA at Cornell University's high-throughput sequencer, used for ME/CFS research.

National Institute of Allergy and Infectious Diseases, or NIAID, from 1991 to 1999, as the chief villain. Straus published a number of studies on ME, some of which psychologized the disease. Straus went on to become the first director of the National Center for Complementary and Alternative Medicine. When he died in 2007, he was warmly remembered by his colleagues and was lauded by the NIH for what was then still called chronic fatigue research.

Joseph Breen is the current chief of the immunoregulation section in the Division of Allergy, Immunology and Transplantation at the NIAID. “Fortunately, perspectives about the disease have changed,” Breen said. “Researchers now have the tools to explore possible etiologies of ME/CFS and future studies should be revealing, especially those with larger cohorts, initiated early after disease onset and with longitudinal follow-up.”

The NIH announcement in September of four grants totaling more than \$7 million for fiscal year 2017, and continuing for the next five

years, signifies a step in official ME recognition. The new NIH grants will support three collaborative research centers and a data-management coordinating center for ME research. One grant is going to researchers at Cornell University led by principal investigator and American Society for Biochemistry and Molecular Biology member Maureen Hanson. A 2016 study in Hanson’s lab found that ME patients’ microbiomes have significantly lower microbial diversity and a higher incidence of pro-inflammatory species than in healthy controls.

Hanson’s work also branches into fatty acid and lipid metabolism. Her lab produced a 2017 paper on a study that found significant disturbances in numerous fatty acid and amino acid metabolism pathways. Levels of energy-related metabolites, such as ATP and ADP, were significantly lower in ME patients. Acetylcarnosine and taurine, important to muscle tissues, also were less abundant.

Hanson and her colleagues at Cornell will use the new NIH grant to study post-exertional malaise using



LILY WILLIAMS

Little is known about how ME affects Lizzie's bodily systems, but the disease prevents her from interacting with her peers or traveling with her family.

neuroimaging, metabolomics and single-cell RNA sequencing.

The researchers will take blood samples before and after the study participants ride stationary bicycles on two consecutive days.

To determine why ME patients usually can't replicate their initial performances, the researchers will search their blood samples for biomarkers.

Hanson's specific role in the project will be to study extracellular vesicles, which transport materials between cells. In healthy people, exercise induces release of these vesicles, which may mediate the beneficial effects of physical activity.

"This is going to be an important study to carry out — at the time we wrote our proposal, there were no published studies about extracellular vesicles in ME," Hanson said.

If patients can fall into severe PEM after even basic activities, how could Hanson's team find ME patients willing to do two days of exercise testing?

"Even though the exercise will likely induce a relapse, most of the patients don't report that they never

recover, otherwise we would never do it," Hanson said of the tests. "In fact, some of these patients ask to return to obtain needed disability documentation. It is right now the most objective way for someone to demonstrate their disability. A lot of them have a great deal of trouble convincing insurance companies or the social security agency that they are actually disabled."

U.S. medical record and insurance billing codes still classify ME as chronic fatigue — as a symptom rather than a disease. Even with a diagnosis, the insurance companies would not cover Lizzie's prescription medications or supplements, which cost the Mooneys upward of \$1,000 each month. One study estimates conservatively that ME patients pay \$8,675 per year for treatments, and the direct cost to the U.S. healthcare system for all patients could top \$7 billion.

Also under the NIH grant, researchers led by Dikoma Shungu at Weill Cornell Medical College will do one of the first neuroimaging tests

An eight-decade mystery

Key moments in myalgic encephalomyelitis history

- 1934:** The earliest case of ME is observed and formally recorded as an outbreak of poliomyelitis among staff at the Los Angeles County General Hospital.
- 1956:** The Lancet recommends the name “benign myalgic encephalomyelitis” to describe an outbreak in London; patients have neurological symptoms, myalgia and a number of other symptoms following an infection.
- 1969:** The World Health Organization classifies the disease for the first time as “benign myalgic encephalomyelitis,” listing it as a neurological disorder.
- 1970:** Two psychiatrists in the U.K. review reports of 15 outbreaks of patients with similar symptoms and deduce that the results are due to hysteria, as they see no physical signs of disease.
- 1978:** An international symposium held at the Royal Society of Medicine drops the term “benign,” as it is not commensurate with symptoms reported by patients.
- 1984:** Recorded instances are sporadic around the U.S. until the Los Angeles Times reports an outbreak on the shore of Lake Tahoe. Before the report, the Centers for Disease Control and Prevention sends two epidemiologists to investigate a severe flu-like illness with persistent symptoms. The epidemiologists return empty-handed just days later.
- 1988:** The CDC names the disease now known as ME a “syndrome of chronic fatigue.”
- 1989:** Two British studies attribute ME to a psychological disorder and a self-perpetuating lack of exercise, representing an investigative trend by psychological and psychiatric researchers.
- 1990:** The CDC receives more than 2,000 calls per month from the public requesting information about a flu that never goes away, according to journalist Hillary Johnson.
- 1991:** Researchers from the Wistar Institute in Philadelphia propose the retrovirus HTLV as a causative agent in a paper published in the Proceedings of the National Academy of Sciences. A blinded follow-up study by the CDC fails to replicate their results.
- 1991:** The National Institutes of Health’s Stephen Straus publishes studies stating ME is a psychological disease and shares his findings at scientific talks and hospital grand rounds around the world. He refuses to comply with Freedom of Information Act requests by reporter Johnson to see his research data. He refuses to release information on how funding for disease research is spent.
- 1996:** Hillary Johnson publishes her book, “Osler’s Web,” about a nine-year investigation into the ME/CFS research community. She alleges that research has been stifled and funds misused.
- 1996:** Congress requests that the General Accounting Office and the Department of Health and Human Services investigate claims made in “Osler’s Web.” Both investigations verify the book’s contents.
- 1999:** The ME/CFS Working Group is established at NIH.
- 2009:** An article published in Science describes a link between murine leukemia virus XMRV and ME/CFS. The study cannot be replicated and is retracted in 2011.
- 2011:** The PACE trial reports in The Lancet that cognitive-behavioral therapy and graded exercise therapy can benefit ME/CFS patients. Patients object to the methodology and results, organizing a petition and FOIA request for release of anonymized data.
- 2015:** David Tuller publishes a lengthy methodological critique of the PACE trial.
- 2016:** Independent analysis of data from the PACE trial by American biostatisticians in collaboration with patients fails to support the study’s conclusions.
- 2016:** Advocates and patients organize across the country under the banner of #MillionsMissing to demand increased funding. Advocates and patients who are well enough to attend speak about how the disease has affected them, hang photos of homebound patients and set out pairs of shoes to represent patients who are too sick to join. Demonstrations expand to 25 cities worldwide in May 2017.
- 2017:** The documentary film “Unrest” is released, chronicling the life of its producer Jennifer Brea, an ME patient.
- 2017:** The NIH announces it will award four grants totaling more than \$7 million to establish centers for ME research.
- 2018:** If high estimates of prevalence are accurate, up to 8 in every 1,000 Americans have ME. Hillary Johnson referred to ME in the 1980s and ’90s as an epidemic; she now calls the disease endemic.

Advocating for their lives

While researchers funded by the federal National Institutes of Health and the private Open Medicine Foundation embark on studies paid for by new grants, patients and advocates continue the push to make myalgic encephalomyelitis more visible.

They spent months organizing dozens of rallies around the world in 2016 and 2017, hoping to raise awareness about ME. Amy Mooney wielded a megaphone in downtown Chicago as part of that #MillionsMissing campaign, which laid out a pair of shoes for each ME sufferer too sick to attend in person.

The ground was a sea of shoes no longer worn by their homebound owners. Another rally is being organized for this May.

The 2017 documentary “Unrest” chronicles the life of Jennifer Brea, an ME patient who is also the film’s producer. It has won or been nominated for more than a dozen awards and recently aired on PBS. Rivka Solomon organized a screening of “Unrest” in November that attracted an audience of 363 — about 100 of whom were Boston healthcare professionals — and was the largest community screening of the film to date. This event earned a statement of support for ME patients from the entire Massachusetts congressional delegation.

“In just the past half-year the film, “Unrest,” is shifting the landscape for us,” Solomon said. “But before that, I would say not much changed for us for 30 years.” She would know; she has been sick for 28.

Solomon also found a champion in Sen. Ed Markey, a Massachusetts Democrat, who held a congressional briefing about ME on Capitol Hill in May 2017.

In Illinois, Amy Mooney worked to pass a proclamation in the state’s House of Representatives, affirming



COURTESY OF ME ACTION

Demonstrations to raise awareness about ME were held in cities around the world in May 2017. Shoes were used to symbolize the patients too ill to leave their beds and join the action. This photo was taken in Birmingham, England.

the state’s commitment to improving quality of care for ME patients. The House encouraged the media to cover the disease and Illinois universities to study ME, recommending that the NIH proportionately fund research and that the Centers for Disease Control and Prevention disseminate proper information. Mooney also hosted a screening of “Unrest” in the Chicago suburb where she lives.

“They’re not promising money or anything at this point,” Mooney said, “but we want universities to say, ‘Oh, this is real,’ and it to be something they respond to and investigate.” Mooney used to be able to work, but now her full-time job is advocating on behalf of her 12-year-old.

Journalist Hillary Johnson continues to report on her website, oslersweb.com.

“By and large, each time I do something for ME advocacy, I pay a price,” Solomon said. “I often end up much sicker than before, and I never know for how long I’ll be in the relapse. It’s pretty scary that advocating for your own life can cause such a detrimental setback in your health. I call this our fundamental conundrum.”

on ME patients experiencing PEM. The other two NIH research centers include a team at Columbia University that will look for microbial agents and evidence for immune responses to microbes and a team at the Jackson Laboratory in Farmington, Connecticut, that will study how the body’s immune system, microbiome and metabolism interact.

The Research Triangle Institute in North Carolina will house the data-management center, bringing data from the three centers into one database for standardization and providing tools for data processing and analytics.

“This is a very important step by the NIH,” Hanson said. “But we need more centers and individual studies relative to the burden of illness and



LILY WILLIAMS

Lizzie lies on a couch at home. Few ME/CFS patients return to full health, even in remission. Recovery is rare, and symptoms often persist for life.

number of people who are ill. The number of research dollars is really inadequate.”

Breen said he hopes that researchers will be encouraged by the NIH’s increased commitment to ME research and will continue to apply for more funds.

“The NIH ME/CFS working group functions as a team and we’re just starting the ME/CFS Collaborative Research Center program,” he said. “In the next five years, we hopefully will grow the community with a network of ME/CFS centers and small investigator-initiated research project grants.”

Millions missing

Rivka Solomon, 55, has had ME for 28 years.

When called for a phone interview, she didn’t answer, even though she had seemed eager to talk during email exchanges to schedule the interview. She called back 25 minutes late.

“Cognitively ... I remembered your call, but then I forgot,” she said. “See, this is what happens. On bad

days, my brain does not work well. And neither does my body. During a relapse it can take me 45 minutes to get up a set of stairs because I have to rest between each step.”

When Solomon was 21, she and her two roommates all got mononucleosis at the same time. Her friends got better. Solomon stayed sick for a year. Then she went through a seven-year period of what she calls a relative remission before falling ill again. She lives in Massachusetts and works from home as a writer and ME advocate, when she has energy.

Solomon represents most ME patients and advocates when she says that the amount of funding ME receives — even with new grants — is way too low.

Journalist Hillary Johnson compares ME to AIDS, for which funding increased drastically “once they realized it could be transmitted.” Many clinicians and researchers Johnson interviewed for “Osler’s Web” in the ’80s and ’90s believed ME had a contagious, infectious cause. In particular geographic locations around the



COURTESY OF RIVKA SOLOMON

Rivka Solomon has had ME for 28 years, and she is a vocal advocate for increased research funding. Here she speaks as the host of a screening of “Unrest,” a 2017 documentary about ME.

world, doctors began seeing clusters of patients with crippling fatigue and neurological problems.

Now, HIV/AIDS receives about \$3 billion in NIH funding each year for biomedical research on treatment, cure, prevention, and co-morbidities and co-infections. An estimated 1.1 million Americans have HIV. Adequate funding has led to HIV drug therapies that allow patients to lead semi-normal lives. ME is nowhere close to having a drug therapy, and its patients are crippled by bodies that cannot perform even minor tasks.

In 2018, still no cause — infectious or otherwise — has been found, even though thousands of papers have found biological abnormalities in ME patients.

Although new technologies and funding now exist, Solomon believes the real reason ME hasn't been elucidated is that the federal government has failed to fund disease research in proportion to ME's high burden of illness. This lack of funding hasn't incentivized new researchers to study ME and has propagated the idea that

ME is psychological, not physical, Solomon says. One highly visible study has helped promote the psychological theory of ME.

The controversial U.K. study, known as the PACE trial, was published in 2011, just seven years ago. The results of the \$8 million experiments were similar to ME studies from the 1980s. PACE researchers asserted that ME patients had a false illness belief, making them reticent to exercise or lead a normal, healthy life, perpetuating feelings of illness. Patients could recover from this false belief, researchers said, through graded exercise therapy and cognitive behavioral therapy to help them realize they were not, in fact, ill at all.

An eight-week exercise program worsened Lizzie Mooney to the point that she was bedridden. And Amy Mooney cites another young patient whose goal for her exercise program was to overcome crippling stomach pain and stop using a wheelchair. The exercise made her sicker.

The PACE trial came under fire in 2015. David Tuller, a senior fellow in



COURTESY OF LINDA TANNENBAUM

Linda Tannenbaum, CEO and president of Open Medicine Foundation, gives a presentation. Her daughter fell ill in 2006 with sudden-onset ME. Tannenbaum has since raised more than \$13 million for research.

public health and journalism at the University of California, Berkeley's School of Public Health, pointed out problems with the study that included author ties to disability insurance companies, a baseline scoring system that rated patients as simultaneously sick enough for the study yet healthy enough to be recovered, and a newsletter of patient testimonials released midway through the study that claimed benefits of the therapy.

"There could be 17 to 20 million of us or more around the world," Solomon said, "and yet they still think we're making this up."

Millions needed

Advocates such as Linda Tannenbaum are concerned that some qualified ME researchers aren't being funded by the NIH. In 2006, Tannenbaum's daughter fell ill with sudden-onset ME. Tannenbaum, who lives in Agoura Hills, California, had worked in clinical lab science for over 23 years and had her own medical laboratory, but she'd never

heard of ME. "We were told that she had something called chronic fatigue syndrome and there was nothing we could do for her other than pain management," she said.

Tannenbaum set out to find a cure. By 2012, she had formed Open Medicine Foundation. She has since raised more than \$13 million, much of it from the less-than-affluent patient community. An anonymous bitcoin philanthropist from the Pineapple Fund gave \$5 million to OMF early in February.

"This disease is real, as emphasized by the caliber of researchers working together on this," said Tannenbaum, who has helped to gather a global collaborative cohort of ME researchers.

OMF's 15-member scientific advisory board includes three Nobel laureates and six National Academy of Science members. Hanson, from Cornell, is on the advisory board but her ME research is not funded by OMF.

Stanford University researchers, already funded by OMF for ME work, applied for but did not receive any of the new NIH grants. So the

Myalgic encephalomyelitis facts

- Many ME patients report never recovering from a flu-like illness, a virus, a fever or some other infectious disease.
- Patients must have symptoms for six months to be diagnosed with ME.
- Up to three-quarters of patients spend a full year seeking a diagnosis; for 29 percent of patients, it takes more than five years.
- ME affects both children and adults; 75 percent of adult patients are female.
- While ME has been observed to persist following mononucleosis infection and has been referred to incorrectly as chronic mononucleosis, there is no evidence that ME is a form of mononucleosis.
- Children experience some different ME symptoms from adults, with more frequent reporting of abdominal pain and rashes.
- In one study, ME was the leading cause of prolonged sickness absence from school for children and staff in the U.K.
- There still is not one diagnostic test specific to ME or one agreed-upon research case definition.
- Two-day cardiopulmonary exercise tests, tilt table tests (where one lies on a table slowly tilted upward to measure how blood pressure and heart rate respond to gravity), and natural killer cell tests (which demonstrate reduced cytotoxicity in ME patients) have been used to indicate disease presence.
- Cognitive dysfunction is well-documented as neurological impairment in ME patients. One study performed PET scans on ME patients and found cognitive impairment in ME patients correlated with brain areas such as the amygdala, thalamus and midbrain.
- The majority of ME studies are done with a tiny cohort due to a lack of research funding.
- The 2015 Institute of Medicine Report analyzed over 9,000 studies on ME and is a good source for a comprehensive ME literature review.

OMF leaders decided to fund another ME/CFS research center at Stanford University, supplying a grant starting at \$1.2 million and continuing for as long as OMF can raise enough funds. More than 20 scientists will make up the OMF-funded center at Stanford, along with a growing working group of more than 30 researchers from top U.S. and international universities, who are not funded by OMF.

The Stanford ME center is led by ASBMB member Ronald W. Davis, director of OMF's scientific advisory board and director of the Stanford Genome Technology Center. Davis' son is severely ill with ME; he cannot leave his room, eat food or even speak. Davis has studied heavy metals and viruses in ME patients. He has coordinated a large -omics study on severely ill patients, a subgroup never studied before, analyzing genome sequences, proteins, metabolites, small RNA molecules and more. Severely ill patients are those who are homebound or bedbound, such as Davis' son, who lacks the energy even to look at people. Davis hopes that his current and future research will help establish a large and open

database where researchers can put new data to use in concert.

"People think they need to create their own big data and keep it to themselves, but this is expensive," Davis said. "The rate-limiting step from publishing and getting ME research done is funding. I wish we had a lot more money to give everyone to make this much faster."

The NIH was reluctant to fund his initial ME observational experiments, Davis said. But observation is needed before any hypotheses and future research directions can be established, he said, especially when so little observation has been done on ME. He hopes data he soon will publish will allow specialized researchers to study ME in their own fields, without the need to do costly and lengthy background research beforehand.

Jose Montoya, an ME physician and professor of medicine at Stanford, published a 2017 paper in the Proceedings of the National Academy of Sciences that analyzed an unusually high number of ME patients and controls as compared to typical ME studies: Serum from 192 patients and 392 healthy controls was analyzed for



LILY WILLIAMS

Once two grades above her age in math and reading levels, Lizzie can now complete only 45 minutes of private home tutoring per day due to the severity of her illness. She is pictured with her tutor, Judith Meyer.

cytokine differences. Immune cells secrete cytokines, or cell-signaling molecules that play a role in inflammation. The signature flu-like symptoms and muscle pain led researchers to believe ME could be an inflammatory disorder.

Montoya and his team found that two cytokines were significantly different in ME patients and healthy controls. TGF-beta, found commonly in the monocytes and macrophages of the immune system as well as intestinal epithelial cells, is viewed as an anti-inflammatory cytokine. TGF-beta was higher in ME patients. Resistin, produced primarily by peripheral blood mononuclear cells, has been shown to increase transcription of pro-inflammatory genes and was lower in severe ME patients but higher in moderate ME patients. In total, Montoya's study found 17 cytokines, 13 of which are pro-inflammatory, that had an upward linear trend when put into context of ME severity. In other words, these cytokines' levels were higher in patients who had more

severe symptoms. The study also cites resistin and another adipokine, leptin, as cytokines secreted by adipose tissue that could be important. Leptin has been found to correlate with fatigue severity, and levels are higher in females. Adipokines contribute to crosstalk between the central nervous system and adipose tissue and could contribute to neuroinflammation and cognitive dysfunction in ME patients. In mice, leptin has demonstrated a recruitment of neutrophils to the brain during sepsis, prompted by administration of lipopolysaccharide.

The new OMF-funded center at Stanford will have three main projects. One will explore the immunological basis of ME through analysis of T cells, the human immune cells that kill their infected own. ME could affect T-cell replication and behavior. This study also will investigate the way personal variations in human leukocyte antigen genes regulate immunity in ME patients. These genes code for the major histocompatibility complex, the cell-surface proteins that



LILY WILLIAMS

If you ask Lizzie what she would do if she weren't sick, she says any number of things, starting with returning to school. Here, she and her father, Don Mooney, share a laugh while studying a map on her bedroom wall.

regulate our immune systems.

The second project will expand OMF's current big-data genome study to patients of varying severities and their families, performing clinical and molecular tests that could provide insight into genetic factors and molecular biomarkers for ME. Right now, it has data from 20 ME patients. The third project will work toward a diagnostic that can distinguish ME blood samples from healthy ones using new technology developed at Stanford. The technology also will be used to test Food and Drug Administration–approved drugs considered for clinical trials on ME patients.

“We need researchers to share their results openly and collaborate and look at ME/CFS through many body systems, genetics, infectious disease, immunology, metabolomics, microbiome and more,” Tannenbaum said. “The urgent need is not only research but awareness in the medical community and teaching new doctors in medical schools to be able to identify and acknowledge this.”

Far from treatment

Mary Dimmock, a 31-year veteran of the pharmaceutical industry, now retired, cites a significant roadblock to a treatment for ME: “Pharma has stayed away from this disease.”

During her time working for pharmaceutical companies, Dimmock did everything from drug metabolism studies to clinical data management to business process improvement initiatives. She saw the considerations that go into pharmaceutical companies' research funding decisions. Before they even will think about investing in a particular drug or treatment, there must be potential patients for clinical trials, Dimmock says. To get a patient into a clinical trial, that patient must be diagnosed. But with ME, according to a 2015 Institute of Medicine Report, up to 91 percent of patients remain undiagnosed.

ME has numbers to support a huge market. “You'd think this would be a slam dunk for pharma,” Dimmock said. “But we don't have agreement on a research definition, don't have doc-

tors treating patients and don't have enough academic researchers."

As someone who has seen what it takes to go from research to a marketable clinical treatment, Dimmock said she thinks the NIH has taken critical steps to attract more researchers and to promote collaboration. She also is encouraged by the work of the different centers, particularly Hanson's focus on understanding the disease pathology after exercise studies.

Dimmock's son has ME. She paid \$65,000 out of pocket in the first year after his diagnosis. He eventually was able to use the two-day exercise study as a way to demonstrate disability.

But Dimmock, Solomon, Mooney and Johnson all worry that the NIH lacks any urgency, either in resolving the stigma of ME or in really ramping up funding. "Because they are taking one or two baby steps at a time, it will take more than a decade to get there," Dimmock said.

Breen at NIH is aware that the agency's decision-making process can take time and might seem a bit obscure. Every research application to the NIH must undergo a rigorous review by experts in the field, both by a scientific review group and by an institute's advisory council or board. It typically takes about six months from the time an investigator submits an application, Breen said.

"The hard part for patients is that the timeline from research to a diagnostic test or therapeutic is never acceptable because there are people hurting now," he said. "It looks very inefficient, but we have an open scope. We need to do more foundational studies for future diagnostics and therapeutics."

Stanford's Davis said understanding and urgency of funding for the disease are low because we just don't see ME patients. They're in their beds or at least at home. Trips to the hospital make them worse, so they don't go. And although most patients aren't dying from ME, they aren't really living either.

"I understand the NIH's predicament but I want them to take responsibility for this," Davis said. "I know it's hard. There are a lot of diseases out there and they're probably all underfunded. But the NIH needs to serve the people of this country and that's where the money is coming from, the people."

Johnson is less forgiving. She remembers ME as a public health crisis. "In 10 years, a majority of people who came down with ME in the 1980s are likely to be dead. The shared memory of an epidemic beginning in the 1980s will be forgotten, and the government may never have to address its failures in the '80s, '90s and this century."

Strides, albeit small, are being made by researchers, who now recognize the role of the microbiome, immune and nervous systems, and metabolism. The number of ME researchers is growing, even with limited funding.

With at least 17 million to 20 million estimated patients around the globe, a researcher entering the field now could "make their mark with minimal effort," Solomon said. Dimmock would agree. "While I appreciate the risk from a pharmaceutical perspective, the time is ripe for academics to get interested in ME," she said. "It is a fascinating biological mystery."

"Here is your chance," Davis tells his students at Stanford.

February marked year three of Lizzie's illness. She hopes ME's mysteries are unraveled soon, so she can trade her Chicago Bears pajamas for jeans and sneakers, leave her bedroom, and go back to school.



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From a Bavarian baccalaureate to bacterial bleach

The new Journal of Biological Chemistry associate editor investigates heat-shock proteins and their relation to bacterial defense mechanisms against hypochlorous acid

By John Arnst

Bleach, generally speaking, is bad news for anything it comes in contact with, whether it's grime, blue jeans or bacteria waging war against your intestinal lining. At the University of Michigan, Ursula Jakob's lab is investigating how to make the bacteria bent on colonizing your gut more sensitive to the bleach, or hypochlorous acid, that your white blood cells deploy against them. This form of bleach differs only slightly from the sodium hypochlorite in cleaning solutions that can strip dyes and burn clumsy hands.

Jakob, who was born in Germany, received her bachelor's degree in 1991 and her Ph.D. in 1995, both from the University of Regensburg in Bavaria. Throughout her college career, the lab she was in studied the heat-shock protein Hsp90 and its effect on protein folding as a molecular chaperone. Her current lab's work involves the heat-shock protein Hsp33, a molecular chaperone that helps protect bacteria against the dangerous effects of bleach.

With a fellowship from the German government, Jakob did her postdoctoral research under James

Bardwell at the University of Michigan, where she is now a professor in the molecular, cellular and developmental biology department and the university's medical school. In 2014, she was elected to membership in the Bavarian Academy of Sciences and Humanities, one of the oldest learned societies in Germany. Since the academy's inception in 1759, its members have included Johann Wolfgang von Goethe, Max Planck, Werner Heisenberg and Albert Einstein.

Jakob joined the ranks of associate editors at the Journal of Biological Chemistry in September. She spoke with John Arnst, ASBMB Today's science writer, about her lab's work exploring molecular chaperones and mechanisms of bleach resistance in bacterial and human cells. The interview has been edited for clarity and length.

What is your group focused on?

One of our most interesting projects involves bleach, which is not only a very effective antimicrobial in household settings but has long been

From the very beginning of my scientific career, we always tried to be on the forefront. From the very beginning, I learned that science is discovering something new.

known to be used in a physiological context — our white blood cells produce bleach, hypochlorous acid, to defend our bodies against infectious disease. We were wondering how bacteria defend themselves against bleach, and in 2008, we found that they produce a protein that gets specially activated in response to bleach and then protects the bacteria from it.

We use bleach in our host defense, and it works well most of the time to kill invading bacteria. However, some of the bacteria do survive and can cause persistent infections, and we still don't know how they manage this feat. Moreover, under extreme conditions, like chronic inflammation in patients that suffer from cystic fibrosis or persistent infections, we see a lot of tissue damage. This is attributed to the excess bleach that's being produced by our white blood cells.

And so the question then was, "What does bleach do, and how do organisms defend themselves against it?" The idea was that if we knew that, we could possibly make bacteria more sensitive to bleach. This might help with boosting the host defense and allowing the host to be more able to deal with bacterial infections while at the same time potentially mitigating the damage in the host. What we figured out is that bleach works as a really potent protein-denaturing agent, essentially boiling bacterial proteins at room temperature. In their defense, bacteria activate a chaperone, Hsp33, which protects the proteins against bleach-induced protein unfolding and aggregation and helps bacteria survive.

In the last few years, we took another approach and asked what

other defense systems bacteria have to deal with bleach. We found that bacteria, in response to bleach treatment, convert a large amount of their ATP into a long chain of phosphates, polyphosphate. This molecule was the pet project of the late Arthur Kornberg in the last 15 years of his life; he was extremely fascinated by this prebiotic molecule and contributed a huge amount to the literature, including the fact that polyphosphate is present in every organism that had been studied so far.

In bacteria, polyphosphate plays a very important part in virulence. So this fits exactly with what we found: When we delete the gene that allows bacteria to make polyphosphate, they become super-sensitive to bleach. They're no longer virulent, they no longer make biofilms as effectively as wild-type bacteria and they make many fewer antibiotic-resistant cells. So, we thought, this is really cool. If polyphosphate was indeed such an essential product in bacteria that they make it specifically under conditions of infections, then targeting that synthesis should make them much more sensitive to the host defense mechanisms.

We recently found a drug already on the market called mesalamine, which is widely used to treat colitis. We published a paper in *Nature Microbiology* a few months back, where we found that we can now target polyphosphate synthesis in bacteria in the intestines with mesalamine. It has basically the same effect as if you delete the enzyme from within the bacteria, making them sensitive to hypochlorous acid. Our hope now is that we can use this drug maybe



COURTESY OF THE UNIVERSITY OF MICHIGAN

In 2000, Jakob received the Burroughs Wellcome Fund Career Award in the Biomedical Sciences, which helped jumpstart her career as an assistant professor at the University of Michigan.



COURTESY OF URSULA JAKOB

Jakob often rides Agave, a Spanish horse she leases at Rosehill Dressage in Northville, Michigan.

alone or in combination with other antibiotics to treat particular persistent infections.

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

I was raised in a family that was very interested in biology and the environment. So it was not surprising to anybody when I decided to study biology. During my second year as a biology undergrad, I got hired in the lab where I ended up doing both my master's thesis and Ph.D. thesis. We studied refolding of antibody fragments. Within about half a year or so after I started working there, my P.I. came to me and said, "I just saw this paper about this heat-shock protein, GroEL, being able to support refolding of a protein. Maybe we should put this into our antibody solution and see whether this helps in our refolding experiment."

The paper that he found in our library was really the landmark paper that started the chaperone era. So I was there when the chaperone field was born, and that was absolutely fascinating to me, to be part of such a new discovery. We were really in this first wave of chaperone research, which involved Hsp90. My first paper, still as an undergraduate, was a last-author Nature paper.

Everything we did was new. We developed the assays ... it was just wonderful; we were in this full discovery mode. From the very beginning of my scientific career, we always tried to be on the forefront. From the very beginning, I learned that science is discovering something new.

When did you first become involved with JBC?

I was trained in a biophysics and physical biochemistry department,

and JBC was always our go-to journal. I had six JBC papers during my graduate career. I've been a reviewer for years, and then I was asked whether I would like to take on an associate editor position at JBC.

What do you do outside the lab? Do you have any advice for balancing life outside of the lab with life inside the lab?

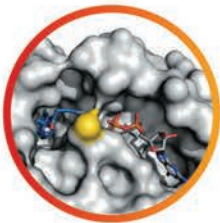
I ride horses and I play tennis. I love riding horses because riding is a little bit like science — you never fully know where they will take you. And I love tennis because it's competitive, and, you know, I'm slightly competitive, so I like that aspect. What I tell young assistant professors, in advisory roles, is that they absolutely need a balance. I had my first child three days after I started my lab, so when I see my daughter, who is now 16, I know exactly how long I've had my lab. And my son was born during my third-year review process.

I think women in general, and this is very generally speaking, have a harder time with this balance between career and family, because they have a tendency to constantly feel guilty. We feel guilty about not being in the lab enough, about not having enough time for our children and of course not spending enough time with our partners, and the easiest thing to let go of is yourself and your friends. So I encourage young assistant professors to get as much help around the house as needed so you don't have to waste the little time that you have with duties that you do not enjoy.



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

2018 ASBMB Special Symposia Series



Frontiers in RAS Pathobiology and Drug Discovery

Sept. 13–16, Stratton, Vt.



Science Outreach: Models, Methods and Measures

Oct. 3–6, New York, N.Y.



Transcriptional Regulation by Chromatin and RNA Polymerase II

Oct. 4–7, Snowbird, Utah



The Many Faces of Kinases and Pseudokinases

Dec. 9–12, San Diego, Calif.

Reminder: ASBMB members save on meeting registration.



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Journal names winners of 2018 Tabor awards

Young investigators to give short talks at ASBMB annual meeting about JBC papers that won them recognition

By Laurel Oldach

The American Society for Biochemistry and Molecular Biology annual meeting in San Diego in April will feature five special Spotlight Talks by the winners of the Journal of Biological Chemistry/Herbert Tabor Young Investigator Awards.

“These are young, promising scientists who are going to present really exciting work and become the plenary lecturers of tomorrow,” said George DeMartino of the University of Texas Southwestern Medical Center, the JBC associate editor who chaired the award selection committee. “This is a chance to see them early on.”

The awards, founded in 2011, honor longtime JBC Editor-in-Chief (now Co-Editor) Herbert Tabor. Once given by associate editors for top-notch conference presentations, the awards as of this year honor first authors of outstanding articles published in JBC. Associate editors found they were reviewing strong research from outside of the specialized areas represented at conferences they attended; the new process expands eligibility to more young researchers.

In an editorial in JBC, Editor-in-Chief Lila Gierasch of the University of Massachusetts Amherst emphasized the editors’ desire “to celebrate and recognize ... the deep talent pool of early investigators who publish their work in the journal.”

To choose the 2018 honorees, a committee of six associate editors collected nominations of notable



COURTESY OF SAHAR FOROUTANNEJAD

Maria Fe Lanfranco provided this drawing by a colleague, which illustrates their prize-winning paper. (see p. 39)

papers published in 2017 from fellow editors and ASBMB members. They assessed each article using comments from reviewers and researchers in the field along with quantitative measures of impact, narrowing from a list of hundreds of nominations to five exceptional articles.

These articles span a range of topics: the kinetics and complex synergy of HIV entry inhibitor molecules, protein structure for bacterial adhesion, a negative feedback loop in iron homeostasis, an optical approach to visualize neuropathology as it forms, and allosteric and cooperativity in a transcription factor responsive to cAMP. Diverse in subject matter, the articles share a novel technical or conceptual approach to a standing problem that impressed the editors.

The new process highlights this work on a broader stage than was offered by the small, focused meetings at which the awards were given in previous years. “I imagine that these talks should be a bit different” than they might have been at a smaller conference, DeMartino said. Larger conferences require presenters to give more context for their work and expose them to questions from diverse disciplines, he explained.

The interdisciplinary audience also brings more attention to the work and more opportunities to collaborate. Presenters at previous ASBMB annual meetings have struck up collaborations with colleagues working in related fields, heard about new assays and approaches, and garnered attention from potential employers in industry and academia.

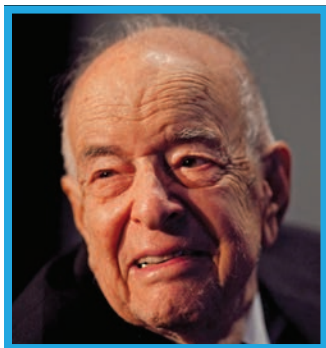
DeMartino can speak to the value of presenting early for a young investigator. “I gave my first scientific talk in Chicago, at an ASBMB meeting,” he said. “It was a great experience; in fact, I made the contact at that meeting that got me my current job — which was my first job.”



Laurel Oldach (loldach@asbmb.org) is a communications intern at the ASBMB. She recently finished her Ph.D. in pharmacology at Johns Hopkins University. These stories about the five 2018

Tabor Award winners are her first assignment for ASBMB Today.

Who is Herbert Tabor?



Now 99 years old, Herbert Tabor is a senior investigator at the National Institute of Diabetes and Digestive and Kidney Diseases. From 1971 to 2010, he served as editor-in-chief for the *Journal of Biological Chemistry*, overseeing its expansion from 1,000 to 4,500 published articles per year and its transition to online publication.

Over the years, he also has authored 31 articles published in JBC, including nine co-authored with his wife, the late Celia White Tabor.

The JBC/Herbert Tabor Young Investigator Awards were conceived to honor him, said Associate Editor George DeMartino of the University of Texas Southwestern Medical Center. “And there’s probably nothing that would honor him more than having good papers published in JBC.”

Here’s a brief look at Tabor’s life and accomplishments:

- 1905:** The *Journal of Biological Chemistry* is founded.
- 1918:** Herbert Tabor is born in New York City.
- 1937:** Tabor graduates from Harvard College.
- 1940:** Tabor meets Celia White on a streetcar in Boston.
- 1941:** Tabor graduates with an M.D. from Harvard Medical School.
- 1942:** Tabor starts an internship at Yale New Haven Hospital, working concurrently in the lab of John Peters.
- 1943:** Tabor joins the war effort as medical officer on a Coast Guard cutter escorting Atlantic convoys.
- 1943:** Tabor is transferred to the National Institutes of Health, joining Sanford Rosenthal’s team to study treatment for burns and traumatic shock.
- 1943:** Tabor’s first article is published in JBC: Tabor and Hastings, “The ionization constant of secondary magnesium phosphate.”
- 1946:** Herb Tabor and Celia White marry.
- 1949:** The Tabors move into commissioned officer housing on the NIH campus, where they raise their children and where Herb Tabor still lives today.
- 1952:** Celia White Tabor joins the Rosenthal lab, starting the Tabors’ shared research.
- 1961:** Tabor joins the editorial board of JBC.
- 1971:** Tabor becomes editor-in-chief of JBC.
- 1975:** The Tabors’ first joint article is published in JBC: H. Tabor and C.W. Tabor, “Isolation, characterization and turnover of glutathionylspermidine from *Escherichia coli*.”
- 1995:** JBC becomes the first scientific journal to be published online.
- 2010:** Tabor steps down as editor-in-chief, becomes co-editor and continues his bench research.
- 2011:** JBC Editor-in-Chief Marty Fedor announces establishment of the JBC/Herbert Tabor Young Investigator Awards to be presented by journal associate editors to presenters at specialized scientific meetings.
- 2013:** Published in JBC 70 years after Tabor’s first JBC article: Chattopadhyay and Tabor, “Polyamines are critical for the induction of the glutamate decarboxylase dependent acid resistance system in *E. coli*.”
- 2017:** JBC Editor-in-Chief Lila Gierasch announces the Tabor awards will honor work on top-notch papers published by JBC.

Researcher recognized for studies of HIV drug synergy

Koree Ahn, a 3-D printing enthusiast, once brought two competing proposed structures of the HIV 1 envelope protein with him to a class discussion. “I was able to present these physical structures so that people could hold them and physically observe” the protein’s features, he recalled.

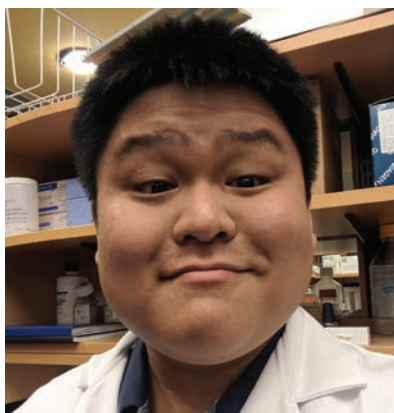
The envelope protein allows the HIV membrane to fuse with a human cell’s. Ahn published a *Journal of Biological Chemistry* paper on drugs that block viral entry by inhibiting the envelope protein’s interaction with surface receptors. The work earned Ahn a 2018 JBC/Herbert Tabor Young Investigator Award.

Ahn laid a foundation for this kinetic and pharmacological research as a freshman at Hamline University in St. Paul, Minnesota. “What I originally thought would be a semester-long résumé builder instead became the four-year-long highlight of my undergraduate education,” Ahn said.

He worked with chemist Olaf Runquist to develop mathematical models of cell differentiation based on colon cancer samples from collaborator Bruce Boman, a professor at the University of Delaware. Over summers, he learned wet lab techniques in the Boman lab in Newark. He went on to graduate school at Thomas Jefferson University in Philadelphia.

“As a person who was from the Midwest, I fell in love with the diversity and the vibrancy of Philadelphia ... and I was really interested in a lot of the research going on there,” he said of his decision to join the university’s program in biochemistry and molecular pharmacology.

Ahn’s doctoral project in Michael Root’s lab at Thomas Jefferson built on models of HIV entry established by colleagues. “All of the groundwork



COURTESY OF KOREE AHN

Koree Ahn studied the interaction between coreceptor antagonists and fusion inhibitors in HIV infection.

was really laid by previous members of the Root lab who had developed this super-quantitative model for how (HIV entry) inhibition works,” he said. He used the lab’s model and a library of entry inhibitors to untangle whether two classes of drugs exhibit synergy when used in combination. Reports in the literature had conflicted; as it turned out, so did results in the Root lab.

Ahn observed synergy that others in the lab had not, “and that led us to different questions, like, ‘What type of fusion inhibitors did you use? Did they bind very tightly to the fusion inhibitor binding site, or very loosely?’” Understanding these technical differences helped guide the team to the cohesive understanding of the factors permitting synergy that they published in *JBC*.

Ahn recently packed up his 3-D printer and moved to Chicago to continue his HIV research.

He now works as a postdoctoral fellow in the lab of Thomas Hope at Northwestern, studying interactions between HIV and molecules present in mucous membranes.

Complex interactions between HIV drugs

HIV enters human cells using an envelope protein that binds to two cell-surface receptors and then pulls the viral membrane near the cell membrane. Two drug classes block this process: coreceptor antagonists block interaction between the envelope protein and one receptor, and fusion inhibitors block membrane juxtaposition.

Because these two drugs act on steps in the same process, they might behave synergistically. Synergy between drugs occurs when the result of treatment with both together is more dramatic than would be expected by adding the two effects. But in fact, results of experiments testing for synergy were variable and confusing.

Koree Ahn and colleagues at Thomas Jefferson University in Philadelphia used a variety of molecules with slight differences to model a complex mechanism for interaction of the two drug classes. Ahn concluded that synergy between the drug classes is possible but dependent on two unexpected factors: the location and strength of fusion inhibitor binding to the envelope protein and the level of coreceptor expressed on the target cell.

The work, published in *JBC* in July, has clinical implications: It suggests that combining the two drug classes may not be an effective treatment strategy. For more on this work, see a companion article in *JBC* by Gregory Melikian of Emory University.

Neuropharmacologist selected for engineering novel mutant dimers

Maria Fe Lanfranco's scientific career has crisscrossed the Western Hemisphere.

Born in Lima, Peru, she moved to the United States after college. "That was a big decision," she said, "but ... if I really wanted to pursue a career in science, I needed to do a Ph.D. outside Peru." In the years since then, she has lived and worked all over the United States.

Lanfranco won a 2018 Journal of Biological Chemistry/Herbert Tabor Young Investigator Award for her work on allostery in an *E. coli* transcription factor carried out as a postdoc at Georgetown University.

With colleagues, she developed an approach to understand how communication across ligand binding sites affects this protein. She published the work in *JBC* in February 2017.

She credits her high school biology teacher with making it "almost a no-brainer" to study science in college.

"I've always been interested in identifying targets for the treatment of pathological disorders," she said. Curiosity about the neuroscience of addiction drew Lanfranco to graduate work in the laboratory of Kathryn Cunningham at the University of Texas Medical Branch in Galveston, where she studied a serotonin receptor involved in cocaine addiction.

She followed her passion for understanding disease to a postdoctoral position studying signaling ethanol addiction with Dorit Ron at the University of California, San Francisco.

She lived in Berkeley and took a yoga teacher training course. "I started doing yoga because I was feeling stressed out — like every student in graduate school," she said with a chuckle. A compelling teacher in Texas had gotten her more involved. In Berkeley, where she passed a yoga



COURTESY OF MARIA FE LANFRANCO

Maria Fe Lanfranco studied allostery in a bacterial transcription factor.

studio every few blocks, Lanfranco later began to teach classes herself.

With her husband, biophysicist Rodrigo Maillard, Lanfranco moved to Washington, D.C., to start his lab at Georgetown. The pair, both originally from Lima, had met in college and married as postdocs.

When Maillard started his lab, he pitched an allostery project to Lanfranco. She was interested in the neuropharmacology angle. To her, allosteric modulators are "a very provocative kind of drug, because it's more interesting to modulate the activity of a receptor, rather than turning it on or off."

After years of working in parallel, Lanfranco said, collaborating with Maillard works because "we complement each other a lot ... but we kind of set some rules in which we wouldn't talk about work at home, because then it would be too much."

Reflecting on her peripatetic pursuit of science, Lanfranco projects a yogic satisfaction: "All of those cities (Lima, Galveston, Berkeley and Washington) have a lot to offer ... each one of them, at that particular time in my life, was the perfect place to be."

Fusing monomers to understand allostery

Maria Fe Lanfranco and colleagues investigated how two identical subunits of an allosterically activated protein communicate about ligand binding.

The cyclic AMP receptor protein, or CRP, is a transcription factor activated through allostery, when binding of a ligand promotes a change in the protein's characteristics at a distant site. CRP has negligible binding to DNA at first, but in complex with the small molecule cAMP, it binds DNA more strongly.

Like many allosterically activated proteins, CRP has two identical subunits. When one binds to cAMP, the other is more likely also to bind, a phenomenon known as cooperativity.

The team studied the intermediate stage, after one cAMP had bound but before the second. It was difficult to isolate this intermediate because it is short-lived and mutating the purified protein to disrupt cAMP binding results in dimers with the mutation in both subunits.

The researchers found a way to mutate just one subunit by cloning a linked pair of monomers. By adding asymmetric cAMP binding mutations to this molecule, they could capture the transient single-cAMP bound dimer more effectively. Binding of a single cAMP molecule was enough to open the DNA binding domain of the transcription factor, thus forming a stable DNA-protein complex.

Chemist peers into neurons to study seeding of alpha-synuclein

Most home bakers get a brown shine on their pretzels by dipping the dough into a boiling bath of water and baking soda. But for Richard J. Karpowicz Jr., it's all about the base.

"I'm a chemist, so I make traditional German lye pretzels with one molar sodium hydroxide," he said. "I wear gloves, and I kick my girlfriend out of the kitchen."

Karpowicz, a postdoctoral researcher at the University of Pennsylvania, received a 2018 Journal of Biological Chemistry/Herbert Tabor Young Investigator Award for other pursuits in chemistry. With his colleagues, Karpowicz developed a new approach to image aggregation and transmission of a protein associated with Parkinson's disease, work that appeared in JBC last year.

Raised in Lawrenceville, New Jersey, Karpowicz went to the University of Delaware as an undergraduate intending to major in chemical engineering. His father, Richard J. Karpowicz Sr., had earned a Ph.D. in chemistry at the University of Delaware and introduced him to scientific thinking at a young age.

"I grew up doing a lot of fishing with him, and he would explain the tides and sunrise and sunset," the younger Karpowicz said. "He always took a scientific perspective on explaining the natural world in a way that was accessible to me as a kid."

In college, Karpowicz fell in love with biochemistry and changed his major. His research on catalyst design with Joseph Fox won him Pfizer and Howard Hughes Medical Institute funding.

Karpowicz's interests have repeatedly pulled him from pure chemistry toward its interface with biology. In graduate school, he intended to



COURTESY OF RICHARD KARPOWICZ JR.

Richard Karpowicz Jr. developed a tag-and-quench fluorescence imaging approach to study Parkinson's proteins.

continue with synthetic organic chemistry but heard about Dali Sames at Columbia University who develops fluorescent neurotransmitter analogues to track vesicle release.

"That's where I got involved in tissue culture, assay development, and biological and biochemical and optics-based methodology," he said.

After earning his Ph.D., Karpowicz wanted to develop techniques to tackle unsolved problems. He joined the lab of Virginia Lee at the Center for Neurodegenerative Disease Research at the University of Pennsylvania.

"When I interviewed here, the most important question was, 'How can we measure internalization of (alpha-synuclein seeds) or where they go inside the cell? How can we shed some light on what actually happens inside a neuron?'"

He pitched a plan that came to fruition in his JBC paper.

And on his cooking hobby, he reflected, "It's fascinating what kind of flavors can develop through different cooking techniques. It's all chemistry, right?"

Watching the spread of neurodegeneration

A number of neurological disorders, including Parkinson's, Alzheimer's and Lou Gehrig's disease (formally known as amyotrophic lateral sclerosis) are caused by aggregation of proteins within neurons. This process can be seeded in cultured neurons by introducing clumps originally formed in a test tube.

Richard Karpowicz Jr. and colleagues developed a new fluorescent approach to track alpha-synuclein clumps only after they are internalized by cells. The researchers tagged the seeds with a fluorescent protein but then quenched all fluorescence outside of the cell. They published the work in June in JBC.

The authors confirmed that added alpha-synuclein, the protein responsible for Parkinson's disease, is taken up and stored for days within the cell. By adding a second, acid-sensitive fluorescent tag, they showed that protein clumps are kept in the acidic environment of the lysosome and that disrupting lysosomal storage leads to increased seeding of new clumps.

This suggested to the authors that just a few events are enough to seed significant aggregations.

For more on this paper, see the article in the November issue of ASBMB Today, "Tracing the path of Parkinson's proteins."

Nutritional biochemist honored for paper on tuning iron levels

Nathan B. Johnson compares experimental biology to another challenging process of optimization, fly fishing: “You go to the stream and see what flies are hatching on the surface or what nymphs there are under rocks, and then you try to match the hatch the best you can. Like science, fly fishing success is dependent on accurate observations, predictions, reproducibility, presentation and luck.”

But, he admits, the analogy can break down: “You can sometimes catch a fish in a day; it’s hard to complete an experiment in a day.”

Johnson won a 2018 Journal of Biological Chemistry/Herbert Tabor Young Investigator Award for his work on iron homeostasis, conducted as a graduate student and postdoc at the University of Wisconsin–Madison and published last year in *JBC*.

It all started with the University of Tennessee Agricultural Extension 4-H program. “I didn’t plan on being a scientist,” Johnson said. “I grew up in rural east Tennessee and was active in a 4-H project, part of the meat product evaluation team.” He followed that track to major in food science and technology. Almost as soon as he started learning the principles of nutritional biochemistry, he realized he would love to teach them.

Biochemistry coursework for a master’s degree in nutritional science introduced him to bench science, another activity he found he enjoyed.

To find out whether he liked research as much as teaching, Johnson took a job as a lab manager in Deborah Segaloff’s lab at the University of Iowa. He managed the lab and worked on structural characterization of gonadotropin receptors. “After doing that for five years, I sort of felt as though I had reached a plateau,”



COURTESY OF NATHAN B. JOHNSON

Nathan B. Johnson studied the complex regulation of the RNA-binding protein IRP1.

he said, and so he decided to pursue a Ph.D.

Johnson joined the program in biochemical and molecular nutrition at the University of Wisconsin-Madison. He was drawn to work in the lab of Richard Eisenstein by the opportunity to design his own project.

“He gave us the freedom to think critically and to work independently, and I thought, ‘That’s what I really need in order to succeed in science,’” Johnson said.

Since leaving Eisenstein’s lab, Johnson has been a postdoc in Rozalyn Anderson’s lab in Madison, studying a transcriptional coactivator upregulated in response to aging and caloric restriction. He also has developed curricula and is the instructor for three online courses on macronutrient metabolism, personalized nutrition and micronutrient metabolism for the new online master’s degree in clinical nutrition program at Madison.

“I’m in the process of transitioning to a full-time teaching role, which was what initially piqued my interest in research,” he said. “It’s sort of neat to come full circle.”

Controlling iron uptake for cell health

Iron levels in a cell need to be just right. Excessive free iron causes accumulation of reactive oxygen species; deficiency causes anemia. Therefore, cells express a complex system of proteins to calibrate iron uptake and storage.

Two iron-response proteins, IRP1 and IRP2, respond to a low cytoplasmic iron level by binding to RNAs, increasing translation of iron-uptake proteins and reducing translation of iron-storage proteins. This response increases cellular iron level. When free iron is adequate, the two proteins are turned off to prevent excessive accumulation.

Until recently, the two IRPs were thought to be inactivated by distinct mechanisms: IRP1 by adding an iron-sulfur group and IRP2 by ubiquitination. Johnson and colleagues explored crosstalk between the two downregulation pathways, demonstrating that nothing in the system is as linear as it had seemed. They published their work in *JBC* in August.

When the iron sulfur-cluster machinery was absent, the researchers saw that IRP1 could be degraded by the ubiquitin ligase that destroys IRP2. They also found that impaired iron-sulfur assembly increases levels of the ubiquitin ligase, indicating that the ligase is an important backup mechanism for IRP turnover.

See related articles in February’s *ASBMB Today* and the Sept. 22 issue of *JBC*.

Researcher honored for studies of oral pathogen that infects heart

Why can a bacterium usually found in the mouth also drive an infection linked to heart failure? How does a nascent bacterial colony in the heart protect itself from being swept away? Catherine Back won a 2018 Journal of Biological Chemistry/Herbert Tabor Young Investigator Award for her work on the mechanism of adhesion between a bacterial fibril protein and human tissues.

The protein, which she characterized while she was a postdoctoral fellow at the University of Bristol, helps the oral bacterial species *Streptococcus gordonii* attach to and colonize human tissues and may contribute to bacterial infection of the heart.

Back's first research experience was as an undergraduate at Bristol, where she worked with microbiologist Howard Jenkinson on an interaction between *S. gordonii* and another species of commensal oral bacteria. She stayed on at Bristol for her Ph.D., extending her undergraduate studies with a closer and more multidisciplinary look at CshA, an adhesion protein.

"I thought it was really interesting to work on a protein that not much was known about," she said.

While Jenkinson remained her primary supervisor, for her project, Back drew on the expertise of three principal investigators from two departments. Jenkinson and Angela Nobbs were frequent collaborators on microbiology research in the dental school, while biochemist Paul Race contributed expertise in protein characterization.



COURTESY OF CATHERINE BACK

Catherine Back found a novel mechanism for streptococcal adhesion to fibronectin.

"I managed to work in both departments, learning microbiology and also structural biology," Back explained. The collaboration between the groups continues to this day. The labs now work together to characterize other bacterial adhesins.

After earning her Ph.D., Back stayed on in Bristol to finish the work described in her JBC article and then moved to the nearby University of Bath to study a new type of vaccine for tuberculosis.

Back grew up in Exeter in Devon, England, and said she enjoys getting outdoors both in Bristol and on visits home. "I often go back to my parents' house in Exeter," she said. "It's near the sea, and near Dartmoor, which is a really nice place to go hiking."

Back recently returned to Bristol to join the lab of Paul Race for a new project, studying antimicrobials from bacteria that colonize deep-sea sponges.

Catching fibronectin to clamp on tightly

Adhesion proteins are key drivers of bacterial colony formation. In the case of *S. gordonii*, the protein CshA contributes to binding to the human extracellular glycoprotein fibronectin.

Because *S. gordonii* can enter the bloodstream and adhere to heart valves, the binding mechanism may have implications for development of heart infections.

Catherine Back and colleagues at the University of Bristol divided a relatively uncharacterized region of the protein into three domains through bioinformatic analyses, publishing their work in JBC in December 2016.

They analyzed each domain's interaction with fibronectin, finding that one of the three domains did not interact. Of the remaining two, dubbed NR1 and NR2, the on and off rates for NR1 were faster, although NR2 was capable of higher affinity binding. They analyzed the structure of both domains, determining that both are responsible for fibronectin binding. The disordered NR1 domain interacts transiently with fibronectin, the so-called catch. After NR1 makes initial contact, NR2 binds more tightly — the clamp.

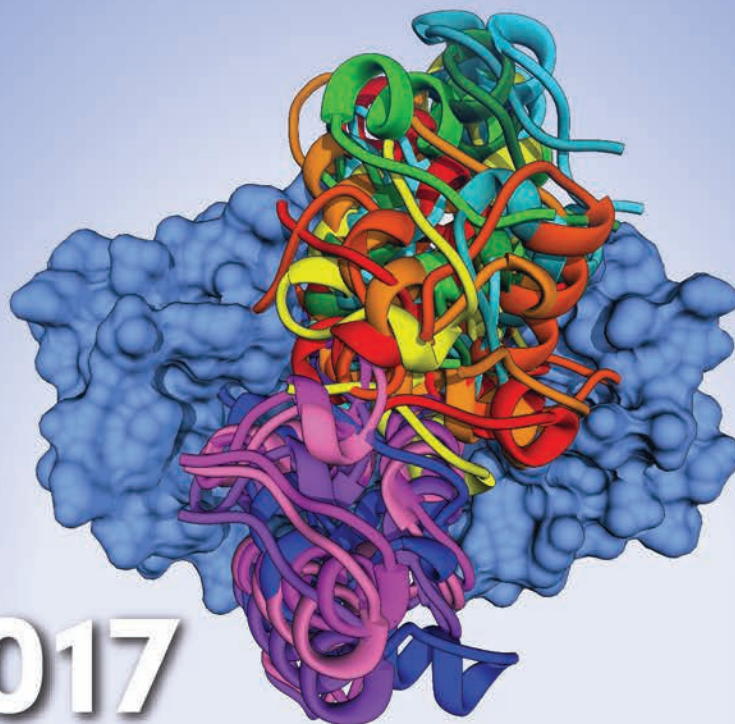
Back suspects the binding she described may be relevant to other pathogens. A number of other streptococci "have CshA-like proteins, which have a similar sequence and may have a similar mechanism of interaction," she said.

Put these talks on your itinerary

Check the ASBMB annual meeting program (www.asbmb.org/meeting2018) for location and timing of the Tabor award winners' Spotlight Talk session, and don't miss the chance to hear from these promising scientists in their own words.

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 **ASBMB**
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What to wear at the annual meeting

A guide for packing light and looking great at scientific conferences

By *Andrea Hadjikyriacou*

As a fashion blogger and scientist, I find the best time to meld my two passions is at a scientific conference. What better place to network with others in your field, learn new things, hear about cutting-edge technologies and also present your work to get great constructive feedback? The best ideas I've had were at conferences. Different perspectives, opinions and outlooks really can help advance your project. Why not make it even better by feeling your best and most confident because of your power outfit? When you feel good, that confidence projects to others. But a huge problem for a lot of people is the question, "What do I actually wear?"

I blogged about style for a previous Experimental Biology/American Society for Biochemistry and Molecular Biology meeting, and it was really fun to see what kind of outfits I could come up with for each day of the conference. As a woman who loves to shop, I had a closet full of clothes that I never wore, mainly because I was lazy but also because I wasn't being creative about putting pieces together. When I finally realized I could mix and match, I was able to put together multiple outfits without packing too many things — especially important when you have to travel by plane.

I've been to several conferences in my time as a graduate student, and each one has its own feel — some are business attire only, some are business casual, some are very casual — so it's hard at first to gauge what to wear.

Sometimes the conference itinerary states the dress code, but most do not, so as a first-time attendee (or even a seasoned veteran), you might not know what to wear. My advice: It never hurts to dress more formally on the first day and see what others are wearing; then you can adjust your clothes accordingly. No need to wear a suit and tie every day if others are more business casual. At the same time, you don't want to be the person who shows up in casual clothes while everyone else is dressed up.

Tips for conference style

- Get a feel for what the conference dress code is. It is always better to be overdressed on the first day than it is to show up in faded jeans and a T-shirt.
- Mix and match your pieces; re-wear the same pants with multiple shirts and tops for instantly different outfits. No one will notice you wore those same black pants yesterday.
- Simple black or dark gray dress pants are my go-to; you can switch out different colored and patterned shirts, sweaters and blouses.
- Capsule pieces, like a white or black shirt, simple T-shirt or tank top, can be layered under other pieces to create a simple outfit when covered by a blazer.
- A vest can add spice and variation to your outfit. You could wear the same (clean) shirt and pants the next day, add the vest, and you have a new look. Same with a sweater if the

conference hall is chilly.

- Use accessories like scarves, fun socks and jewelry to your advantage. This can spice up an outfit without filling your suitcase.
- You don't have to go out and buy expensive dress shoes; sure, they can complete a look, but more and more labels are coming out with dressier sneakers and flats. A simple black or dark gray shoe can match well with your outfit. Avoid running shoes or gym sneakers if possible.
- Do wear comfortable shoes (but they can still be stylish). Heels can be great, but bring a pair of flats in your bag to change in case those heels start to hurt after hours of standing.
- One of my shoe tricks: Wear boots under wide-legged pants — comfy and stylish.
- Avoid wearing sneakers and ripped or faded jeans. You want to make a good impression and look professional, especially when you are presenting your poster, giving a talk or meeting other scientists.
- That being said, you can still wear nice jeans. I would opt for a darker wash of denim with a nice pair of shoes or boots and an ironed button-up dress shirt or a flattering blouse. It's a good go-to conference look.
- A blazer can always be added for a touch of professionalism; you can class up those dark jeans and a top with a blazer, and voila — an instant outfit that's both professional and casual.
- Make sure you iron whatever you wear. Wrinkles can look messy and



PHOTOS OF ANDREA COURTESY OF TINA LAWSON, NICOLE BECKERMAN, QAIS AL-HADID AND ANDREA HADJIKYRIACOU
PHOTOS OF ASBMB STAFFERS AND SHOES BY EMILY HUFF/ASBMB.

It's always a good idea to dress up on the first day of a conference. Left, ASBMB science policy analyst André Porter wears a blazer and tie with dress pants. Right, fashion blogger Andrea Hadjikyriacou opts for a simple dress and jacket; just remember to pack some flats if you wear high heels like Andrea's (see below).



You can't go wrong with a pair of black shoes. Opt for a classic style and comfortable heel. Add a pop of color with your socks.



Casual flats are fine, but avoid running shoes and gym sneakers. These gray suede lace-ups and strappy brown flats strike just the right note.



Dark pants and a nice dress shirt or blouse make a great go-to look when you're at a conference, as demonstrated by fashion blogger Andrea Hadjikyriacou, below, and ASBMB public affairs manager Daniel Pham, above.



ASBMB science writer John Arnst, below, and fashion blogger Andrea Hadjikyriacou, above, show how you can dress up jeans or pants and a simple shirt with a classic blazer. A good look for your poster presentation.



For a more casual way to stay warm in a chilly conference hall, wear a stylish cardigan like MCP editor for manuscript integrity Saddiq Zahari, above, or pop on a zippered jacket like fashion blogger Andrea Hadjikyriacou, below.



unprofessional.

- If you're packing light, make sure you have laundry access — and be prepared to do some spot cleaning. Pack a stain-remover pen.
- Avoid T-shirts or other clothing that display slogans, logos, brand



names and so on. The simpler the better.

- If you wear make up, remember simple always wins. There's no need to be super flashy; neutral makeup with a pop of color on your lips can go a long way.



Andrea Hadjikyriacou (andrea@phdfashionista.com) is a postdoctoral scholar in industry/biotech by day and a fashion blogger at PhD Fashionista by night. She started her blog in graduate school to show the world that scientists can be stylish too. You can find her blog at www.phdfashionista.com and on Instagram and Twitter @phd_fashionista.

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A love of teaching and the chemistry of living organisms

Ana Maria Barral is an assistant professor at the National University in Costa Mesa, California, a member of the American Society for Biochemistry and Molecular Biology Public Outreach Committee and a member of the ASBMB Today editorial advisory board. In this month's Research Spotlight, she discusses her involvement in teaching research and the experiences that led to her career.

Tell us about your current career position.

My university is primarily a teaching institution, although the faculty has a requirement and support for research also. My research explores the microbes attaching to plastic in coastal waters, and I also am involved in teaching research, particularly how to incorporate research in undergraduate education and flipped learning, wherein most lectures are delivered outside the classroom and students can dedicate in-class time to problem solving and more active learning

What experiences and decisions enabled you to reach your current position?

Mine was a conventional academic research scientist's path, but during grad school I was involved in a lot of teaching and training. As a postdoc, I realized I missed the interactions with students and the challenges and joys of teaching, and I decided not to become a traditional academic. I



COURTESY OF ANA MARIA BARRAL

As the child of two doctors, one also a researcher, Ana Maria Barral grew up surrounded by science.

spent a few years working at a biotech company and teaching as an adjunct at different colleges while learning more about the science of teaching. Gaining expertise in innovative teaching approaches helped me to land my current position.

How did you first become interested in science?

My parents were both medical doctors, and my mother did physiology research, so science has been present in my life since childhood. I read many books detailing the lives and discoveries of scientists and dreamed about becoming one. However, I knew I did not want to be a physician, and biology did not attract me, because I thought it was all about animals and plants. Chemistry was interesting, but it felt a bit dry.

Everything changed when I learned about biochemistry; I remember how excited I was about a chemistry that looked at living organisms.

Were there times when you failed at something critical to your path? How did you get back on track?

Many times. I've run the gamut from saying no to opportunities that felt too scary to being overeager about interesting results without double-checking everything. How to regroup? Well, one has to accept not being perfect and that it is OK to make mistakes, and be kind to oneself. It is human to err. Then, just pick up the pieces and keep going. It will all pass. Learn from the experience. Personally, I like to have more than one project going (both in science and in my personal life) so setbacks in one can be balanced with successes in others.

What advice would you give to young persons from underrepresented backgrounds who want to pursue a career in science similar to yours?

Be brave. Be bold. Network as much as you can, and look for mentors. Never say no to an opportunity, because you don't know when the next one will come. Be who you are. Be authentic.

What are your hobbies?

I love traveling, particularly going off-roading to remote places. Running. Photography. Backyard work. Paddle boarding and the ocean in general. Reading. Music.

What was the last book you read?

Assuming this is about nonscience books, I am currently reading Diana Gabaldon's "Outlander series"; the latest I finished was "The Fiery Cross." She has a science background, and I enjoy reading her biology commentaries through the books. I just discovered Nnedi Okorafor (great science fiction) and got started on Sheryl Sandberg's "Option B." Science-wise, I am slowly winding my way through Michael Quinn Patton's book on qualitative research. It is eye-opening and gives me a lot of exciting ideas for assessing teaching innovations.

Do you have any heroes, heroines, mentors or role models? If so, how have they influenced you?

There are many people I admire for what they have done and achieved in life. But my role models are those who live their lives to the fullest, in accordance with their principles, and are very accomplished and still humble and kind. I know a few people like that, and I aspire to be like them.

What is it that keeps you working hard every day?

I am very lucky that I love what I do. As a laboratory scientist, my impact on the world was minuscule, while as an educator, I feel I can influence others' lives in a positive way. My students tend to be older, so I also learn a lot from them. Even

better, I have my research projects, in which I can involve students. One of my greatest joys is to see students who hadn't thought about becoming scientists do and enjoy science.

About the Research Spotlight

The American Society for Biochemistry and Molecular Biology's Research Spotlight highlights distinguished biomolecular and biomedical scientists from diverse backgrounds as a way to inspire up-and-coming scientists to pursue careers in the molecular life sciences. Eligible candidates include Ph.D. students, postdoctoral fellows, and new or established faculty and researchers. To nominate a colleague for this feature, contact education@asbmb.org.

Grant Writing Workshop

June 14–16, 2018, Washington, D.C.
Deadline for nominations is April 13.



www.asbmb.org/grantwriting

 **ASBMB**
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Sparking the flame of science

Supported by an ASBMB grant, Salisbury University students guide children through activities in biology

By Gabrielle Voithofer

One-fifth of all jobs in the U.S. workforce are related to science, technology, engineering or math, according to the STEM Education Coalition, and the STEM career field is predicted to grow as much as 13 percent in the decade between 2012 and 2022.

The American Society for Biochemistry and Molecular Biology Student Chapter at Salisbury University wanted to explore ways that teachers and people in STEM fields could work together to spark children's interest in STEM and lifelong learning. With funds from a Student Chapters Outreach Grant, we worked with the department of biological

sciences at SU to hold two outreach events to inspire interest in biology in children living in Wicomico County, a rural area on the eastern shore of Maryland.

Patti Erickson, an SU associate professor, organized field trips for students and teachers from the Wicomico County Thinking and Doing program for fourth graders. More than 100 students visited SU's department of biological sciences; they ran gel electrophoresis and DNA extraction tests, learned about phenylketonuria and green fluorescent protein, and toured some of the SU facilities. The labs were run by professors and students supported by volunteers

from the ASBMB Student Chapter and the department of biological sciences.

The ASBMB Student Chapter executive board also organized a student-led event called DNA Discovery, a day of activities at a branch of the Wicomico County Public Library. Callista Brown, secretary of chapter, obtained materials and led the event. Erickson and chapter volunteers led 10 children ages 6 to 12 through three activities: DNA isolation, candy and foam DNA structures, and a Mystery Code worksheet. In the DNA isolation activity, the participants used Gatorade, detergent and alcohol to make DNA from



PHOTOS COURTESY OF LAUREN DELONG

Salisbury University students help participants assemble their candy DNA structures during the Wicomico County Library outreach event. Left, Mariah Passwaters-Stamper; center, sitting at the table, Jeremie Barbosa; and right in red, Gabrielle Voithofer.



Andrea Carmack, ASBMB Student Chapter treasurer, helps a participant complete a nucleotide matching worksheet during the Wicomico County Library outreach event.

their own cheek cells visible to the naked eye and then placed the white threads into microcentrifuge tubes as necklaces. The volunteers explained the structure of DNA and taught the children about nucleotide base pairing with foam model and let them create their own DNA molecules with candy. For the Mystery Code worksheet, students used the base pairing rules they had learned from

the DNA structure activities to spell out a “secret” message. The students particularly loved putting their DNA into a necklace and making the DNA candy models, according to a review survey. Most said they were happy to learn something new.

Andrea Carmack, the Student Chapter’s treasurer, said she was “excited to share her love of biology with a younger generation.” Vice Pres-

ident Jamie Barbosa called the experience “mutually enriching for both the young students as well as myself.”

I personally enjoyed this experience because it allowed me to participate in something that involved two things I am passionate about: science and volunteerism. It was impressive to witness young kids just enjoy the process of learning.

After the activities, Student Chapter members decided they needed to improve the feedback process. In a later outreach program, we asked multiple-choice instead of short-answer questions. We also offered snacks as an incentive to complete the survey. This feedback is important to improve future outreach events. As a chapter, we hope to organize more events like these and continue to be active in our community.

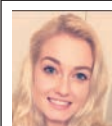
The Student Chapters Outreach Grant Program

Twice a year, the ASBMB awards grants of up to \$500 to help its Student Chapters bring science activities to their communities. The funds can be used to support existing outreach activities as well as to help pilot new activities. This grant program is an exciting way to encourage our Student Chapters to be more active in their engagement with the local community.

These grants support a variety of programs — everything from the University of Arizona’s Blastoff! Summer Science Camp to the Marymount Manhattan College organ donation drive to the Salisbury University biology activities described on this page. The goal is to bring science to the public and encourage participation and partnerships in science outreach.

The grant program is sponsored by the ASBMB Student Chapters and Public Outreach Committee. In addition to funding, successful applicants have exclusive access to the committee’s outreach expertise and resources.

Don’t miss out on this exciting opportunity. The next deadline for applications is April 16. Each chapter may apply once a year. For detailed instructions, sample applications and more information, go to the Outreach section of asbmb.org and click on Funding.



Gabrielle Voithofer (gvoithofer1@gulls.salisbury.edu) is a biology and economics major in her second year at Salisbury University and the social media and public relations chair of Salisbury’s ASBMB Student Chapter. This article originally appeared on The Substrate, the online newsletter for ASBMB Student Chapters.

Leadership: the sock's-eye view

Editor's note: This is the first in an occasional series of essays from a writer who has his ear to the ground when it comes to life in the lab.

I was standing at the counter of the juice bar in Logan Airport, ordering my breakfast, when I felt a shadow fall over me. Behind me towered a man well over 6 feet tall. His spiked hair stood up like a row of fenceposts, and his smile gleamed. The creases on his pinstriped shirt looked like they'd cut a steak. As I moved aside to wait for my drink, he approached the counter. The man at the cash register said warmly, "What can I get you, Governor?"

Then it hit me. The stately blonde sitting at the table, the one who looked like Ann Romney — that was Ann Romney. And this was Mitt Romney. It was 2013 and he had recently lost the presidential election, but, feeling a little thunderstruck, I thought he still looked every inch a president.

Primates may be conditioned to look for certain physical traits in an alpha. Mitt Romney had those in spades. But what about the rest of us? The less than eagle-eyed? The height challenged? (In the interests of full disclosure, I should tell you — I am a sock puppet.) Dare I say the nerdy types? Can we not also be leaders? Of course, the answer is yes, we can, and in some cases we absolutely must step up. Here are the top six things I've learned about leadership from helping to manage a large-ish group of graduate students for the past dozen years:

1. If you don't feel like a natural-born leader, try imitation. We've all heard versions of this before — for example, dress for the job you want, not the one you have. I'd take it a step further. When I was a postdoc, there was a snappy young scientist at our institute — I'll call her Marilyn Mertozi — who walked on water.

She was so good, it seemed she could walk on any solvent. I took her bioorganic chemistry course, and I suspect I learned a thing or two about arrow pushing. The more enduring lesson, however, was about confidence and how to project it, which I learned by observing her. I noticed that several women in the class picked up on this too. Whether the change was made consciously or not, soon there was a small flock of Marilyn clones, imitating her dress, her diction and even her ticks.

It's said that graduate students often pick up something of their advisor's style. It helps if your advisor is someone you can relate to. There are still very few sock puppets in science, and I admit it has been difficult finding an appropriate role model. But when I'm about to give an important talk or advocate for myself in front of my boss, I still put on my best Marilyn impersonation, and I go out guns a-blazing.

2. "Boss" is a four-letter word; however, "leader" has six letters. Research labs, by and large, are not populated by quarterbacks. Many of us went into science because we appreciated working independently or in highly collaborative structures, with big tents and round tables. To many scientists, the word "boss" may have a highly pejorative connotation. You may prefer the more inspiring word "leader." I'm here to tell you that being a leader is a good thing and probably something you should aspire to, regardless of your actual job title. Why? Read on.

3. A leader finds the hole. When I was a graduate student, I worked on a collaborative project with an assistant professor who was notoriously disheveled. He was at the stage of his career where he still worked in the lab, or tried to, though he probably should have stayed away.

The many bleach stains and acid holes in his clothes were testaments to his folly. In fact, we students had a game we liked to play called "Where's the hole?" The first person to find the hole in our advisor's clothing on any given day was the winner. It never took long.

I think of that now when I work with graduate students in the lab. Some have terrific qualities to recommend them; but everyone, without fail, also has some nagging flaw. Maybe they're a little bit careless or lazy. Maybe they give up too fast — or not fast enough — when an experiment isn't working. Perhaps they can't assemble a sentence or make a figure to save their life. Like the Scarecrow, the Lion and the Tin Man, every one of your ragtag band will have a problem. And just like the Great Oz, as their leader, it's your job to find the hole and help them fix it.

4. A leader makes s**t sandwiches. As a young sock, I visited the beaches at Normandy, France. Like many visitors, I was awestruck, imagining boat after boat dispensing scared young soldiers onto the shore under a rain of bullets and mortar fire. I always wondered how their commanding officers were able to marshal them up the beach and into enemy lines. Surely, such techniques must be sufficient for motivating discouraged students to go back into the lab?

A few years back, we had an Air Force captain in our graduate program. Though he'd not seen warfare of the Normandy variety, he had nonetheless completed a great deal of officer training. Now was my chance to learn: How does the military teach officers to lead?

In partial answer to my question, the captain referred me to a chestnut of a book — Dale Carnegie's "How to Win Friends and Influence People" — and a recipe of sorts that his Air

Force colleagues had derived from it. He said that when they needed to criticize or correct someone at their own rank or above, he and his fellow officers would cushion the blow by wedging it between two compliments: the so-called “s**t sandwich.”

Much more direct criticism from officer to underling would be completely acceptable; however, even recruits sometimes had a hard time hearing criticisms when dished out too directly.

And so it goes in the laboratory. The student’s shortcomings are only too clear. He fails to keep an organized notebook. As a consequence, no one else in the lab can understand let alone repeat his experiments. You’ve warned him about this a thousand times. You are so frustrated, you want to roll up the notebook and whack him over the head with it. Instead, you offer:

“I notice you’re working very hard in the lab lately, little Timmy.” (BREAD)

“You’ve really got to record your methods much more carefully, however.” (S**T)

“That way, everyone in the lab will get to see exactly how you work your magic!” (BREAD)

Sounds like little Timmy has just been served.

5. Sometimes, a leader just has to pick up the damn clock. A famous chemist/biochemist from the University of Illinois — let’s call him Yi Lu — once told me a story.

A big clock hung on the wall over the door to his students’ group office. One day, someone slammed the door too vigorously, apparently, because the clock fell off the wall onto the floor in the middle of the doorway and smashed into several pieces. In order to enter or leave the office, the students had to step over the messy remains of the clock. Professor Lu watched them do this all day long from his office across the hall. He grew increasingly frustrated. Would no one stop and pick up the clock — if not to replace it then just to remove

a potential tripping hazard? Quitting time was approaching, and still no one had dared to touch the broken clock. Finally, Professor Lu himself came with a broom and wastebasket and took care of the mess.

When I was a postdoc, there was a time when there were 12 of us, each more ambitious than the next, all sharing the same cramped lab space. No one had time for good manners or even basic sanitation and — needless to say — the lab was an incredible mess. One day, my co-worker Mike (now a faculty member and father of two) rounded us up and said: “We’re having a lab cleanup. All of us. This afternoon.”

Whether he or she has the requisite title or authority, the person with whom the buck stops is, by virtue of taking action, the leader. You don’t have to have a fancy title or position to exert this kind of quotidian leadership; you just need to be responsible. And let me tell you, these sorts of innate leaders are lab gold.

6. Some of the most effective leaders are the least visible. In an episode of the cartoon “Futurama,” Bender, the robot, floats out into deep space. After many weeks, he drifts toward a mysterious nebula that speaks to him. The entity has been quietly monitoring Bender’s journey through the cosmos, including a time when Bender harbored a microscopic civilization that thought he was God. Bender asks the entity if it is God. It replies, “Possibly.” Bender tells him, “You know, I was God once.”

“Yes,” says the entity. “You were doing well, until everyone died.”

The entity then gives some advice on how to do a more effective job as God. The same advice might as well apply to those of us in more mundane positions of leadership: “If you do too much, then people become dependent on you. If you do too little, they lose hope ... When you do things right, people won’t be sure you’ve done anything at all.”

Now there’s a meme that you can hang your hat on.

About the author



COURTESY OF MOHAMMED REFAI

Sock Puppet, Ph.D., started his career as a teaching assistant.

Gamma rays created the Hulk. The bite of a radioactive spider turned Peter Parker into Spider-man. When an assistant professor was asked to teach a large introductory biochemistry course, without sufficient funds for a teaching assistant, Sock Puppet TA was born. Since then, Sock Puppet has attended many classes and earned undergraduate and Ph.D. degrees in biochemistry. Sock Puppet, Ph.D., is employed as a research scientist in a Mountain West university and has seen a thing or two in his many years in and around academia. He knows what lurks in the back of the -80 °C freezer as well as the bottom of the sock drawer, and he counts many struggling graduate students and young faculty among his friends. When Sock Puppet is not wrangling graduate students, he enjoys jogging, skiing, macramé and searching for his long-lost twin brother in and around the dryer. (Email Sock Puppet, Ph.D., at sockpuppetphd@gmail.com.)



Science prepared me for cancer treatments, but nothing prepared me for surviving

By Jennifer L. Gooch

The aftermath of cancer treatments is a little like getting your car back from someone you lent it to only to find a new dent in the bumper, stains on the upholstery and an extra 100,000 miles on the odometer. And then the person you lent it to helpfully points out, “But it still runs!”

I am grateful to have completed cancer treatments and gotten my car back, and I’m thrilled that it still runs.

As a scientist who did her dissertation research on signaling pathways that make breast cancer cells grow, I knew a fair amount about the mechanisms and even treatments for breast cancer before my own diagnosis. For example, I knew that by the time a tumor is palpable, it usually already has spread to the lymph nodes. Mine was and it had. I also knew that being positive for human epidermal growth factor 2, known as Her2, meant that I was going to be treated with targeted therapies that were the direct results of molecular research from the past few decades. That felt strange and wonderful.

However, there was an entire phase of cancer treatments that I was wholly unprepared for — surviving.

In June of 2014, I was diagnosed with breast cancer barely 24 hours after my first mammogram. I was 40 years old. The biopsy results defined the cancer as triple-positive (the tumor expressed estrogen receptors, progesterone receptors and Her2)



ALL PHOTOS COURTESY OF JENNIFER L. GOOCH

Left: Jennifer L. Gooch received chemo treatments through a port in her chest; the four drugs took about six hours to infuse. Right: Six months after finishing chemo, she had regrown enough hair to stop wearing a wig.

invasive ductal carcinoma, and a positron emission tomography scan further confirmed that I had node-positive, clinical stage 2B disease.

Three weeks after that first-ever mammogram, I received my initial cocktail of neoadjuvant chemotherapy — taxotere, carboplatin, trastuzumab, and pretuzumab, or TCH+P.

During my training, the clinical fellows and other oncologists in the department would comment that chemotherapy for breast cancer is “relatively tolerable” compared to regimens for other cancers.

And, in truth, it was manageable. The side effects were predictable: taxotere and carboplatin attacked all fast-

growing cells in my body. So my hair fell out, my blood counts dropped and the lining of my gastrointestinal tract thinned (and I had a lingering metallic taste in my mouth thanks to the platinum). The side effects of the monoclonal antibodies targeting Her2 were less acute but added upper respiratory irritation and skin changes to the mix. With each cycle, the fatigue was more intense as my body worked to replace all the cells killed by chemotherapy.

Following chemotherapy, my treatment plan included surgery (a mastectomy and axillary node removal) as well as radiation. Finally, I completed a full year of trastuzumab infusions



Gooch worked all through her treatments and recovery; here, she gives an interview about a newly funded grant.

and started a five-year course of treatment with an aromatase inhibitor.

Clinically, mine is a success story. My oncologist once told me I was a “textbook” example of how oncologists want chemotherapy to go. I was able to work through most of the treatments, taking a few days off when needed during chemo and two weeks following surgery. I had no unexpected side effects and no cardiac damage. I bought a nice wig that resembled my own hair so closely that many people did not know that I was undergoing cancer treatments until, months later, I revealed my very short, newly regrown hair.

In short, my car was returned to me (minus cancer) with a flurry of pink celebratory certificates of completion from my cancer team.

It wasn’t until I really started driving that car again that I started to appreciate all the things that were different. There were changes to my body and mind that weren’t part of the molecular biology of cancer I had studied or the focus of most cancer research.

The cytotoxic drugs damaged, perhaps permanently, the nerves in my left foot and hand. In addition to the pins-and-needles sensations and the pain with cold temperatures, my coordination is poor and I have fallen several times. I have Hashimoto thyroiditis, a lesser-known side effect of breast cancer treatments in which your body develops antibodies against your thyroid, preventing the production of thyroid hormones. I take a daily supplement of levothyroxine to

prevent the weight gain, hair loss and memory impairment associated with hypothyroidism. The combination of chemotherapy and ongoing treatment with an aromatase inhibitor means that I also manage daily chronic joint pain. Finally, I struggle with aphasia — most often, the image of the item is in my mind, but I simply cannot match a word to it. At other times, the word I choose is simply the wrong one, a particularly unfortunate affliction when lecturing to students. These are part of my new normal.

In the longer term, I am at increased risk of heart disease, osteoporosis, lymphedema and secondary cancers due to my treatment regimen. Not to mention recurrence of breast cancer.

And now we come to the sword



One year and 20 days after she was diagnosed, Gooch's cancer team presented her with pink certificates to mark the completion of her treatment.

of Damocles. Statistically, about one in three women diagnosed with stage 1-3 breast cancer will at some point be rediagnosed with stage 4, metastatic disease. And unlike other types of cancer, for the majority of women with breast cancer, there are no markers to detect with a blood test and no regular scans (other than mammography for local recurrence, if a patient still has breasts) once treatments are completed that will detect metastatic

disease. Studies have shown that the difference in detection by screening versus a patient experiencing symptoms and seeing his/her doctor is only a matter of months. And the outcome is the same — metastatic breast cancer is treatable but not curable.

As a scientist, I am familiar with the statistics around overall survival of different types and stages of breast cancer. But I am an N of 1. My outcome is binary. Either I am cured of

my disease or I will die from it. Living with this uncertainty is not something science or medicine can prepare you for.

I have had a hard time articulating to my doctors both the physical and the mental toll surviving cancer has taken, even though I am certain that many survivors have similar experiences. Complaining might make it seem that I am ungrateful for their life-saving work. After all, the car runs, right?

The American Cancer Society estimates that there are now more than 15 million cancer survivors in the United States, a number that, thankfully, is projected to continue growing. My hope is that, with that growth, survivorship will become a more integrated part of cancer treatment plans — and an increased focus of scientific research.



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Questions?

Send them to Comfort Dorn, ASBMB Today managing editor, at cdorn@asbmb.org.



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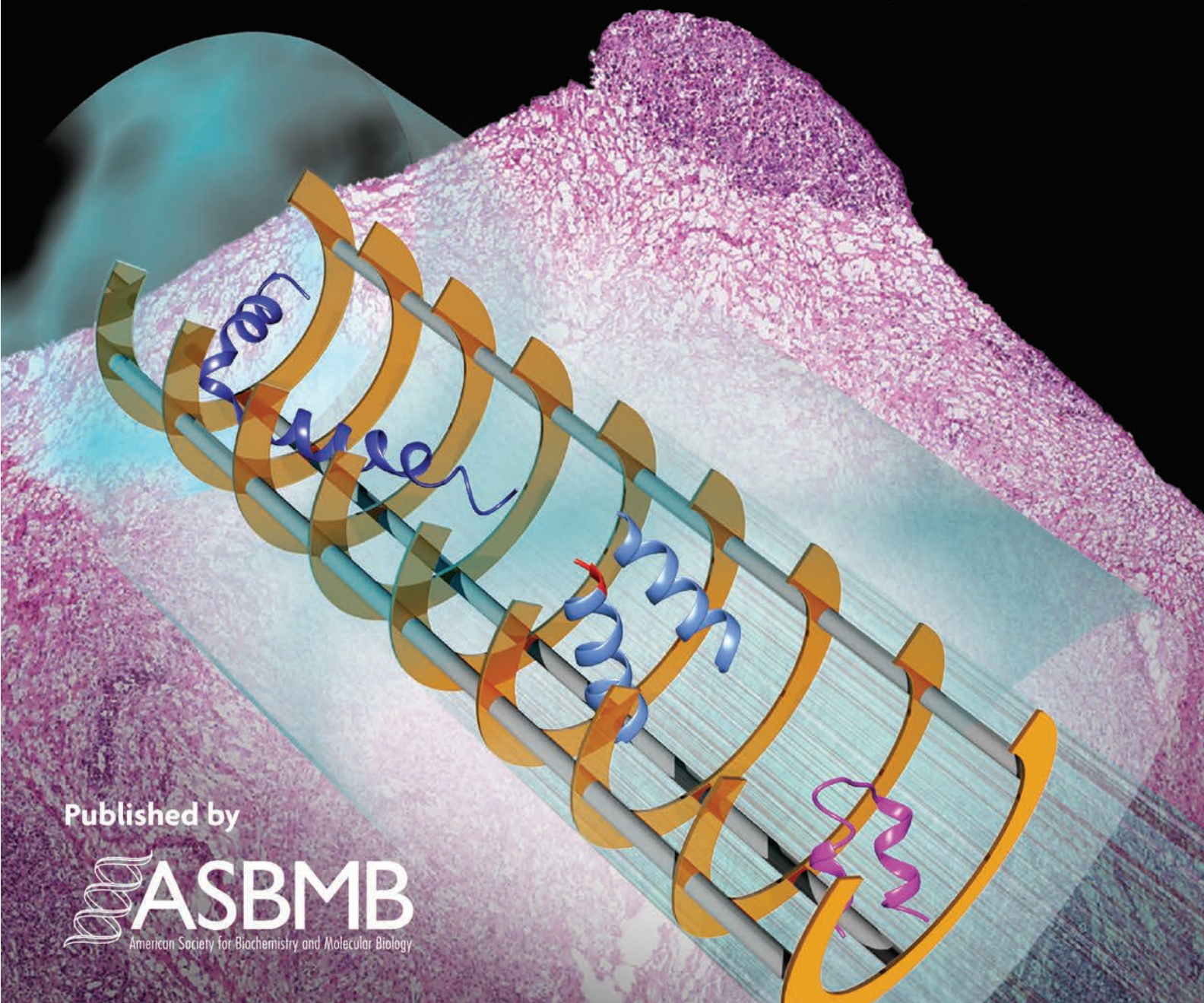
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