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ASBMB TODAY

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

THE BEST OF BMB 2022

ALSO: HOLIDAY GIFTS FOR SCIENTISTS

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American Society for Biochemistry and Molecular Biology

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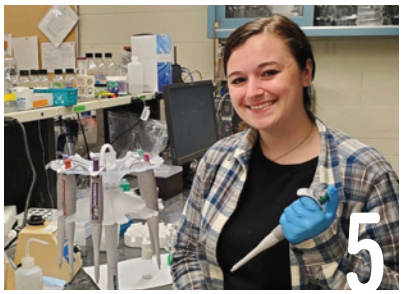
CONTENTS

NEWS



FEATURES

PERSPECTIVES

48

ASBMB TODAY
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Fun in Seattle

By Ann Stock

We all know that the best part of any American Society for Biochemistry and Molecular Biology annual meeting is immersion in cutting-edge science — and Discover BMB 2023 will be no exception.

I've found, however, that informal interactions — chatting with other scientists over coffee or meals or just hanging out in the exhibit hall — are often just as enjoyable and productive as the formal conference program. And organizers have designed Discover BMB, our first independent annual meeting in recent years, with plenty of opportunities for such socializing from beginning to end, both within and beyond the Seattle Convention Center walls.

Along with the traditional exhibitors, career development activities and meet-the-experts sessions in the exhibit hall, we'll introduce some new activities, including a photographer to take professional headshots, chair yoga to relax and refresh, and games and scavenger hunts — just for fun.

We'll close out each day with poster sessions and interest group meetups (with refreshments!) — a great way to connect with colleagues just before you leave the hall for dinner and evening socializing.

Be sure you make plans to explore Seattle. I recently chatted with John Scott, an ASBMB fellow and a professor at the University of Washington, and he reminded me of all the city's fun destinations. Grab a cup of coffee at the original Starbucks store just half a mile from the convention center. Or try artisanal roasts at one of the many coffee houses. Whatever your preference, coffee is practically synonymous with Seattle.

The venerable nine-acre Pike Place Market near the waterfront is a fun destination for lunch or dinner. The iconic Seattle Space Needle and adjoining Chihuly Garden and Glass are just one mile (a single monorail stop) from the convention center. Or hop on a ferry to see the Seattle skyline from the water. Bainbridge Island is just a 35-minute ride across Puget Sound.

Finally, for some fishy fun, Discover BMB will close with a reception at the Seattle Aquarium — a great chance to mingle with all your old and new friends while exploring spectacular exhibits of birds, fish, mammals, and cephalopods and other invertebrates indigenous to the Pacific Northwest. When you're making travel plans, be sure to allow time to cap off the meeting with this Tuesday evening event.

Of course, Discover BMB 2023 will continue our tradition of great science with an exciting program coordinated by co-chairs Karen Allen and Craig Cameron and the planning committee. There's still time for you to showcase your research. Late-breaking abstract submissions open Dec. 12 and continue through Jan. 18.

Ann Stock (stock@cabm.rutgers.edu) is a professor of biochemistry and molecular biology at the Robert Wood Johnson Medical School at Rutgers and resident faculty member at the Center for Advanced Biotechnology and Medicine. She became the ASBMB's president in July.

Raines wins Khorana Prize

Ron Raines, a professor at the Massachusetts Institute of Technology, has won the 2022 Khorana Prize from the Royal Society of Chemistry in recognition of his work at the junction of chemistry and biology.

RAINES

Raines uses the ideas and tools of chemistry to understand and control life processes. Most of his work is related to proteins. His research group has discovered a ribonuclease that is in a multisite human clinical trial as an anti-cancer agent. They revealed that unappreciated forces — the n→π* interaction, between peptide backbone carbonyls and backbone or side chain carbonyls, and the C5 hydrogen bond, between the amide proton and carbonyl oxygen of the same amino acid — stabilize all proteins. The team also has translated its work by creating human-scale synthetic collagens more stable than any found in nature and developed processes to synthesize proteins, catalyze their folding and facilitate their entry into human cells.

In 1968, H. Gobind Khorana won the Nobel Prize in physiology or medicine for his interpretation of the genetic code. Notably, the year 2022 marks the 100th anniversary of Khorana's birth. The Khorana Prize is awarded for outstanding contributions through work at the chemistry and life science interface. The prize consists of £3,000, a medal and certificate, and an honorific lecture tour in the U.K.

This year's Khorana Prize is especially congruous, Raines said: He was an undergraduate student at MIT while Khorana was a professor there. Moreover, both Khorana and Raines were once faculty members in the biochemistry department at the University of Wisconsin–Madison, and both moved to the chemistry department at MIT.

Johnson wins Pew scholarship

Elizabeth Johnson, an assistant professor at Cornell University, has been named to the newest class of Pew biomedical scholars. The 22 scholars were chosen from almost 200 applicants.

JOHNSON

Johnson studies how the fats in human milk interact with the infant microbiome to support the generation of beneficial metabolites. Her lab also is interested more broadly in interactions between the diet, the microbiome and the host. They developed a method called BOSSS that uses click chemistry to fluorescently label metabolites derived from a certain dietary source and then isolates fluorescent microbes to identify specific strains that interact with specific dietary lipids. Using this approach, Johnson's lab recently identified the bacterial enzyme that converts cholesterol to cholesterol-3-sulfate, which can bind to DNA methyltransferases and influence inflammatory status.

Johnson was an undergraduate at Spelman College and earned her Ph.D. at Princeton University, studying RNA dynamics to understand how cells survive quiescence, or cell cycle arrest. She was a postdoc at Cornell and in Ruth Ley's lab at the Max Planck Institute for Developmental Biology, where she studied sphingolipid production by gut microbes. The Pew Scholars Program in the Biomedical Sciences provides funding relevant to advancing human health to investigators in their first few years at the assistant professor level by making grants to academic institutions to support the scholars' independent research.

Kuriyan to take over as dean at Vanderbilt med school

John Kuriyan, a distinguished professor of molecular and cell biology at the University of California, Berkeley, and a Howard Hughes Medical Institute investigator, has been named the next dean of the Vanderbilt University School of Medicine Basic Sciences.

KURIYAN

Kuriyan succeeds Lawrence Marnett, also an American Society for Biochemistry and Molecular Biology member, who was named founding dean of the basic sciences school in 2016 after the university separated from Vanderbilt University Medical Center.

After Kuriyan takes over on Jan. 1, Marnett plans to take a sabbatical and

CORRECTIONS

A Q&A in our September issue, "How life began merits a preceding discussion of what life actually is," several times misstated the title of the book being discussed. The correct title is "From Molecules to Cells: The Origin of Life on Earth."

In the article "Preventing missed diagnoses of hyperekplexia in newborns" in the November issue, Ghada Aboheimed was referred to by incorrect pronouns. She is a woman.

then return to the faculty. "I am excited for John's leadership," Marnett said in a press release. "He will be a beacon for attracting the very best biomedical scientists to campus."

Kuriyan's research focuses on conformational changes and posttranslational modifications that switch on activity in signaling molecules involved in signal transduction. His lab has studied autophosphorylation, subunit exchange, redox changes and dimerization in proteins including tyrosine kinases, such as Src and Btk; the calcium-activated kinase CaMKII; and various proteins involved in signaling downstream of receptor tyrosine kinases including the Ras activator SOS. They previously studied the structures of proteins involved in DNA replication, including polymerase sliding clamp complexes. The lab has a whimsical tradition of illustrating their articles with art in the style of international postage stamps.

Kuriyan grew up in India and studied chemistry for two years at the University of Madras before transferring to Juniata College for his bachelor's degree. He earned a Ph.D. in physical chemistry at the Massachusetts Institute of Technology and continued to work with graduate advisers Martin Karplus and Gregory Petsko during a postdoctoral fellowship at Harvard University before starting as a professor at Rockefeller University.

Kuriyan is an elected member of the National Academy of Sciences and the National Academy of Medicine, a fellow of the American Academy of Arts and Sciences and a foreign member of the Royal Society. Among many honors, he received the ASBMB–Merck award in 2009. He is editor-in-chief of the journal Protein Science.

Hargrove named chair at Iowa State

Mark Hargrove, a professor of biochemistry, biophysics and molecular biology at Iowa State University, is the new chair of his department. His appointment started July 1 and is set to last five years.

Hargrove studies the structure, function and folding of heme proteins, with an interest in the differences between their interactions with diatomic gases including oxygen, carbon monoxide and nitric oxide. His lab also investigates the importance of inorganic nitrogen compounds in respiration and fermentation by anaerobic bacteria, which relies on heme proteins.

HARGROVE

Hargrove previously had served as the associate chair of his department and chair of a collegewide curriculum committee. He has received several teaching awards since starting at Iowa State University.

Hargrove studied chemistry and biology at the University of Nebraska–Lincoln and earned his Ph.D. in biochemistry and cell biology at Rice University in Houston.

Sigma Xi chapter elects Fuanta

René Fuanta, an assistant professor of chemistry and biochemistry at East Stroudsburg University in Pennsylvania, has been elected associate director of the Mid-Atlantic chapter of Sigma Xi. His term began July 1.

Fuanta studies shikimate kinase, an enzyme found in plants and microbes that acts in the biosyn-

thesis of aromatic amino acids. His lab is interested in using shikimate kinase inhibitors to block growth of Mycobacterium tuberculosis and has published on several possible shikimate kinase inhibitors. Some of the most interesting candidates were identified in a high-throughput screen of marine sponge metabolites. Fuanta's lab also targets other key bacterial enzymes in M. tuberculosis and Pseudomonas aeroginosa using QTOF–MS and other biophysical methods.

Fuanta earned his bachelor's degree at the University of Buea in Cameroon and his Ph.D. in biochemistry from Auburn University. He is a member of the ASBMB Today editorial advisory board and a contributor to the magazine.

FUANTA

Sigma Xi is a scientific honor society of scientists and engineers. Fuanta will serve as the chapter's associate director for three years and simultaneously is serving on the editorial advisory board of the society's magazine, American Scientist.

Bui lands poster prize

Arden Bui, a member of the ASBMB Student Chapter at St. Bonaventure University, won an undergraduate poster presentation award at a research symposium sponsored by the Mid-Atlantic section of the American Society of Plant Biologists and the University of Maryland, College Park, in May.

Bui, a senior majoring in biochemistry, studied how the splicing regulator called serine/arginine-rich 45, or SR45, affects the sperm transcriptome in Arabidopsis. Her co-authors in the project included Leigha Haberly, a classmate, and Christopher Chin, a recent graduate of St. Bonaventure.

The team conducted the research in the lab of Xiao-Ning Zhang, a St. Bonaventure professor and director of the school's biochemistry program and ASBMB Student Chapter. Zhang has studied Arabidopsis pre-mRNA splicing with a focus on SR45 for some years, finding roles for the protein in plant growth, heat and cold stress responses, and reproduction.

BUI

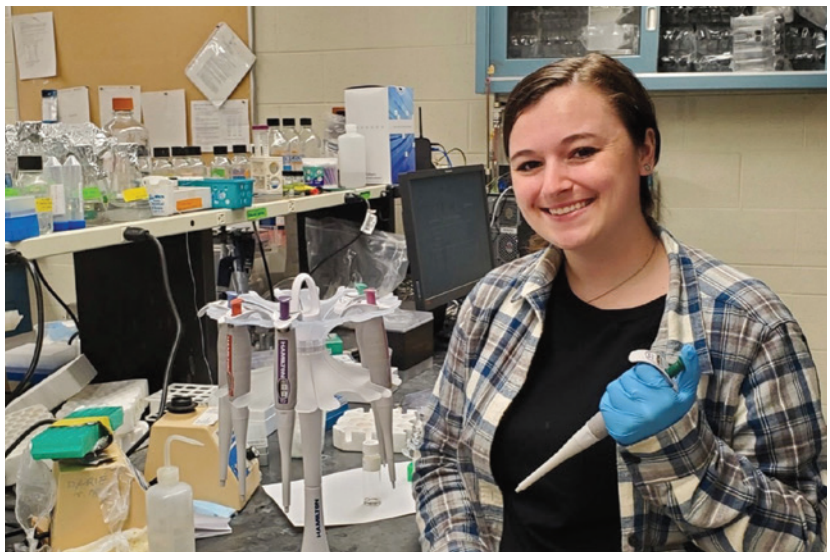
Pipette grant for Whitham follows meeting

You never know what opportunities may arise from a scientific meeting. Just ask graduate student **Danielle Whitham** of Clarkson University, the owner of a new set of pipettes funded by the Hamilton Company's pipette grant.

"I had heard about this grant opportunity at the ASBMB conference I recently attended," Whitham, a student in the biochemistry and proteomics group with chemistry and biomolecular science professor Costel Darie, told her university's press office. "I decided to apply for the grant and was surprised to see that we were chosen to receive it."

Whitham's research, which she presented at the ASBMB annual meeting in Philadelphia, focuses on protein biomarkers for breast cancer, in search of which she screens serum and breast milk from women with cancer and healthy controls. Identifying breast cancer early in young women is of particular interest because mammography is less effective in younger, denser tissues. Darie's lab has reported some preliminary success in finding proteins that are differentially expressed between breast milk from donors without cancer and donors whose cancer was diagnosed either before or after their donation.

The Hamilton Company is funding monthly $1,000 credits throughout 2022 to support teaching and research labs in purchasing its products.



COURTESY OF DANIELLE WHITHAM

Danielle Whitham won a grant for these new pipettes from the Hamilton Company.

STEAM scholarship for Gandhi

Khushi Gandhi, a sophomore at Northeastern University and a member of the school's American Society for Biochemistry and Molecular Biology Student Chapter, has received a scholarship from the educational nonprofit organization Aspire2STEAM.

GANDHI

Gandhi, who is studying biochemistry with a minor in public health on the premedical track, aspires to become an obstetrician–gynecologist and bring novel treatments to bear on female infertility. Since December 2021, she has worked in the lab of ASBMB member Mary Jo Ondrechen, helping senior students on a computational chemistry project seeking new metabolic tracers for positron emission tomography imaging. She also has worked as a shadow/intern with the Health Administration of Pennsylvania Emergency Management Team and in a lung cancer screening lab at Massachusetts General Hospital, and she spent the past summer interning in a neurosurgery practice.

Aspire2STEAM is a nonprofit that supports scholarships for women and girls seeking a college education or other training and certification in science, technology, engineering, mathematics or the arts.

Rising graduates on a high note

Jessie Rising, a member of the ASBMB Student Chapter at Manhattan College and president of the college's biology honor society, was valedictorian of her graduating class in May.

Biology professor Bruce Shockey told Manhattan College's newspaper, The Quadrangle, that Rising was a natural mentor, often helping other students in her lab classes. She also spoke to accepted students and at orientation about the biology department, and she coordinated volunteers for the biology honor society; she put in more than 100 hours as a counselor on the Crisis Text Hotline.

RISING

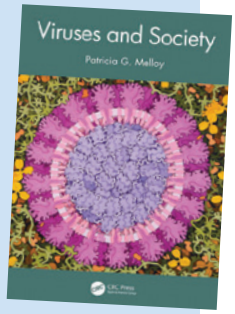
Rising also recently was inducted into the ASBMB honor society, Chi Omega Lambda, which recognizes exceptional juniors and seniors pursuing degrees in the molecular life sciences at institutions with ASBMB Student Chapters. In addition to her strong academic record, Rising was a student athlete for all four years at Manhattan and was pitcher and captain of the softball team.

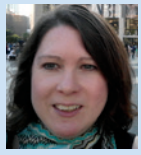
BOOKS BY MEMBERS

Viruses and Society

By Patricia Melloy
professor of biological sciences
Fairleigh Dickinson University

"Viruses and Society" is geared toward professionals and students in college-level introductory biology courses devoted to understanding viruses, vaccines and their global impact. In approachable and simplified language, the book introduces cells, DNA and viruses themselves. This is followed by a review of how the immune system works and how scientists and physicians harness the immune system to protect people through vaccines. Specific chapters focus on the 1918 influenza pandemic, the fight to eradicate polio, the HIV/AIDS pandemic and the current COVID-19 crisis. Additionally, the book reviews the uses of viruses in genetic engineering and gene therapy. It concludes by describing public health initiatives to keep emerging viruses in check and the role of scientific communication in how viruses are perceived and have an impact on our society.





MELLOY

— CRC Press

Are you an ASBMB member who has published a book recently?

If so, we'd like to feature your work in an upcoming issue of ASBMB Today. Please email a synopsis (under 100 words), an image of the book's cover and your headshot to asbmbtoday@asbmb.org.

Brenda Crews

Brenda Ann Campbell Crews, a senior research specialist at Vanderbilt University, died Jan. 18 at age 72. Crews contributed to several research programs at Vanderbilt, publishing more than 100 papers during her half-century career.

Crews was born Dec. 22, 1949, in Nashville, Tennessee. She played basketball and graduated from high school as valedictorian. She fed her passion for science by pursuing a degree in biology at Vanderbilt.

After graduating cum laude in 1971, Crews accepted a position in the laboratory of Stanley Cohen at Vanderbilt's biochemistry department, marking the beginning of a 51-year career in biomedical research. (Cohen won, with Rita Levi–Montalcini, the 1986 Nobel Prize in physiology or medicine for the discovery of growth factors.)

Crews also supported the laboratories of Leon Cunningham and Peter Gettins, contributing to research on alpha 2-macroglobulin and antithrombin III.

In 1994, she began working with Lawrence Marnett on the role of cyclooxygenase 2 enzyme in cancers affecting the digestive tract. In a recent tribute to Crews, Marnett recalled her as a "superb scientist" who was "constantly reading the literature" and a "great experimentalist who planned carefully and conducted meticulously."

Crews' more than 100 papers reflect her vast repertoire of skills and knowledge; 64 of those papers were from Marnett's lab. "Brenda was fearless experimentally," Marnett wrote. "She did protein purification, enzyme assays, cell imaging, signal transduction, in vivo pharmacology and much more. She managed our lab; she drafted all our animal protocols."

In 2004, Crews was the first recipient of the Laboratory Science Award for Excellence in Basic Research at Vanderbilt.

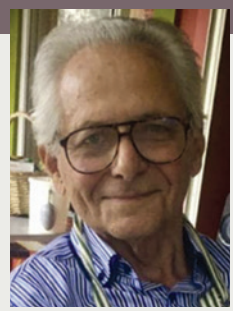
Crews was instrumental in creating a work environment infused with optimism, camaraderie and respect. Marnett described her as a caring and loving person with a strong moral compass, always available to provide personal and professional guidance and support to everyone in the lab and especially to international trainees.

She also made the lab a fun place. During a 2016 student colloquium, Marlene Jayne, secretary to the biochemistry department for 40 years, recalled how much Crews enjoyed tricking Cohen on April Fools' Day.

Crews is survived by daughter Heather Carmichael, son Jonathan Crews and four grandchildren.

— Andrea Pereyra

German A. Camejo



German A. Camejo, a globally recognized researcher in the field of lipoproteins who started a new era in atherosclerosis research, died Nov. 29, 2021, at the age of 85 in Gothenburg, Sweden.

Camejo was born in Venezuela in 1936. At the Universidad Central de Venezuela in Caracas, he studied with Werner G. Jaffé as an undergraduate. He moved to New York to obtain his Ph.D. from Albert Einstein College of Medicine and then returned to Caracas, where he started his academic career at the Universidad Central de Venezuela. He moved to the Venezuelan Research Institute as a principal researcher and deputy director; with the help of his lab's dedicated research, the institute achieved international recognition.

In 1986, Camejo and his wife, Eva, visited the Wallenberg Laboratory at Sahlgrenska University Hospital at the University of Gothenburg, Sweden, on a sabbatical leave and decided to stay there. He joined the lab as a professor of clinical biochemistry. In 1990, he joined AstraZeneca as a principal investigator in metabolism and head of the department of biochemistry. After his retirement from AstraZeneca at the age of 75, he joined the department of clinical chemistry at the Karolinska Institute, Stockholm, as an associate researcher.

Camejo spent his entire career studying the lipoprotein–proteoglycan interaction; his findings about the ionic interaction between positively charged apolipoproteins and the negatively charged surface of proteoglycans opened up a new avenue for studying atherosclerosis. He was also a leader in the development and characterization of PPAR modulators as a PI at AstraZeneca.

Among the awards Camejo received for his work were the Medal Francisco de Miranda for Academic Merit in 1988 and the Humberto Fernandez Moran Medal for Science Achievements in 2009. He also served as the president of the Venezuelan Atherosclerosis Society.

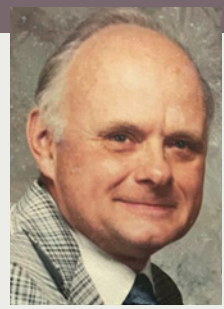
Camejo joined the American Society for Biochemistry and Molecular Biology in 2011. He was a member of the Journal of Lipid Research editorial board for more than 20 years, and the journal honored him with a tribute article in May. Throughout his research career, he published more than 200 research articles in peer-reviewed journals with 8,307 citations.

In addition to his scientific life, Camejo loved to spend his time cooking and trekking in the forests of Sweden.

He is survived by his wife, Eva, and children, Teobaldo, German A. Jr., Maqui, and Sarah Elena, and their families.

— Swarnali Roy

Clark Bublitz



Clark Bublitz, a metabolic enzymologist and a member of the American Society for Biochemistry and Molecular Biology since 1963, died Feb. 23. He was 94.

Born Dec. 8, 1927, in Merrill, Wisconsin, he was the son of Clark and Florence Bublitz. He attended the Pillsbury Military Academy in Owatonna, Minnesota, and then joined the Army near the end of World War II and was stationed in Rome.

After the war, Bublitz earned a Ph.D. in biochemistry from the University of Chicago. He then spent a year as a postdoctoral fellow at the Max Plank Institute in Germany, where he worked with Feodor Lynen, who later shared the 1964 Nobel Prize in physiology or medicine.

Bublitz joined the faculty at the Johns Hopkins University School of Medicine as an assistant professor. While at Hopkins, he met Deborah Keirstead, a medical student. They were married in 1958. Bublitz spent a year at St. Louis University in Missouri before moving to the University of Colorado Medical Center in Denver, where he remained until his retirement.

Bublitz studied enzymes involved in metabolism in the rat liver, beginning in the 1950s with enzymes that phosphorylate glycerol. He later focused on L-gulonate, a six-carbon metabolite that is an important intermediate between glucose and the pentose phosphate pathway. In the 1960s, collaborating frequently with Albert Lehninger, he studied the conversion of gulonate into ascorbic acid, or vitamin C.

Bublitz was an enthusiastic hiker, tennis player and Green Bay Packers fan.

He is survived by his wife, Deborah; five children, Nancy Dyer, Susan Schooleman, Philip Bublitz, Caroline Emsermann and Elizabeth Bublitz, and their spouses; and eight grandchildren.

Upcoming ASBMB events and deadlines

DECEMBER

3 *International Day of Persons with Disabilities*

12 Discover BMB late-breaking abstract submission site opens

6 Deuel early registration deadline

31 **Renew your ASBMB membership!**

JANUARY

10 Deuel abstract deadline

18 Discover BMB late-breaking abstract submission deadline (poster presentation only)

31 Discover BMB early bird registration deadline

31 Deuel deadline for cancellation/refunds

FEBRUARY

Black History Month

1 Deuel registration deadline

14 Discover BMB housing deadline

Dedicated to sharing science

Introduced to scientific research through her university's ASBMB Student Chapter, Lema Abuoqab works to make sure other students can have the same experience.

By Laura McCormick

Lema Abuoqab has always been drawn to science. She chose to attend Tufts University in Boston because the school offers a strong liberal arts education with access to world-class labs and hospitals — the best of both worlds.

However, Abuoqab started at Tufts in the fall of 2020, when undergraduate access to research labs was limited due to COVID-19.

Luckily, the Tufts American Society for Biochemistry and Molecular Biology Student Chapter — also known as the Tufts Biology Research Club, or TBR— quickly adapted to help first-years like Abuoqab. TBR developed the Virtual Adjacent Program, an online journal club that introduced new students to scientific research. Participants improved their skills in reading papers and interpreting data. As active Tufts researchers were invited to join the meetings, students also made valuable connections.

Following one such journal club, Abuoqab was struck by the work of Perrie O'Tierney–Ginn's laboratory and joined it as an undergraduate researcher in May 2021. Simultaneously, she joined the TBR executive board, or e-board, to play a larger role in the club's activities.

Abuoqab eagerly dove into research, studying the relationship between physical activity during pregnancy and placental lipid transport. With the help of an ASBMB travel award, she presented her work at the 2022 ASBMB annual meeting in Philadelphia. She loved the excitement of the conference.

"Just being in that atmosphere … was honestly the greatest thing ever," she said.

Although TBR is a vibrant club, Abuoqab and Ze'ev Drukker, who also serves on the e-board, were the only members to attend the meeting. Afterward, they began brainstorming a way to share the energy of a scientific conference with more club members.

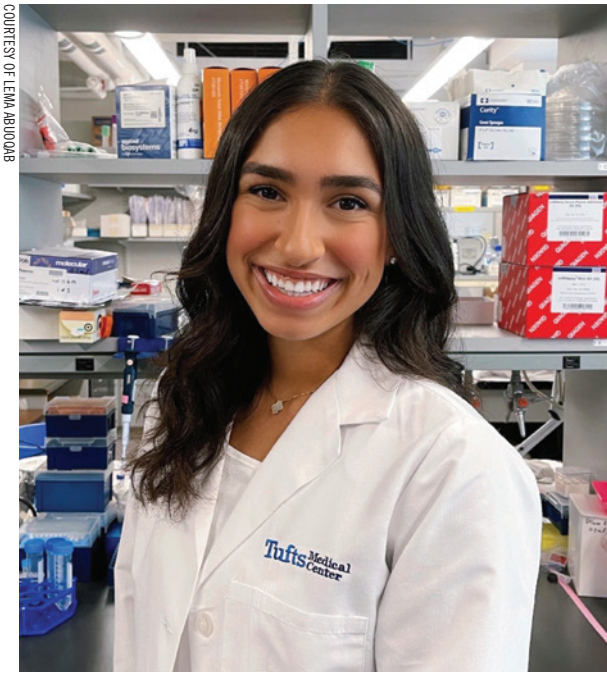
As a result, TBR plans to host its inaugural scientific conference at Tufts in spring 2023, and the members will make it open to all undergraduates across Boston. This spirit is typical of the club, Abuoqab noted.

"We are super dedicated to helping other students get as many opportunities and involved in research as possible," she said.

This year, Abuoqab is serving as club secretary and the director of conferences, building on her previous experience as speaker series coordinator.

Abuoqab aspires to be a pediatric orthopedic surgeon. She became interested in the field after shadowing at a local hospital, but her younger sister's scoliosis diagnosis helped cement her decision. Motivated by the words of her sister's doctor, Abuoqab authored a short booklet, "Embrace Your Brace," to reassure children that wearing a brace does not limit them.

COURTESY OF LEMA ABUOQAB



Lema Abuoqab serves as secretary and director of conferences for the Tufts University ASBMB Student Chapter.

Her passion for medical and science communication continues. Abuoqab also wrote and illustrated a children's book, "Eric's Brain Elementary." Based on a class project, it takes readers on a fun and factual tour of the brain. Her next venture is focused on the digestive system, and she hopes to develop the concept into a series of books about the human body.

Laura McCormick (lemccorm@email.unc.edu) is a graduate student in cell biology and physiology at the University of North Carolina at Chapel Hill. Follow her on Twitter: @le_mccorm.

2022 SEWER SCHOLARSHIP WINNERS ANNOUNCED

The American Society for Biochemistry and Molecular Biology is pleased to announce the recipients of the 2022 Marion B. Sewer Distinguished Scholarship.

The ASBMB's Maximizing Access Committee created this award in 2016 to support undergraduate students who demonstrate an interest in the fields of biochemistry and molecular biology and enhance the diversity of science. This year, thanks in part to a generous donation from New England Biolabs, the ASBMB is awarding ten $2,000 scholarships that will be applied to undergraduate tuition costs.

The award honors Marion B. Sewer, who died in January 2016 at age 43. Sewer was a principal investigator on projects devoted to increasing participation among historically underrepresented groups and furthering student training. Within the ASBMB, she organized the MAC's Interactive Mentoring Activities for Grantsmanship Enhancement workshop program for postdoctoral fellows and early-career scientists, known as IMAGE, which addresses disparities in scientists' ability to secure federal research grants. She also wrote about issues that historically underrepresented scientists face, such as impostor syndrome.

Here, the ten recipients of the 2022 Sewer scholarship describe their personal goals and how they promote diversity. Their statements have been edited.

Moyofoluwa (Rachel) Aguda, University at Buffalo

My career goal is to become a physician–scientist working directly with patients while seeking applicable knowledge that can improve health through research. As a physician–scientist, I hope to bridge the communication gap between research, patients and their health treatment plans, while encouraging the rise of more physician–scientists. After graduation, I will take a gap year to fulfill my obligation to the National Institutes of Health as a trainee before applying to M.D.–Ph.D. programs.

Rita Anoh, Mount St. Mary's University

After graduating with a double major in biochemistry and French, I intend to pursue my Ph.D. in biochemistry and structural biology and explore other areas of interest such as genetics and molecular biology during my training. As a scientist, my goal is to make science more accessible and to be a good mentor to trainees. I am passionate about not only inviting those from underrepresented backgrounds but also maintaining their active presence in the science community and fostering meaningful and productive experiences.

Sara Gallegos, Virginia Polytechnic Institute and State University

I aspire to advocate for easier access to science, technology, engineering and mathematics and provide mentorship for others seeking it. As a part of this, I would like to see literature and research more accessible and understandable to the general public. I have been proud to serve underserved communities at Virginia Tech. As a Howard Hughes Medical Institute student fellow, I represent members of historically underrepresented groups within the biochemistry department and attend student-led panels on how the university can advocate for diversity, equity and inclusion within STEM fields.

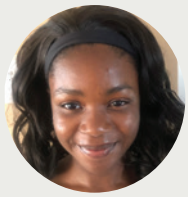
Natasha Garcia Rodriguez, University of Texas Rio Grande Valley

My goal is to attend naturopathic medical school at the Sonoram University of Health Sciences and continue gaining research experience at the Ric Scalzo Institute for Botanical Research. After completing these goals, I will be able to contribute a unique perspective to both naturopathic medicine and research, and I hope to serve as an ethnic minority woman health professional and

researcher in my community, making a positive and productive impact on patients, students and science.

Michelle Haigbea, College of the Holy Cross

My career goal is to become a pharmacist and use my pharmacy degree to act as a trusted link between medical doctors and patients. Pharmacists double check the dose of medication and its interactions with other medications to improve patient experience and health. Pharmacists are among the most accessible health care professionals because they commonly work in community settings. With the busyness of life and the rise of many diseases and illnesses, I wish to be a professional who is accessible over the counter, with or without appointment.

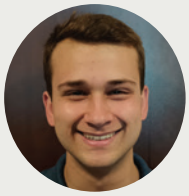


Phinn Markson, Edgewood College

I am a first-generation community college transfer student and a biology major. I intend to go on for a Ph.D. in research at the intersection of life sciences, data sciences and social sciences so I can facilitate increasing diversity and equity in research by decreasing bias in data collection. The life sciences hold solutions to numerous threats to humanity. To accomplish these solutions, life sciences must acknowledge the historical role we have played in structural sexism and racism. I hope to work toward this end by bridging data gaps and creating more equitable research questions.

Taylor McGee, Hampden–Sydney College

My primary research interest is anti-HIV cell therapy, and I will be applying to relevant Ph.D. programs and international fellowships. I would like to be a professor and be able to provide holistic and transformative mentorship experiences in much the same way that my professors have provided meaningful, transformative experiences for me.



Katie Nuñez, Towson University

After graduating with a degree in molecular biology, biochemistry and bioinformatics, I plan to pursue a postbaccalaureate fellowship at the National Institutes of Health to gain experiences with translational research. I then will apply to doctoral programs for immunology or molecular biology. I plan to remain in the field of immunology or branch into molecular medicine as a researcher, as I enjoy my current research surrounding septic shock. Figuring out the inner workings of the human immune system and exploring research and treatments of the disease has been very rewarding.

Sam J. Shepard, University of North Carolina at Asheville

As an aspiring physician–scientist, I hope to take an interdisciplinary approach to better understanding and treating diseases. Additionally, as a trans scientist with core values of anti-racism and anti-oppression, I am committed to building inroads for historically excluded groups to excel in and enjoy science and medicine. My scientific interests center around the cellular mechanisms of cancer, immunology and the mitochondria. I am currently looking for postbaccalaureate research opportunities to explore these interests further before applying to MD-PhD programs.

Myrah Sheriff, University of Texas at Austin

I plan to attend medical school to pursue a career as a pediatrician. My choice of career is largely due to my own experience with having surgery on my face at a very young age. I always have wanted to provide medical care to young children, and I have a sincere interest in helping patients cope with the repercussions of surgery, both positive and negative. I am interested in spreading education about medical resources and improving access to primary care physicians, especially in my father's village of Assin–Fosu, Ghana. I would love to set up a donation program where secondhand equipment from the U.S. could be sent to improve conditions in developing nations.

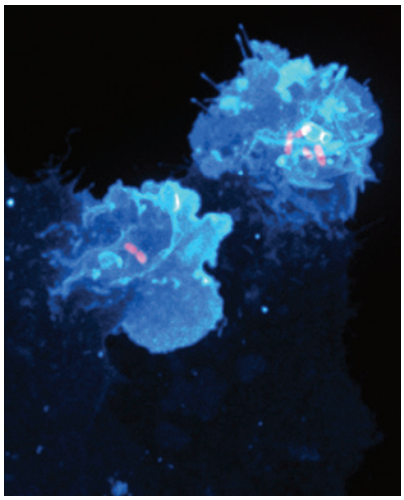
Unconventional phosphoinositide synthesis

By Greg Fairn & Jayatee Ray

Salmonella and Shigella bacteria cause or contribute to human diseases ranging from acute food poisoning to life-threatening typhoid fever and gall bladder cancer. Both are on a World Health Organization list of priority pathogens for developing new antibiotics. To help combat the effects of these bacteria, our lab is studying the way they synthesize the tiny lipids known as 3-phosphoinositides to hijack the host.

These two bacteria can inject bacterial proteins called effectors into target human cells, allowing them to acquire nutrients and reproduce in the cell. Researchers have described one such effector in Salmonella, SopB, and its homolog in Shigella, IpgD, as phosphatidylinositol 4,5-bisphosphate, or PI4,5P_2, phosphatases. These phosphatases deplete PI4,5P_2, an important lipid in human cells for proper actin dynamics, endocytosis and ion channel regulation.

Although they deplete PI4,5P_2, these bacterial phosphatases increase two other phosphoinositides, PI3,4P_2 and PI3,4,5P_3. Production of these two lipids stimulates the activation of small GTPases, including Rac1 and Cdc42, that induce robust and localized plasma membrane ruffling near the site of bacterial attachment. Ultimately, the bacteria invade and hijack the host cells. Production of PI3,4P_2 and PI3,4,5P_3 also promotes the survival of the now-infected cell by activating the serine/threonine protein kinase Akt and other downstream pathways.



COURTESY OF GREG FAIRN AND GLENN WALPOLE

When cells are invaded by Salmonella (pink), the lipid PI3,4P2 (light blue) is very intense around the bacteria.

How could a phosphatase seemingly increase the levels of phosphoinositides typically produced by kinases? For years, researchers thought that SopB and IpgD somehow were activating multiple host phosphoinositide 3-kinases, or PI3Ks. Inhibiting individual PI3Ks did not prevent the function of the effectors and the production of PI3,4P_2 and PI3,4,5P_3. Could the ability to produce PI3,4P_2 and PI3,4,5P_3 be intrinsic to SopB and IpgD? In support of this notion, researchers established that the catalytic cysteine residue in the active site was required for both the reduction of PI4,5P_2 and the production of PI3,4P_2/PI3,4,5P_3.

SopB and IpgD are homologs of human phosphoinositide phosphatases, such as synaptojanin and INPP4B, that are related to the larger family of protein tyrosine phosphatases. These phosphatases contain active cysteine residues, and as part of the enzymatic cycle, there is a cysteine–phosphate intermediate that then is hydrolyzed by water. SopB and IpgD operate on the membrane surface, raising the possibility that another lipid, not water, could attack the cysteine–phosphate intermediate. In this situation, the effector would behave as a phosphotransferase and not a phosphatase.

Armed with this hypothesis, we demonstrated that SopB could generate PI3,4,5P_3/PI3,4P_2 in a test tube when supplied with only PI4,5P_2 as a substrate. SopB is a very active phosphatase; if given enough time, the phosphoinositides are reduced to PI and the free inorganic phosphate. Given the redundancy of PI3Ks in mammalian cells, we used baker's yeast, which naturally lacks class I and II PI3Ks and remains viable even when the sole class III PI3K is inactivated. When we introduced SopB into these mutant yeast cells, which contain ample amounts of PI4,5P_2 but no PI3K activity, PI3,4P_2 was formed.

Greg Fairn (gfairn@dal.ca) is a professor of pathology at Dalhousie University.

Jayatee Ray (jy231522@dal.ca) is a graduate student studying pathology at Dalhousie University.

A new way to target mosquito-borne viruses

By Chloe Kirk

Dengue and Zika are two mosquito-borne viruses that have evaded effective vaccine development for decades. Affecting approximately 400 million people annually, they are members of the Flaviviridae family, a group of RNA viruses that are closely related in structure.

While a handful of approved vaccines exist for certain flaviviruses in humans, including the dengue vaccine Dengvaxia, there is still significant room to improve the safety and efficacy of these vaccines, most of which show poor efficacy in animal studies and waning immunity in humans. The traditional approach uses a live-attenuated, or weakened, form of the virus that causes a disease to make the corresponding vaccine. Replication production has been a major challenge in vaccine development for flaviviruses, as live-attenuated virus vaccines have difficulty replicating evenly.

Thanh Phan and Matthew Hvasta, Ph.D. students in Brian Kuhlman's lab at the University of North Carolina at Chapel Hill, set out to improve dengue and Zika vaccines. Instead of the traditional live-attenuated virus approach, they used small sections, or subunits, of the virus as a way for the vaccine to recognize and target the virus. In a recent paper in the **Journal of Biological Chemistry**, the team writes about the development of this subunit vaccine, which Phan and Hvasta describe as "putting two Tetris pieces together and having them fit as tightly as possible."

Their research has led the two to use a soluble version of the envelope proteins, or sE, on the surface of the dengue and Zika viruses as candidates for vaccine antigens. For sE proteins to be a viable subunit vaccine, they must be easy to produce and maintain stability in the correct conformation.

Previous work in the Kuhlman lab also took this divergent vaccine approach by identifying specific dengue mutations to stabilize sE proteins for dengue serotype DENV2, which significantly raised expression yields. Phan and Hvasta used this information to test the same mutations of Zika and the remaining dengue serotypes (DENV1, 3 and 4) by searching for and mutating similar residues as those mutated for DENV2. They found increased stability as well as a fourfold to 250-fold increase in production yields.

Creating a stable, high-expression sE protein opens the door for improved dengue and Zika vaccines as well as the potential to target other viruses in the Flaviviridae family, such as yellow fever. The next steps for this project are to perform mouse studies and measure the immune response to these sE proteins.

"Our goal is to develop a safe vaccine for dengue viruses, which will directly affect countries in the (sub) tropical areas of the world where dengue is endemic," Phan and Hvasta wrote in an email. "A safe dengue vaccine will allow these nations to reallocate funds from what would usually be used to treat dengue to hopefully being able to treat other health care necessities."

DOI: 10.1016/j.jbc.2022.102079

Chloe Kirk (cck22@miami.edu) is working toward her Ph.D. in biochemistry and molecular biology at the University of Miami. Her interests are science research, communication and outreach. Follow her on Twitter: @chloeckirk

How proteolysis controls the Legionnaires' pathogen

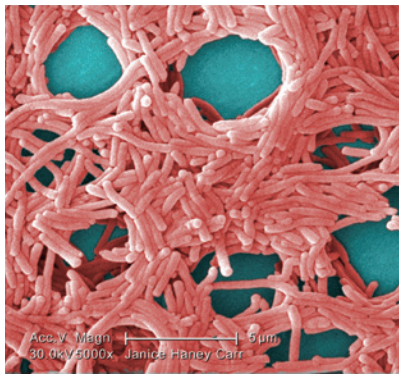
By Inayah Entzminger

Legionnaires' disease is a severe pneumonia caused by breathing or swallowing water containing the bacterial pathogen Legionella pneumophila, which has a biphasic life cycle — a replicative phase when the bacteria are nonvirulent and a transmissive phase when they are virulent.

Researchers at the Run Ze Laboratory for Gastrointestinal Microbiome Study at Sun Yat-sen University in Guangzhou, China, have discovered that the biphasic life cycle depends on regulation of protein homeostasis by caseinolytic protease–dependent proteolysis. In their paper published in the journal **Molecular & Cellular Proteomics**, Zhenhuang Ge and co-authors describe how this ClpP-dependent proteolysis directly or indirectly plays a regulatory role in cellular events in L. pneumophila.

Ge described the team's previous results on the physiology and pathogenesis of the ClpP protease homologue in L. pneumophila: "We found that ClpP is required for the transmission traits and cell division (and) impairs the virulence of L. pneumophila and the optimal translocation of effector proteins."

This study continued that research, investigating the profiles of global protein abundance during replicative-to-transmissive phase transitions. During the virulence phase, approximately 330 effector proteins are translocated into host cells, triggering direct manipulation of host cell signaling pathways. However, this translocation is not simultaneous, which hints at a temporal control mechanism for the effector proteins. Ge's team found similar temporal control mechanisms in proteomic experiments where some proteins were synthesized only during the replicative phase and not the transmissive phase.



JANICE HANEY CARR / CDC

This colorized scanning electron micrograph shows a large group of Gram-negative Legionella pneumophila bacteria.

These controls have allowed L. pneumophila to adapt to face many environments, both natural and human-made. The bacteria colonize water from 0 C to 60 C and in the pH range of 5.5 to 9.2. It can be found in water systems such as showerheads and faucets and even windshield fluid tanks of vehicles.

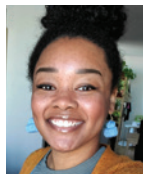
"(L. pneumophila) do the right things at the right time to complete the biological cycle; otherwise the disruption will have devastating consequences," Ge explained, comparing the bacteria's pattern to a human's daily habits. "In the alternation of day and night, we rest at night and work during the day to ensure a healthy and long-lasting life."

The ClpP-dependent proteolysis study directly compared protein abundances during the replicative and transmissive phases. During the replicative phase, the proteins associated with ribosome, amino sugar, nucleotide sugar and biotin metabolism pathways were enriched most significantly. These are all pathways associated with replication and growth. In contrast, during the transmissive phase, flagellar assembly proteins, signal transduction proteins, and proteins associated with microbial metabolic pathways such as propanoate and ketone body metabolism were more enriched.

When L. pneumophila cells lacked ClpP, the metabolic pathways of both the replicative and transmissive phases were disordered. The signaling alarmone ppGpp is a trigger for L. pneumophila differentiation. The expression of SpoT, an enzyme that controls the accumulation of ppGpp in response to fatty acid depletion, almost completely restored the life cycle transition of L. pneumophila, but virulence never was recovered. This demonstrated that bacterial virulence requires ClpP regulation of the effector proteins and secretion system

DOI: 10.1016/j.mcpro.2022.100233

Inayah Entzminger (ientzminger@gradcenter.cuny.edu) is a doctoral student at the City University of New York Graduate Center, researching the positive RNA strand barley yellow dwarf virus.



Can stress protect mycobacteria?

By Anna Hu

Every now and then, what seems like a minor observation leads to a multiyear journey.

Yasu Morita's lab at the University of Massachusetts Amherst studies the pathogenesis of mycobacteria, a genus that includes tuberculosis- and leprosy-causing species. Specifically, they study the multilayered plasma membrane and cell wall system that protect these bacteria — from antiseptic cleaning agents, for instance.

While working on an unrelated project, lab members noticed that membrane fluidization led two membrane glycolipids (lipids with a carbohydrate attached via glycosidic bond) called phosphatidylinositol mannosides, or PIMs, to undergo acylation. The two triacylated PIMs were transformed into their tetraacylated forms.

The lab's study exploring the conditions for and effects of this acylation recently was published in the **Journal of Lipid Research**. Peter Nguyen, at the time an undergraduate researcher in the Morita lab, was first author on the paper. "We wanted to study this phenomenon, this physiological response to a membrane fluidizing, because we thought it might be significant to how mycobacterial cells can respond to certain stresses, like environmental threats," he said.

Early on, the lab decided to take a systematic approach. Early experiments showed that PIMs are the only major class of bacterial lipids affected by benzyl alcohol, a membrane fluidizer, and that the effect is a biological response (as opposed to an experimental artifact). The scientists also tested other types of membrane stressors, ultimately finding that only membrane fluidizers caused the full acylation effect.

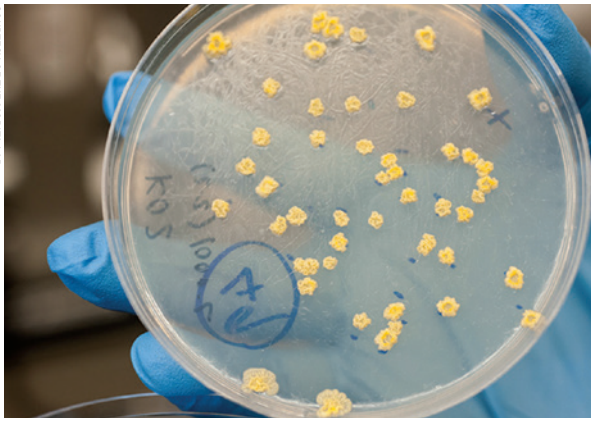
This particular result came about halfway through the experimental process, which was a relief, Nguyen said. "If there was anything (else) being thrown at it that caused acylation, it would have been a much different story."

One surprising result came when the scientists examined the reaction kinetics of acylation. As with all the experiments, they used high-performance thin-layer chromatography to visualize the presence of each PIM qualitatively and a mannose standard curve to find relative quantities. A time course experiment showed that the conversion of triacylated to tetraacylated PIMs took just 20 minutes — one of the fastest cases of mass lipid conversions seen to date. Most mass conversions of mature lipids take several hours, so this reaction's speed indicates an enzymatic mechanism independent of protein synthesis.

The researchers don't know what this enzyme is, but Nguyen said, "It seems to play a significant role in what's happening in response to environmental threats."

They have shown that rapid PIM acylation is conserved among mycobacteria including the tuberculosis pathogen. Now, they need to identify the acyltransferase to understand better how these cells respond to stress, he added. "A lot of the membrane synthesis in mycobacteria is not well (understood), which is a big issue because tuberculosis is still a huge public health threat."

The researchers also looked at some practical implications of PIM acylation by testing the response of



COURTESY OF THE MORITA LAB

Membrane fluidizers such as benzyl alcohol disrupt mycobacterial membranes, leading to inositol acylation of phosphatidylinositol mannosides.

Mycobacterium smegmatis, a nonpathogenic cousin of Mycobacterium tuberculosis, to antiseptic detergents benzethonium chloride and sodium dodecyl sulfate, or BTC and SDS, with and without a membrane fluidizing pretreatment. While the SDS sensitivity was unaffected by benzyl alcohol fluidization, the pretreated cells were far more resistant to BTC than their untreated counterparts.

The team hypothesizes that increased PIM acylation strengthens the membrane and thus the bacteria's defenses. While it's not great news for humans trying to avoid life-threatening diseases, the results bring researchers one step closer to understanding how mycobacteria membranes work and, by extension, how we can counter them.

DOI: 10.1016/j.jlr.2022.100262

Anna Hu (ahu4@wellesley.edu) earned her bachelor's degree in biochemistry from Wellesley College and is now a research assistant at the Harvard School of Public Health. She is a volunteer writer for ASBMB Today.

From the journals

By Ken Farabaugh & Nivedita Uday Hedgekar

We offer summaries of papers recently published in the **Journal of Biological Chemistry,** the **Journal of Lipid Research** and **Molecular & Cellular Proteomics**.

Biased hormonal signaling

The parathyroid hormone-related protein, or PTHrP, is involved in many developmental processes, including breast, bone and tooth formation. PTHrP has been shown to initiate two simultaneous downstream G protein–coupled receptor signaling cascades triggered by secondary messengers cAMP and Ca^{2+}. In addition, PTHrP is alternatively spliced in the body, but most of our knowledge of its various roles is based on studies performed with its 36–amino acid N-terminal fragment rather than the whole protein.

Karina Peña and others in Jean-Pierre Vilardaga's laboratory at the University of Pittsburgh investigated the effects of downstream signaling using the whole 141–amino acid protein hormone. Using techniques such as FRET to record real-time cAMP production, the researchers confirmed that the N-terminal PTHrP fragment induces a transient cAMP response, while the complete PTHrP induces a sustained cAMP response. Furthermore, using an antagonist that blocks this sustained cAMP production, they showed this signaling was dependent on ligand–receptor complexes at the cell surface, rather than those being cycled via endocytosis. The team proposed that a positively charged sequence not present in the N-terminal PTHrP allows the hormone to attach to the cell surface.

Together, these findings suggest PTHrP signaling is biased toward cAMP production at the cell membrane rather than Ca^{2+}-based downstream signaling.

The work was published in the **Journal of Biological Chemistry**.
DOI: 10.1016/j.jbc.2022.102332

Probing weaknesses in the T cell surface

T cells are white blood cells that play a central role in the body's adaptive immune response. In particular, cytotoxic T cells, or CD8+ T cells, promote tumor-cell killing and are used in cancer therapy.

Researchers know the cell surface proteome, or surfaceome, mediates T cell interactions with the external environment but do not yet fully understand how external factors affect that surfaceome. Immunosuppressive factors in the tumor microenvironment, or TME, can impair T cell function and limit the antitumor immune response by changing cell surface receptors and surface proteins.

To study surface proteome remodeling in T cells in greater detail, James Byrnes and a research team at the University of California, San Francisco, performed quantitative cell surface proteomics on primary human CD8+ T cells to determine how immunosuppressive TME factors, Tregs (regulatory T cells a specialized subpopulation of T cells that act to suppress immune response), and hypoxia affected the activated CD8+ surfaceome. Consistent with suppressed cell activation, the Tregs partly reversed activation-induced changes in CD8+ T cells. Hypoxia triggered large-scale surfaceomic remodeling consistent with a general cellular response to the metabolic demands of a low-oxygen environment. In both conditions, the researchers saw reduced expression of proteins primarily involved in nutrient transport. These changes could limit T cell nutrient uptake during activation and, subsequently, T cell proliferation.

These findings were recently published in the journal **Molecular & Cellular Proteomics**.
DOI: 10.1016/j.mcpro.2022.100217

A new way to measure lipoprotein(a)

Lipoprotein(a), or Lp(a), is a genetic risk factor for cardiovascular disease and aortic stenosis. Similar in composition to low-density lipoprotein, Lp(a) is characterized by the carbohydrate-rich apolipoprotein(a), or apo(a), which imparts distinct pathophysiological and metabolic characteristics.

Apo(a) contains repeated kringle structures, or KIV, which are protein domains that fold into large loops stabilized by three disulfide linkages. KIV are formed by 10 subtypes (KIV1 to KIV10), each present as a single copy except for KIV2, which is present in a variable number, ranging from one to more than 40 identical repeats, in different individuals. Thus, people may inherit apo(a) molecular weight ranging from about 300 to 800 kilodaltons. This means plasma levels of Lp(a) will be over- or underestimated, making it challenging to measure Lp(a) levels accurately.

Santica Marcovina of Medpace Reference Laboratories and a team of

researchers recently developed a new isoform-independent sandwich Lp(a) enzyme-linked immunosorbent assay, or ELISA, to measure Lp(a). The test captures Lp(a) with monoclonal antibody LPA4 primarily directed to an epitope in apo(a) KIV2 and detects it with monoclonal antibody LPA-KIV9 directed to a single antigenic site present on KIV9.

When tested on 64 samples with known apo(a) isoforms, the new assay performed as well as standard methods. A recent paper in the **Journal of Lipid Research** describes the development and validation of the assay, which the researchers believe will benefit research laboratories that are trying to eliminate the confounding bias generated by heterogenous apo(a) isoform sizes.
DOI:10.1016/j.jlr.2022.100239

Uncovering a source of metabolized cholesterol

Once absorbed by the body, cholesterol is converted to cholesteryl esters to facilitate efficient transport. Although lipoproteins can take up free cholesterol, it is confined to their outer surface. With conversion to cholesteryl esters, more cholesterol can be packaged inside lipoproteins, vastly increasing the lipoproteins' capacity and allowing cholesterol to move more efficiently through the bloodstream.

Mutations in the lecithin–cholesterol acyltransferase, or LCAT, gene cause familial LCAT deficiency, or FLD, a very rare metabolic disorder that impairs the body's ability to esterify cholesterol. LCAT is the only enzyme to esterify cholesterol in plasma, whereas sterol O-acyltransferases 1 and 2, or SOAT1 and SOAT2, esterify cellular cholesterol in cells.

Patients with FLD have severe high-density lipoprotein deficiency, hypertriglyceridemia and an increased ratio of unesterified to total cholesterol. However, recent patient studies showed that despite the absence of LCAT activity, carriers have circulating cholesterol esters, or CEs, and their plasma levels are highly variable.

Chiara Pavanello of the Università degli Studi di Milano and a team of researchers evaluated the origin of circulating CEs in plasma samples from carriers of LCAT deficiency. To their surprise, they found that, in the absence of LCAT-derived CEs, CEs present in apoB-containing lipoproteins derived from hepatic and intestinal SOAT2. This work has been detailed in a recent publication in the **Journal of Lipid Research**.

This is significant because other studies have shown that the types of CEs that predominate in plasma contribute to the relative degree of atherogenicity (formation of abnormal fatty or lipid masses in arterial walls).
DOI: 10.1016/j.jlr.2022.100232

Exciting peptide drugs for heart disease

Atrial fibrillation, a heart disease characterized by faster and often irregular heartbeats, is associated with passive stretching of heart chamber muscle. While current treatments are expensive and have negative side effects, drugs that target the excitatory current-mediating stretch-activated channels, or SACs, in the heart could be extremely effective.

The venom from a species of tarantula can inhibit similar mechanosensitive ion channels. In a recent study in the **Journal of Biological Chemistry**, a team of researchers from Xuzhou Medical University in China sought to identify features of the venom molecule GsMTx4, such as the inhibitor–cystine knot or specific loop folds, that could be used to enhance the specificity of peptide drugs against SACs.

RYAN HYDE / UNSPLASH

The venom molecule GsMTx4 was isolated from the Chilean flame tarantula Grammostola spatulata, which is native to South America.

The authors designed two types of short peptides that were capable of specifically inhibiting a stretch-activated potassium channel also known as SAKcaC. One peptide consisted of a short loop region of GsMTx4, and the other mimicked the fold of this region.

The finding that both types of peptides could inhibit normal SAKcaC but not modified inactive SAKcaC indicated that these peptides act on the mechanical gating of the ion channel. This could form the basis of a new strategy for anti-arrhythmic drug development.
DOI: 10.1016/j.jbc.2022.102326

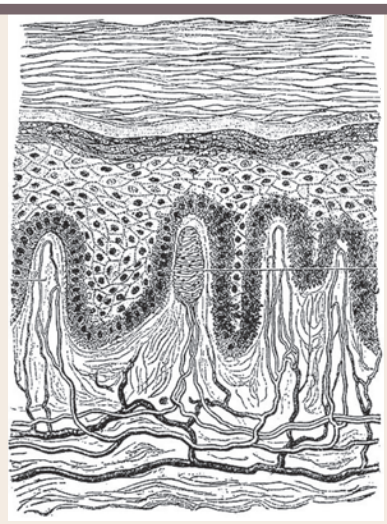
—Ken Farabaugh

A better mode for counting ceramides

Ceramides are important lipids in the intercellular spaces of the stratum corneum, or SC, the outermost layer of the epidermis. These structurally varied and complex sphingolipids contain derivatives of sphingosine bases in amide linkage with a variety of fatty acids. Epidermal ceramides have varying chain length, type and extent of hydroxylation, saturation, and other variables. They play an essential role in structuring and maintaining the skin's water permeability.

Although researchers have found ceramides with long-chain bases, or LCBs, of various lengths in the stratum corneum, no one has published a quantitative analysis yet. Previous measures using liquid chromatography–mass spectrometry or liquid chromatography–tandem mass spectrometry, known as LC-MS and LC-MS/MS, have reported between 100 and 400 ceramide species. These studies have drawbacks, however; ceramide species are reported solely based on the sum of their LCB and FA chain lengths, or coverage of ceramide species is less thorough due to low sensitivity of product ion scanning analysis.

Madoka Suzuki and a team of researchers at Hokkaido University, Japan, recently conducted LC-MS/MS on SC ceramides using the specialized multiple reaction monitoring mode, which can detect and quantify multiple molecular species in a single measurement. Using this method, the researchers detected individual ceramide species differing in both the LCB and FA chain lengths and quantified the largest number of ceramide species reported to date (1,327 unbound ceramides and 254 protein-bound ceramides). Their recent study in the **Journal of Lipid Research** provides a molecular basis for elucidating human SC ceramide diversity and the pathogenesis of skin disorders.
DOI: 10.1016/j.jlr.2022.100235



HENRY VANDYKE CARTER/WIKIMEDIA COMMONS

Researchers have found a new way to count ceramides in the stratum corneum, the outermost layer of the skin, shown at the top of this illustration of all layers of the epidermis.

— Nivedita Uday Hedgekar

Improving single-cell proteomics two ways

Single-cell proteomics, or scMS, uses liquid chromatography–mass spectrometry based proteomics. As this technology evolves, researchers need to better understand the proteome, both the proteins quantified per cell and the quantitative performance thereof. However, multiplexing scMS is challenging; high ion injection times and high-resolution spectra are needed to quantify the single-cell signal.

A new real-time search, or RTS, on the Orbitrap Eclipse Tribrid mass spectrometer combined with synchronous precursor selection–triple-stage mass spectrometry, or SPS-MS3, acquisition could help researchers measure samples that are multiplexed using isobaric tags. To show this, Benjamin Furtwängler and a team of researchers from the University of Copenhagen, the Technical University of Denmark and other institutions compared classical MS2 acquisition to RTS-MS3 and a new RTS-MS2 acquisition method called RETICLE and found that both RTS methods outperformed classical MS2.

The researchers recently published their findings in the journal **Molecular & Cellular Proteomics**. They found that scMS data acquisition using the tribrid design in combination with RTS can result in better scMS data sets. RTS-MS3 provided similar proteome coverage to MS2 at higher quantitative accuracy, whereas RETICLE resulted in higher proteome coverage. Thus, RETICLE could be especially useful for high-throughput applications, such as building single-cell atlases, whereas RTS-MS3 could provide the accuracy needed to model complex protein networks.
DOI: 10.1016/j.mcpro.2022.100219

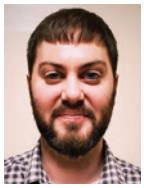
RNA sensing of basic pH

One strategy used by bacteria to regulate gene expression is a folded structure of the 5'-untranslated

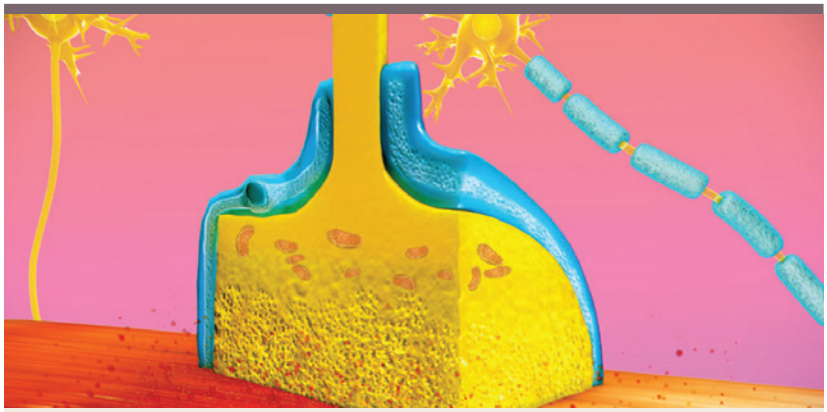
regions of messenger RNAs, also known as a riboswitch, which can obscure the ribosome binding site. One such riboswitch is the pH-responsive element, or PRE, which blocks translation of the mRNA at neutral pH but unfolds and refolds at alkaline (basic) pH, allowing the ribosome to translate the message into protein. Previous studies have suggested that alkaline pH–induced pausing of the RNA polymerase during transcription allows time for the PRE to refold into a translationally active form.

In a recent study published in the **Journal of Biological Chemistry**, Christine Stephen and Tatiana Mishanina at the University of California, San Diego, demonstrate that alkaline pH does affect RNA polymerase pausing but in the other direction — it actually decreases the length of the pause. These results suggest that the RNA itself may be involved in sensing high pH and may induce its own conformational change to allow co-transcriptional translation independent of RNA polymerase pausing. The authors propose that a pH-induced change in 3D RNA structure could lead to the observed effects and expand our knowledge of the repertoire of mechanisms of gene regulation.
DOI: 10.1016/j.jbc.2022.102302

Ken Farabaugh (kfarabaugh@asbmb.org) is the ASBMB's science editor.



Nivedita Uday Hegdekar (nivedita.hegdekar@gmail.com) is a recent Ph.D. graduate in biochemistry and molecular biology from the University of Maryland, Baltimore. Follow her on Twitter: @NiveditaHegdek1.



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Neurons stimulate the muscle cells by producing acetylcholine or similar substances at the neuromuscular junction, causing contraction of the muscle fibers.

Muscling in on a signaling pathway

Muscle-specific receptor tyrosine kinase, or MuSK, plays an essential role in forming neuromuscular junctions. It is activated by a nerve-derived proteoglycan called agrin through low-density lipoprotein receptor–related protein 4, or LRP4. Several neuromuscular diseases are associated with the MuSK signaling pathway; in one of these, myasthenia gravis, autoantibodies target various components of that pathway. Similarly, mutations in genes that function within the pathway characterize congenital myasthenic syndromes.

Researchers use MuSK-activating antibody, an agonist antibody, or Ab, to explore the benefits of MuSK activation at the neuromuscular junction. In two recent studies, this Ab acted in an LRP4-independent manner in mouse models of amyotrophic lateral sclerosis. Both studies reported delayed denervation upon treatment with the MuSK agonist Ab, with notable differences in downstream functional outcomes. Given these observations, Hanna Budayeva and a team of researchers at Genentech used Ab to compare direct MuSK activation to coreceptor sequestration and assess how much Ab-mediated MuSK activation recapitulates the physiological agrin-mediated activation.

The team performed dose–response and time-course experiments on C2C12 myotubes and systematically compared site-specific phosphorylation downstream of MuSK activation by agrin and MuSK-activating Ab. Using mass spectrometry–based proteomics, they tested two MuSK agonists, and observed novel but similar intracellular responses at known and newly identified MuSK signaling components. Among these responses was inducible tyrosine phosphorylation of multiple Rab GTPases that was blocked by MuSK inhibition. Moreover, mutation of this site in Rab10 disrupted association with its interacting proteins.

The researchers characterized MuSK signaling in depth and identified a role for Rab GTPases in the downstream signaling of this MuSK pathway. These findings were recently published in the journal **Molecular & Cellular Proteomics**.
DOI: 10.1016/j.mcpro.2022.100221

— Nivedita Uday Hedgekar

THE BEST OF BMB 2022

By Laurel Oldach

For the second consecutive year, the ASBMB Today team is proud to present a list of exciting developments in biochemistry and molecular biology. This year's nominees, chosen from ASBMB member nominations and significant science headlines throughout the year, illuminate several trends.

The revolution in structural biology launched by a new generation of powerful computational models has continued to spread, bringing multiprotein structural complexes into reach. Meanwhile, researchers are finding new ways to understand more flexible proteins' structures, exploring ensemble modeling and evolutionary constraints on intrinsically disordered regions.

High-throughput studies continue to flourish. Single-cell transcriptomics and spatial transcriptomics can yield powerful insights when wielded in combination. Ribosome profiling and metabolomics are uncovering new insights into how cells regulate basic homeostatic challenges and how organisms respond to stimuli.

Other studies show how drug development is being influenced by computational tools that aim to save time in the lab, from peptide design to enzymatic activity prediction.

Still, there is sometimes no substitute for in-depth investigation of a single target, as revealed by one study that dug in to find that an enzyme's true function is nothing like what was annotated — and that it carries out a reaction never before observed in nature.

We applaud the authors of this year's Best of BMB nominees and look forward to a new year filled with even more exciting discoveries.

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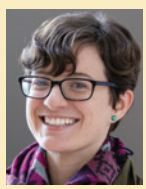


Evolutionary constraints on disordered proteins

Roughly 40% of the proteome is intrinsically disordered; these proteins and domains behave differently from structured proteins, rarely adopting just one stable structure. Instead, it can be useful to think of them dynamically moving through a wide range of favorable conformations known as an ensemble.

Many structured proteins are under evolutionary pressure that constrains how much they can change over time. Too large a shift in amino acid sequence may compromise function, unless a secondary change happens to compensate. For intrinsically disordered proteins, however, it is more difficult to determine whether ensembles undergo the same selection pressure. Multiple sequence alignments often show significant changes to a disordered region's primary amino acid sequence, sometimes including dramatic changes in length.

"If a protein is under selection, you expect (sequence) conservation, and we couldn't see it," said Lucia Chemes, a professor at Argentina's Universidad Nacional de San Martín. Still, studies of disordered proteins have made it clear over time that they have important conserved functions. Chemes said, "There's evidence that there must be conservation of function — so how does this happen, if the sequence changes so much?"

To find out, Chemes' team chose as a model system an adenovirus protein that disrupts a host transcription–repression complex. The viral protein must work rapidly early in infection, when its levels are low, to hijack the host cell cycle. Therefore, high-affinity binding is very important.

How much the viral protein can disrupt the complex depends on two short linear motifs that associate directly with the translation repressor, but the lab found that the strength of binding is also governed by an intrinsically disordered region that connects the two linear motifs. Using proteins constructed of the two motifs separated by different linkers, the researchers confirmed that the linkers have the optimal length to tether the linear motifs closely enough together to reach their binding sites and boost binding affinity at both sites. Any longer, and the linear motifs could flop through too many conformations, missing their binding target, while a shorter linker prevented both linear motifs from binding at once.

When comparing homologous proteins from viruses targeting different mammalian species, whose linear sequences varied in length from 40 to 75 amino acids, the lab was surprised to find that all-atom structural modeling predicted a consistent end-to-end distance.

About 40% of the proteome is thought to be disordered. Researchers are beginning to explore the evolutionary rules that govern these proteins.

Closer packing and lower density of charge per residues enabled longer linear sequences to pack into the same length as shorter ones. That confirmed that evolutionary constraints on the ensemble structure ensured its function, even when its sequence fluctuated.

"It's clear that there's more conserved than meets the eye when you see an alignment," Chemes said. But the conserved feature defining an ensemble may not always be end-to-end distance. The next challenge for the field will be to identify the features that need to be conserved in each intrinsically disordered protein.

Giant, intricate structures

Structural biologists increasingly are able to determine in intricate detail the baroque structures of large protein complexes with important roles in the cell. This year, that was especially clear with the nuclear pore complex, or NPC.

A special issue of the journal Science featured five papers that tackled the NPC from various angles and in different species, in what senior editor Di Jiang called "a triumph of experimental structural biology."

The nuclear pore complex includes four rings built from symmetrically repeated patterns of about 30 nucleoporin proteins. The complex is enormous, comprising roughly 1,000 protein subunits in total. This structure controls access to the nucleus, selectively allowing cargo such as signaling proteins and mRNAs in or out of the nucleus. It also, researchers recently have shown, can dilate and contract, changing the diameter of the central channel by almost 50%.

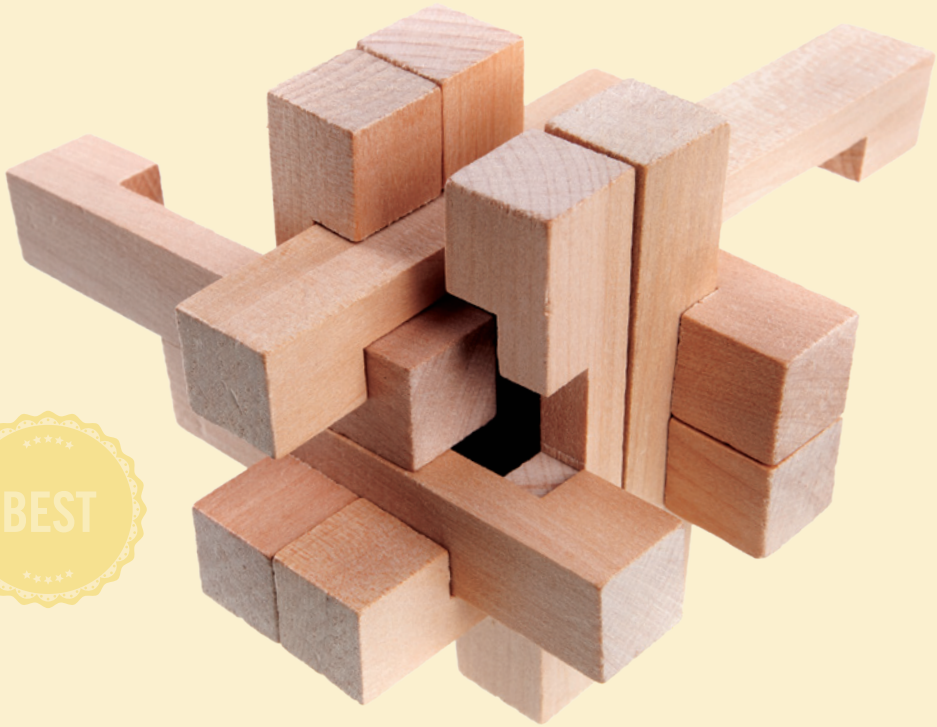
Building on advances in the structure of the human NPC's core rings published in 2016, three research teams tackled the cytoplasmic face of the NPC in human, frog and yeast cells. Each combined knowledge about the structures of individual nucleoporins and small groups of proteins, determined through biochemistry, crystallography or protein structure prediction, with larger-scale but blurrier models of the NPC as a whole derived from cryo-electron microscopy or tomography. Hao Wu, a structural biologist at Harvard Medical School who led one of the research teams, compared the workflow to solving a jigsaw puzzle by fitting the smaller subunits into the larger complex's outlines.

One of the three teams that studied the cytoplasmic face, led by André Hoelz at Caltech, also published a second paper investigating linker nucleoporins buried deep in the core in the nuclear envelope. The team probed the combination of flexible and tight crosslinks that allow the inner channel of the NPC to dilate but also constrain its expansion.

A fourth team, from Martin Beck's lab at the Max Planck Institute of Biophysics, published an integrative structural analysis that took on the whole NPC. The researchers used cryo-electron tomography to develop a model of the whole complex in its constricted and dilated conformations along with structural prediction to figure out multiple possible conformations of uncharacterized scaffold nucleoporins. Like the researchers studying the cytoplasmic face of the NPC, the team then fit these subunits into a larger model — this one equipped for molecular dynamics simulations that enabled them to predict how the pore complex as a whole might move.

The work has important implications for how the cell builds one of its most complex machines and for understanding how various molecules pass in and out of the nucleus. It also has inspired researchers to use similar techniques to tackle other large complexes.

"We are now looking at other highly complex structures," Wu said.



Much like working a three-dimensional puzzle, researchers solved the structure of the nuclear pore complex by fitting the known subunit structures into a vague outline of the whole.

Cataloging itty-bitty proteins in large numbers

The gap-free human genome was at last officially completed this year after researchers pieced together the final highly repetitive regions. It includes about 19,400 protein-coding genes in its 3 billion base pairs — but more may be as yet undescribed.

Initial bioinformatics limited protein-coding gene status to open reading frames, or ORFs, 100 amino acids or longer, on the grounds that there are millions of potential ORFs in the transcriptome, and it is likely that many of the shortest appear by chance.

However, ribosome profiling, a technique to sequence messenger RNA captured in the act of being translated, has, over the years, identified thousands of shorter translation products. Many, currently annotated as long noncoding RNAs or untranslated regions of coding mRNAs, have been found in unexpected parts of the genome.

Research on a few of these translated sequences suggests that some of them play important regulatory roles. Nick Ingolia, co-developer of ribosome profiling techniques, said, "We now have several nice examples from a number of (research) groups" of translated products that currently are not annotated as protein-coding genes. "The whole field is trying to sort out order of magnitude; it could be five or 5,000. It's probably somewhere in between."

This year, a team of 35 investigators announced plans to survey the landscape of small translation products. Examining seven recent ribosome profiling studies, they found 7,264 small translation products ranging from 100 to 16 amino acids long. Roughly half of those appeared in multiple data sets. According to Ariel Bazzini at the Stowers Institute for Medical Research, who, like Ingolia, collaborated on this project, there could be many more; the study used conservative numbers and omitted many high-quality ribosome profiling data sets that could have been surveyed for small translation products.

Having assembled this data set, the team now hopes to start probing evolutionary conservation of these small ORFs and whether their associated proteins appear in cells. Validating these small translation products will not be without challenges. The smaller a protein is, the more difficult it is to detect using mass spectrometry and the harder it is to make alterations such as affinity tagging without dramatically altering the end product.

The next step is to understand why these ORFs are translated and whether their products are stable in the cell. Bazzini said that some translation products from so-called untranslated regions of mRNAs act irrespective of their own sequence to regulate the abundance of the main coding protein in the transcript. Small ORFs also perhaps could be translated at random or only in disease contexts such as cancer that disrupt many regulatory pathways. Ascertaining that these proteins really are translated and looking to understand their functions is the consortium's next planned step.

To study the effects of a microprotein, researchers first have to know it exists. A new project aims to develop a catalog of small open reading frames that will be available through bioinformatics archives such as GenBank.

Meanwhile, the known short proteins can be difficult to find out about, since their identification often is buried in supplementary data sets. Databases including Ensembl, the Human Genome Organization, the Human Proteome Organization, Uniprot and Protein Atlas are working to standardize nomenclature and annotations for these small proteins so knowledge of their existence can reach beyond functional geneticists.

Predicting PROTAC properties

In recent decades, molecules that co-opt the ubiquitination system to degrade target proteins have opened up new drug targets by eliminating the need for an active site or a binding pocket. Proteolysis-targeting chimeras, or PROTACs, work by bringing together a drug target protein and a ubiquitin ligase. If it works as intended, PROTAC-induced proximity leads to target ubiquitinated and proteasomal degradation, removing the target from the cell. But sometimes the process stalls out.

"Sometimes binding can happen, but ubiquitination cannot," said Nan Bai, a scientist at Amgen. Bai and colleagues sought to predict this undesirable outcome by modeling the many conformations that a multiprotein structure can adopt, in a workflow they reported in the Journal of Biological Chemistry.

PROTAC efficacy depends on two successful events. First, the drug must link its target protein with a ubiquitin ligase substrate receptor into what often is called a ternary complex; second, it must bring the ternary complex into a larger ubiquitin ligase holoenzyme where ubiquitin can be transferred onto a lysine in the target protein.

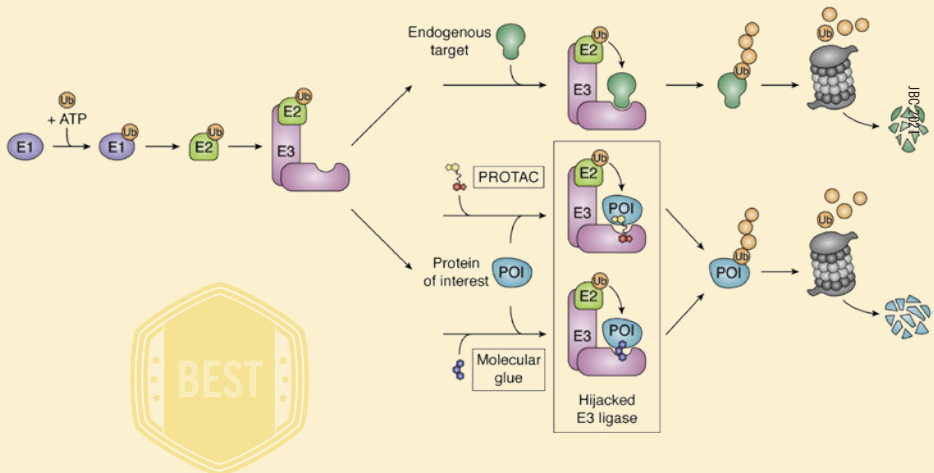
According to Bai, more effort has focused on predicting ternary complex formation, in part because it is easier. Her work focuses on the second step, triggering degradation. Her team used ensemble modeling to determine the most likely collection of conformations that a target PROTAC–ligase complex could adopt. They fit the most energetically favorable structures into the five most common conformations that a multiple-protein E3 ligase holoenzyme can adopt. In the resulting array of potential complexes, they searched for surface lysines eligible for ubiquitination on a target within reach of the holoenzyme. They scored each potential structure, deeming a complex unproductive if it predicted a steric clash or no lysines within the enzyme's active zone. Then they predicted a compound's overall ubiquitination efficiency based on the percentage of ensemble structures classed as productive.

To validate this model, the researchers tested it on PROTAC–target pairs reported to form productive complexes with published structures and found good agreement. The model also suggested an explanation for perplexing previous results where a family of closely related kinases bound comparably to a PROTAC but showed dramatically different degradation rates. Among the poorly degraded targets, the team found a smaller proportion of possibly productive holoenzyme conformations. Collaborators at Promega conducted cellular assays of target degradation that bolstered support for the model.

Sara Humphreys, a principal scientist at Amgen, is senior author on the paper. "Before embarking on this work, a priori for an uncharacterized binding site on a protein, you really wouldn't know" whether it would function as a PROTAC, she said.

While it provides useful information, Humphreys said, the model has not completely taken over the drug developers' conversations about which molecules should advance in preclinical development. Although ubiquitination of a target is essential, it is not all there is to PROTAC efficacy; a target's rate of synthesis, a complex's proteasome recruitment, and the dynamics of ubiquitin chain elongation and deubiquitination can all affect whether a target is destroyed. In the future, other tools may tackle these variables.

PROTACs use the cell's own ubiquitination system (top line) to drive degradation of a protein of interest for proteasomal degradation.



A macrocyclic lipid and the enzyme that makes it

There's a lot to adapt to when home is a hydrothermal vent deep in the ocean. For starters, the water can be hot enough to melt a lipid bilayer.

One of many adaptations that extremophilic microorganisms called archaea make to survive their superheated, high-pressure and frequently acidic environments is remodeling their cellular membranes. Instead of two layers of lipids, archaea can link two glycerolipids by their tails to form a large, cyclic lipid called GDGT with head groups on both the intracellular and extracellular surfaces.

"GDGT was discovered decades ago, but no one knew what enzyme made it," said Cody Lloyd, a graduate student at Pennsylvania State University.

Biosynthetic pathways that researchers had already worked out accounted for the lipid's precursors but left out a single puzzling step. Somehow, the archaea must catalyze an end-to-end joining of two unreactive carbon chains. The reaction seemed to require radical chemistry, which frequently uses oxygen — but the organism in question is an obligate anaerobe.

Lloyd came across the enzyme by accident. With Amie Boal and colleagues in Squire Booker's and William Metcalf's labs, he reported in Nature this year its identity, its reaction mechanism and that it links the two carbons using a whole new type of radical chemistry.

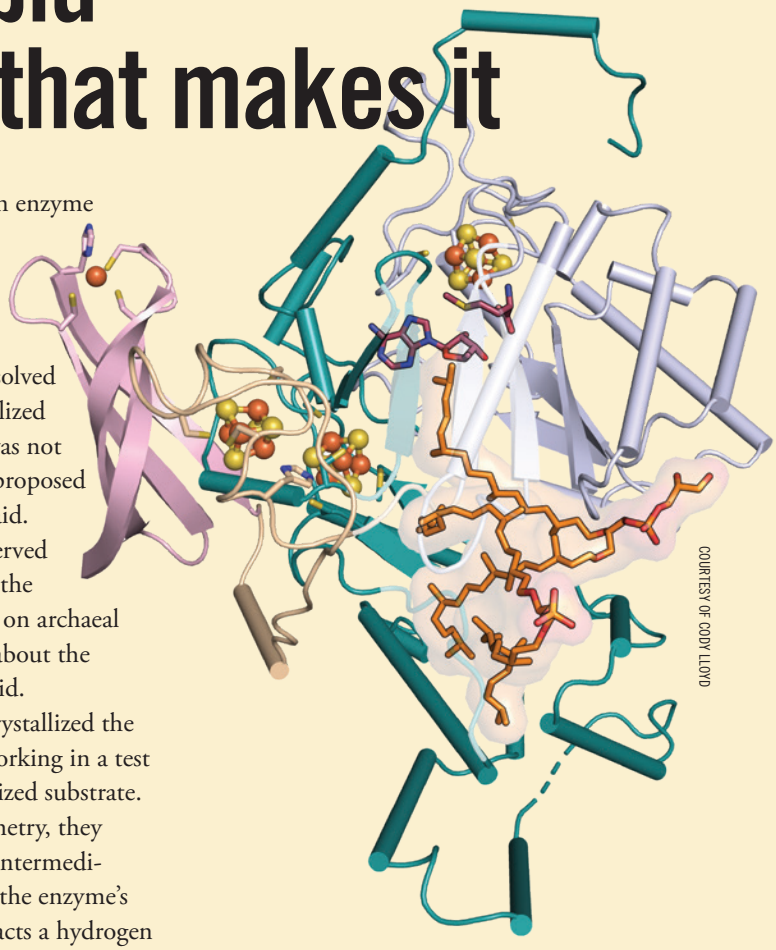
While studying an enzyme believed to be a methyltransferase, Lloyd struggled to observe its reported activity. "When we solved the structure, we realized that the active site was not consistent with the proposed reaction at all," he said.

Instead, they observed two lipids bound to the protein. Reading up on archaeal lipids, they learned about the mysterious cyclic lipid.

The researchers crystallized the protein and got it working in a test tube using a synthesized substrate. Using mass spectrometry, they captured a reaction intermediate that illuminated the enzyme's mechanism. It abstracts a hydrogen atom from the last carbon of two saturated lipid molecules and uses an iron–sulfur cluster to stabilize one radical intermediate until the second is ready to react.

No one had ever observed an enzyme using an iron–sulfur cluster to tame a high-energy radical; the cofactor is usually involved in redox reactions. The reaction itself is also exciting for biochemists and synthetic chemists because sp3-hybridized carbons are notoriously nonreactive. Catalyzing a new bond between them is difficult in the lab and never had been observed before in nature.

"This project was thrilling," said Booker, Lloyd's research adviser



COURTESY OF CODY LLOYD

A research team at Penn State captured this structure of the GDGT-synthesizing enzyme bound to its substrates.

— and it stayed thrilling even when a Stanford group identified a GDGT-synthesizing ortholog a few months before the paper came out. "However, Cody's work, besides providing the structure of the enzyme, settled a major conundrum in the field involving the nature of the substrate, and demonstrated for the first time one strategy that nature uses to link completely unactivated sp3-hybridized carbons."

Advancing structural biology to blazing speed

AlphaFold continues to impress structural biologists with the unprecedented number of protein structures it makes available.

The algorithm, written by Alphabet subsidiary DeepMind, was introduced at the Critical Assessment of Protein Structure Prediction contest, where it made headlines in December 2020 by achieving predictions with up to 90% agreement with newly solved crystals.

AlphaFold uses information from several sources to predict a protein's 3D structure. It integrates multiple sequence alignments, which can trace a protein's evolutionary conservation, with the predicted interatomic distance for each pair of amino acids to generate the predicted coordinates of every residue in a protein.

This year, DeepMind, in collaboration with the European Bioinformatics Institute, released more than 200 million protein structure predictions, roughly 25 terabytes of data that cover nearly all of the protein sequences known to the UniProt database. By comparison, about 180,000 experimentally validated structures have been deposited to the Protein Data Bank in its 50 years of existence.

Structural biologist Karen Allen of Boston University wrote, "There is no doubt that the use of AlphaFold and machine learning is making the biggest impact in structural biology … inform(ing) therapeutic discovery, protein engineering and the elucidation of enzyme mechanisms."

The tool has enabled structural analysis of proteins that have yet to be crystallized or studied using cryo-electron microscopy, has helped put the pieces of large complexes together (see "Giant, intricate structures" on page 22), and is being used to design and test new ligands for known proteins. Its prediction quality remains best for protein domains with more orderly structures and with some homology to a known structure. Still, for applications from protein engineering to predicting interactions and multimer structures, it has revolutionized the field.

Paul Craig, a biochemist at Rochester Institute of Technology, noted that biologists soon will need stronger search engines to look for commonalities among millions of structural models. "We have 214 million AlphaFold structures now," he said. "How many of those are kinases? How many are hydrolases? And how many look like my protein of interest?"

Protein structures with important functions tend to be even more strongly conserved than amino acid sequences — but are comparatively difficult to detect. To find common structural features, researchers need a tool that will sort through the whole universe of known structures and identify those that match a known input. Craig recently began using a search engine called Foldseek, introduced in a preprint this year, which can compare a protein query to a 3D structure database roughly 1,000 times faster than other available structural search engines.

Foldseek architect Martin Steinegger, an assistant professor at Seoul National University, said it works by translating structural information into what he calls a structural alphabet that describes each residue in relation to its nearest neighbors. With atomic coordinates thus condensed, the algorithm can use techniques from bioinformatic tools such as BLAST to look for structural similarity.

According to Steinegger, few computational tools have been scaled up to AlphaFold levels. However, he expects to see many more in the coming years.

WORLD HISTORY ENCYCLOPEDIA

The structure homology search engine Foldseek converts structural information about each amino acid in a protein into what inventor Martin Steinegger calls a structural alphabet, in order to use bioinformatics tools that can scan through many sequences rapidly.

Increasingly versatile peptide drugs for diabetes

Diabetes affects an estimated 37 million Americans. The disease affects the body's control of circulating sugar, usually through changes in tissue responses to insulin.

Incretins, peptide hormones that influence insulin secretion, have emerged in recent decades as drug targets for diabetes. Glucagon-like peptide 1 receptor agonists, peptide drugs that mimic the incretin GLP-1, improve glycemic control among diabetic patients. But they are less effective than the much more invasive treatment of bariatric surgery, which leaves pharmaceutical researchers wondering whether these drugs can be improved.

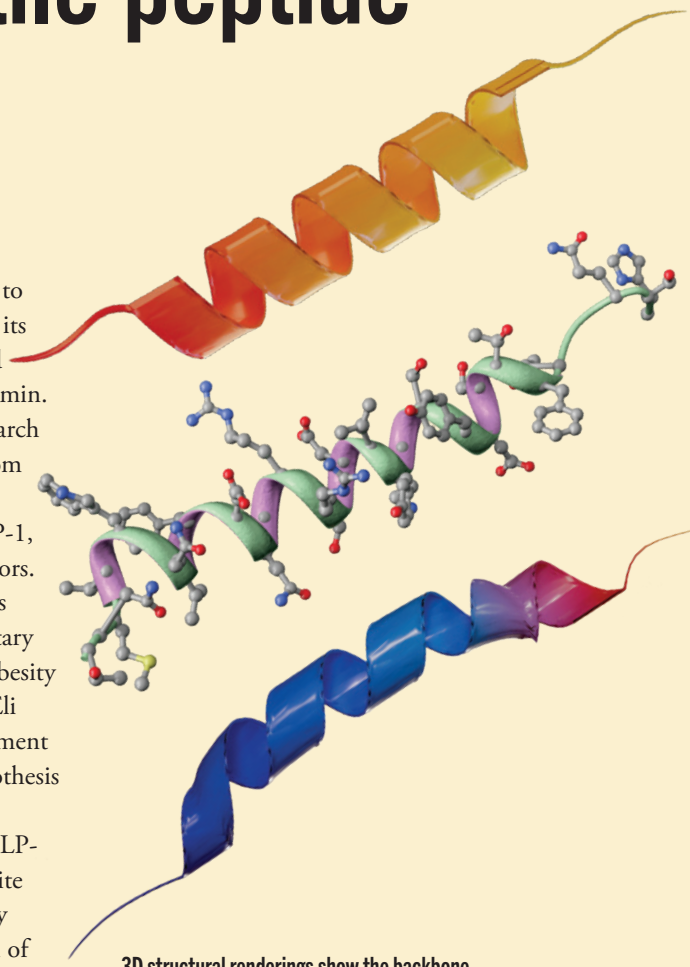
Scientists have looked to other incretins, beginning with glucose-dependent insulinotropic polypeptide, or GIP. GLP-1 and GIP have a similar alpha-helical structure and significant sequence overlap, and both are released from the gastrointestinal tract to reduce circulating glucose by stimulating insulin secretion.

This year, the U.S. Food and Drug Administration approved the first peptide drug that works as a bifunctional agonist of both GLP-1 and GIP receptors. The drug, tirzepatide, causes weight loss and improves cardiometabolic and glycemic outcomes in diabetic patients. Its amino acid sequence, based on GIP, is engineered to bind both GIP and GLP-1 receptors, with modifications to boost its half-life by reducing its susceptibility to proteases and improving its binding to albumin.

Meanwhile, industrial research labs are looking to expand from bifunctional to trifunctional peptide drugs that target GLP-1, GIP and also glucagon receptors. Adding glucagon to the mix is expected to have complementary effects on glycemic control, obesity and diabetes. Researchers at Eli Lilly and Co. wrote in a statement to ASBMB Today, "Our hypothesis considers that GLP-1 reduces appetite and GIP enhances GLP-1-induced reduction of appetite and glucagon enhances energy expenditure and combination of all those effects may produce more weight loss."

This year, two papers published in the journal Cell Metabolism reported on trifunctional agonists that can activate all three receptors. Both drugs' sequences use insights from alignment and 3D structural examination to merge the features of each peptide that are important for receptor binding and balance potency against all three receptors. In obese mice and monkeys, the triple agonists reduced body weight even in animals that lacked the GLP-1 receptor.

Both drugs were tested in humans in small preliminary trials. Sanofi discontinued work on its drug in 2019 after the preliminary human trial; Eli Lilly has continued to develop its drug, with two effectiveness and safety trials set to begin this year. These may be the first of many; in their paper, the Lilly scientists observed that "targeting all 3 of these receptors has evolved into the next generation of drug development for treatment of T2D and obesity."



3D structural renderings show the backbone structures of GLP-1, glucagon and GIP. Researchers are exploring ways to combine the three peptides, which are very similar in structure but rarely released into the bloodstream at the same time, into a drug that combines the signaling effects of all three.

An exercise molecule?

Thoroughbred race horses have among the animal world's most dramatic metabolic increases after exercise. They also show a significant increase in lactoylphenylalanine, or Lac-Phe, as do other mammals after exercise.

When Jonathan Long phoned the racetrack, he thought he probably sounded crazy. The Stanford biochemist had read once that thoroughbreds' metabolism increases 45-fold after a race, and when his lab identified what they thought might be an exercise hormone, he was eager to find out whether it appeared in horses too. But to find out, he needed samples of the horses' blood.

"To my surprise and my delight, the other guy on the line said, 'Well, that's easy,' because racehorses are routinely drug tested," Long said. By the next week, his lab's freezers contained what he described as buckets of leftover horse blood, courtesy of the anti-doping team at Golden Gate Field.

Exercise is an inexpensive tonic for many ills. It benefits metabolism, sleep, mood, inflammation, glycemic control and many other physiological functions. But although most scientists agree that exercise is beneficial, our understanding of how it works biochemically has lagged behind the observation that it does work.

In a metabolomics study comparing the plasma of mice before and after a sprint on a mouse-sized treadmill, and of horses before and after a race, researchers in Long's and several collaborating labs may have found a partial answer. They reported that the small molecule that increased in concentration most dramatically after a workout — even more than lactate, a sugar breakdown product that famously increases when aerobic respiration is high —had never been studied in an exercise context. That molecule, dubbed Lac-Phe, forms through enzymatic conjugation of lactate with the amino acid phenylalanine.

According to Long, metabolic mass spectra can be difficult to annotate, with as many as 80% of detected molecules never receiving identification. While other studies had found peaks that match Lac-Phe, they had not identified it correctly — or sometimes at all.

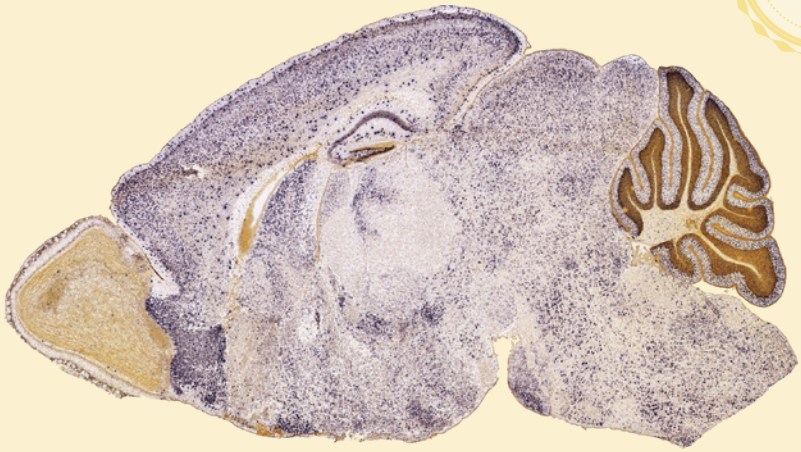
The authors found that several other lactosylated amino acids also were induced, to a smaller degree, in exercised plasma. However, Long said, Lac-Phe "was like Colonel Mustard with a candlestick in the living room."

In contrast to other metabolomic studies that identified changing molecules without exploring their impacts, this study investigated the effects of Lac-Phe injection into sedentary mice. In mice with diet-induced obesity, but not in lean mice, they found that the molecules reduced food intake, adipose mass and overall body weight. Mice that lack the enzyme that generates Lac-Phe tend to weigh more over time and don't lose weight in response to exercise. The authors concluded that Lac-Phe inhibits feeding and obesity, through mechanisms that have yet to be clarified.

Long's lab has continued to hunt for the Lac-Phe receptor, and while he's cagey about what they've found so far, he does say that he doubts it's a G protein–coupled receptor, and he has his suspicions about the brain regions involved in its appetite-suppressing effects.

More insights are probably on the horizon. In 2019, a group called the Molecular Transducers of Physical Activity Consortium began a large-scale study of the multiomic effects of resistance and endurance exercise in roughly 2,000 people, including both the metabolomics in which Long specializes and also proteomic, epigenomic, lipidomic and transcriptomic analyses. While the consortium has released its first data set, its organizers caution that a few controls still need to be completed before researchers can draw firm conclusions.

Spatial transcriptomics sharpens distinctions between brains



ALLEN INSTITUTE FOR BRAIN SCIENCE / WIKIMEDIA COMMONS

In contrast with in situ hybridization experiments like this one, which shows where in the mouse brain a single transcript is located, spatial transcriptomics experiments can give researchers information about the whereabouts of many transcripts at once.

Single-cell RNA sequencing is becoming a workhorse of transcriptomics, giving researchers details on transcription in individual cells and a sense of both tissue-level heterogeneity and how many cell types are present. As powerful as single-cell techniques are, they pose a challenge in that tissues must be dissociated to be analyzed. This can cost contextual information in tissues where a cell's position is important.

In the brain, for example, many functions depend on interactions between adjacent cells. Based on single-cell sequencing, researchers have identified multiple types of both inhibitory and excitatory neurons in the brain and dozens of subtypes of glia, or nonneuronal cells. But to learn more about how position affects function and how this diversity of cell types arises, researchers need more information about which cells are where — a question for spatial transcriptomics.

There are several ways to assay the transcriptome without losing spatial information. Researchers can microdissect tiny, defined portions of tissues for RNA sequencing assays; they can capture nucleic acids in a known, spatially defined pattern before single-cell sequencing; or they can hybridize fluorescent probes to RNA and image it in thin tissue sections, sometimes after expanding the tissue. Scientists have struggled to strike a balance between spatial resolution and the number of transcripts they can assay at once.

In the journal Science, a Harvard team used a multiplexed in situ hybridization technique called MERFISH, which assays tissue slices for a selection of thousands of genes, to identify dozens of cell types in multiple regions of the mouse and human cortexes. The researchers spotted numerous interesting distinctions between the two species; for example, the human cortex is composed of a higher proportion of glia and inhibitory neurons than the mouse cortex. Human brains were also much more apt to show soma, or cell body, interactions between distinct cell types, particularly neurons and glial cells, suggesting more complex contact-mediated relationships between these cells.

In another paper in Science, researchers based at Yale and the University of Wisconsin–Madison, compared human, macaque, chimpanzee and marmoset brain regions responsible for cognition, identifying subtle differences in important genes, such as a dopamine-producing enzyme, in certain cell types by region.

These techniques have yet to capture single cells in space. However, researchers are developing ways to get closer. A method published in the journal Nature Biotechnology this year by a research team from across Europe merges expression signatures from single-cell RNA sequencing experiments with spatial transcriptomic location from a sparse subset of these transcripts. By combining the data, the method can determine which classes of cells exist in each location and which type most likely occupies a given location. Other scientists at Harvard are working on ways to determine likely boundaries between cells based on their transcriptomes.

What's in the structural vaccine designer's toolbox?

A Q&A with Jason McLellan

By Laurel Oldach

VIVIAN ABAGIU / THE UNIVERSITY OF TEXAS AT AUSTIN

In a 2021 photo, Jason McLellan holds a 3D model of the SARS-CoV-2 spike protein.

Vaccines work by introducing an antigen and training the immune system to raise neutralizing antibodies. One challenge in vaccine design is that many viral surface proteins are shape shifters, undergoing radical conformation changes during the process of infection. Antibodies that target the wrong conformation may do little to prevent infection. Vaccines that present only one stabilized conformation surmount this problem — but they sometimes take some protein engineering.

Not long after the SARS-CoV-2 genome was reported, Jason McLellan's lab determined the structure of its spike protein and made a key substitution, adding two proline amino acids to stabilize the antigen in a shape the immune system targets more effectively. Pfizer, Moderna, Novavax and Johnson & Johnson used this modification in their COVID-19 vaccines.

In recognition of this work and his team's continuing studies of the virus that causes COVID-19, McLellan has received several prizes this year. From the Texas Academy of Medicine, Engineering, Science and Technology, he received the O'Donnell Award. He was a national finalist for the Blavatnik Prize, and he recently received the inaugural McGuire Prize, which recognizes high-impact work by a member of the Dartmouth College community. (McLellan was a professor at Dartmouth before moving to his current position at the University of Texas at Austin.)

ASBMB Today talked to McLellan about how his lab approaches protein engineering for vaccine design, the noncoronavirus projects they are pursuing and future pandemic preparedness. This interview has been edited.

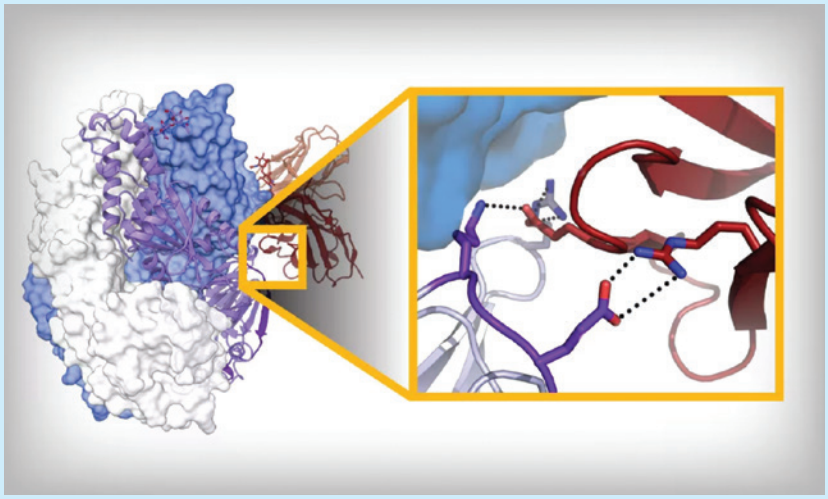
Q. Tell me about how your lab tackles vaccine design.

We start with a protein structure, usually from X-ray or electron microscopy. Then, once we have the structures, we're ready to analyze the protein and figure out the optimized sequences that we want to use for an antigen. Recently, we've been working at UT with the Machine Learning Lab, a really excellent computer science group, to try to predict which substitutions will increase melting temperature. That's been fun. They don't know much about proteins, I don't know much about machine learning, but we're making solid progress.

Many times, we first need an antibody to stabilize and trap a protein and then engineer the molecule to use as a vaccine. Sometimes we are able get the structure and engineer a molecule that we then use as bait to pull out antibodies (from recovered patients' serum) to use for antibody-based prophylaxis. So it's really nice synergy.

Q. Let's say you have a bunch of conformations from a protein that's shifting around. What's in the protein engineering toolbox for stabilizing it?

Depending on the protein, there are different approaches for structure-based vaccine design. Something that we're known for is stabilizing class 1 viral fusion proteins, which start off in one conformation (pre-fusion), go through a series of rearrangements and end up in another (post-fusion). (Author's note: McLellan's lab has worked on proteins in this family from coronaviruses, respiratory syncytial virus, metapneumoviruses and others.)



JASON MCLELLAN/THE UNIVERSITY OF TEXAS AT AUSTIN

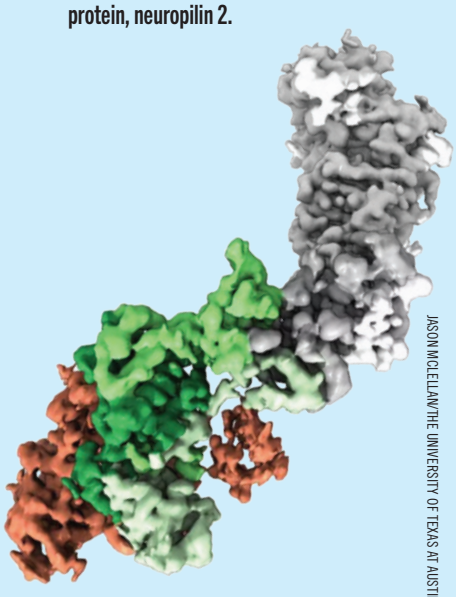
A structure McLellan's lab published earlier this year shows binding between a monoclonal antibody and a protein from human metapneumovirus.

We generally know both conformations, and we can infer intermediates; we know pretty well now which region unfolds first, followed by what's next. And not the whole protein changes, either; about 50% stays the same. So we can start to say, "How can we make amino acid substitutions that bond moving regions to the nonmoving region?"

In some of the best cases, you can get a disulfide bond: One cysteine in the unmoving, one cysteine in the moving, and that just locks it — as long as that bond forms. Otherwise, we try to fill little cavities. You're generally taught that proteins are packed very well for stability, which is true, but not for a protein that has to undergo conformational change; it needs to have evolved instability. So we try to find those regions that are unstable. Those are some of the tricks: We're trying to add salt bridges, add hydrogen bonds, fill cavities, make disulfide bonds and use prolines to help reduce backbone flexibility.

> "Recently, we've been working at UT with the machine learning lab, a really excellent computer science group, to try to predict which substitutions will increase melting temperature. That's been fun."

A structure McLellan's lab published earlier this year shows a protein from human cytomegalovirus binding to its human receptor protein, neuropilin 2.



JASON MCLELLAN/THE UNIVERSITY OF TEXAS AT AUSTIN

Q. Gotcha. Does the cavity filling use a small molecule?

No, amino acid side chains. For example, in the case of respiratory syncytial virus, or RSV, F protein, there is a pocket with a serine pointing toward it. We mutated that to phenylalanine, and the phenylalanine just fills the pocket. And so now you're getting some additional van der Waals interactions and also making it really unfavorable to pull that phenylalanine into a solvent of water molecules. We actually have considered using small molecules to stabilize that; it just becomes a little unclear as a Food and Drug Administration regulatory issue: Is it an excipient? So we try to do it with amino acid substitutions, generally small to large.

Q. You mention RSV; I understand there's an RSV vaccine study underway that uses a stabilized antigen you developed. Besides phenylalanine, what else worked best to stabilize that antigen?

So the one I created at the Vaccine Research Center (at the National Institutes of Health) has a disulfide and two cavity-filling substitutions, and that was enough to lock it. One of the big companies has licensed that one. Among other companies — GlaxoSmithKline, Pfizer and Janssen — it's not actually clear what they've chosen. But it's essentially the same molecule, just a different substitution. I think in the big three, it's primarily disulfide bonds, cavity-filling substitutions — and a proline. Janssen has a proline one that was beautiful and was our inspiration for the coronavirus proline stabilization.

I've worked with Janssen since 2013, so I solved the structure of their prefusion RSV F protein, and this proline — how it works is beautiful. When we got the structure of the coronavirus HKU1 spike when I was at Dartmouth, we decided to proline scan this region, and that worked. (Author's note: HKU1 is a coronavirus first found in humans in 2004.) We got the two prolines in this region that work to stabilize MERS-CoV and SARS-CoV, and ultimately that was incorporated into all the SARS-CoV-2 vaccines authorized for use in the U.S.

Q. How much of your process is design, and how much is just trying things out?

There has to be some trying things out, because protein folding is such a black box. There are changes we make that you bet with as much as you can that it's going to work, and then you try to express it and there's nothing. There's no protein made. Presumably at some intermediate, there's some folding thing. But we're not at a state where we can predict that yet. So what we're trying to do is go from an infinite number of permutations down to at least a testable number of 100 or so and then do combinations. We'd love to start to use more machine learning and narrow it down even more. The experimental part is the slowest part. So if we can even triage for an earlier stage, that would help speed things up.

Some people will still say that the protein folding problem hasn't been solved because we don't

know anything about the folding intermediates in the pathway or what folds first. AlphaFold looks at coevolution to give you the final structure — which is different than all our simulations with explicit water molecules that really try to tease out what is folding and how. (Editor's note: To learn more about AlphaFold, turn to page 26.) We don't know that. It gives us the final answer, which in many cases is good enough. But sometimes, if we actually could understand the folding problem, we'd probably realize why some of our substitutions kill expression or don't work well.

Q. You mentioned sometimes starting with an antibody to lock your antigen into one shape. Where do you go looking for those antibodies?

In my lab, we don't do the antibody isolation, but we partner with a lot of people who do. The best antibodies are often from people who have recovered from an infection. A lot of it does come down to sample access: Who has access to rare disease samples? It was really hard getting blood samples of MERS-CoV survivors. But fortunately, for respiratory syncytial virus and metapneumovirus, we can just bleed our friends; we've all been infected at some point. It's the more exotic ones where it could be hard to obtain them.

Q. I could imagine those rare infections could also be the ones that you're potentially a little bit more concerned about?

Yeah. There's a big push for prototype pathogen pandemic preparedness and trying to figure out, of the 26 viral families, which ones are most likely to cause a pandemic so we can start doing prospective vaccine development.

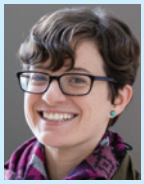
VIVIAN ABAGIU / THE UNIVERSITY OF TEXAS AT AUSTIN

Cryo-electron microscopy is a critical technique for McLellan's lab.

We might not know which family member emerges as the pandemic threat. But maybe we will have already learned things that can be applied broadly to the family, in much the same way we first stabilized MERS-CoV and SARS-CoV and HKU1, which allowed us to stabilize SARS-CoV-2 even though it wasn't on our radar. Trying to get some of these things that are more exotic, it can be tricky. There might not be many human infections — something like Nipah virus doesn't affect a lot of humans each year — but that's a major target now.

"There's a big push for prototype pathogen pandemic preparedness and trying to figure out, of the 26 viral families, which ones are most likely to cause a pandemic so we can start doing prospective vaccine development."

Laurel Oldach (loldach@asbmb.org) is a science writer for the ASBMB. Follow her on Twitter: @LaurelOld.



Nobel Prize honors click and bioorthogonal chemistry

Chemists Sharpless, Meldal and chemical biologist Bertozzi recognized

By Laurel Oldach

This year's Nobel Prize in chemistry was awarded to Barry Sharpless, Morten Meldal and Carolyn Bertozzi "for the development of click chemistry and bioorthogonal chemistry." Their work enables rapid, predictable and high-yield chemical combination of reactants, including biomolecules. Click chemistry that can be carried out in cells, also known as bioorthogonal chemistry, is of particular interest to the life sciences community because it has applications in microscopy, molecular labeling and drug development.

"It is wonderful to see the prize awarded in a field that spans both chemistry and biology, and to have Carolyn Bertozzi recognized for her foundational contributions to the field that she literally named," ASBMB president Ann Stock wrote in an email. "The clever synthetic strategies pioneered by the three prize winners are widely used in research laboratories and have opened the door for development of biotherapeutics."

Click chemistry

Click chemistry solves the problem of how to drive forward a chemical reaction in a specific site on a molecule. Sharpless, a chemist at Scripps Research in La Jolla, California, developed click chemistry about 20 years ago. (He also received a Nobel Prize in 2001 for unrelated work developing chirally catalyzed oxidation reactions.)

In a paper published in the journal Angewandte Chemie in 2001, Sharpless and colleagues outlined the concept, which draws inspiration from polymerization reactions found in nature that link two carbon atoms through a third, different atom. Click chemistry, they explained, is "a set of powerful, highly reliable and selective reactions" that use chemical tags that are highly reactive, but only with one another, to create bonds between any pair of molecules, with limited side reactions.

The range of suitable chemical tags available at the time was limited. Some of the best options, such as a pair including an azide, which has three nitrogen atoms linked by double bonds, and an alkyne, which has two carbon atoms linked by a triple bond, required high heat or other challenging reaction conditions.

Meldal, a chemist at the University of Copenhagen, discovered with colleagues in 2002 that a reaction between an azide and an alkyne functional group could proceed rapidly at room temperature and in aqueous solutions if a copper catalyst was available.

Olof Ramstrom, a professor at the University of Massachusetts, Lowell, and the member of the chemistry Nobel committee who explained the

prize to the media at a press conference, called the catalyzed azide–alkyne reaction "click chemistry's crown jewel." In fact, he noted, for many researchers, the azide–alkyne reaction has become synonymous with click chemistry. It is widely used in synthetic and materials chemistry, including for manufacturing at industrial scales.

The concept of precisely targeting a reaction to a single molecule was extremely appealing to life scientists, but the copper catalyst required for the azide–alkyne reaction can be toxic to living cells. Bertozzi, a chemical biologist at the University of California, San Francisco, sought ways to achieve equally selective reactions in living cells.

In 2004, Bertozzi and her team developed a chemical tag using a strained alkyne that reacted with an azide without requiring copper. In the paper announcing their work, the group noted that the reaction could go forward in living cells without harming them. They termed the reaction bioorthogonal chemistry, meaning that it could be done in cells without interfering with or being affected by their complex chemical environments.

Bioorthogonal chemistry and its applications

Kevan Shokat, a professor at the University of California, San Francisco, was a graduate student at the same time as Bertozzi. "Bioorthogonal reactions allow chemical biologists to track down vanishingly rare components in extremely complex chemical reactions," he wrote in an email to ASBMB Today.

With scope to assay nucleic acids, proteins and small molecules, he added, "its versatility is transformative."

COURTESY OF CAROLYN BERTOZZI

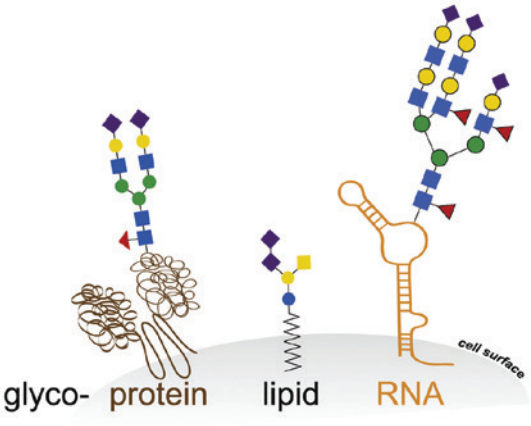
Carolyn Bertozzi won a MacArthur fellowship at the age of 33 and since then has been named a Howard Hughes Medical Institute investigator and an elected member of both the National Academy of Sciences and the National Academy of Medicine.

For Bertozzi and her team, the biomolecules of greatest interest were glycans, sugar-based polymers that make up the bulk of many cellular surfaces but have historically received less attention than nucleic acids and proteins.

With a bioorthogonal reaction in hand, Bertozzi's lab used it to pursue their longstanding interest in glycobiology. They developed metabolically engineered cells that would take up sugars modified with an azide and incorporate them into glycans, which then could be labeled with bright fluorescent molecules for microscopy or with other organic molecules that could bind drugs or recruit immune cells.

Several colleagues noted Bertozzi's role in bringing both chemical biology and glycobiology more attention. "She's a glycoambassador," said glycobiologist Iain Wilson of the

In 2004, Bertozzi and her team developed an azide-alkyne reaction that did not require copper, meaning it could happen in living cells without harming them. They termed the reaction bioorthogonal chemistry, meaning that it could be done in cells without interfering with or being affected by their complex chemical environments.



Researchers have long known that glycolipids and glycoproteins are present on the cell surface. Work in the Bertozzi lab revealed what Ryan Flynn describes as the "third hand" — glycoRNA.

University of Natural Resources and Life Sciences in Vienna.

Two of the most exciting current applications for biorthogonal chemistry, Bertozzi said in a press conference with the Nobel committee, are to deliver drugs to precise destinations in living tissue and as a tool "to discover new types of molecule that we didn't even know existed, because we have a new way of looking at them."

One such molecule came out of Bertozzi's lab, which reported in a 2021 article in the journal Cell the discovery of a new type of hybrid molecule, glycosylated RNA, on the surface of cells. According to Ryan Flynn, the paper's first author, who was then a postdoc in the lab, the finding would have been impossible without the ability to label molecules in cells without chemical interference from a bivalent copper catalyst.

A living playground

As a mentor, Flynn said, Bertozzi was thoughtful and intent. "When you're talking to her, she's hyperpresent and thinks incredibly deeply about what you're saying. … In the context of being hilariously busy all the time, the ability to do this for whomever she's speaking to is special."

Yamuna Krishnan, a chemical biologist at the University of Chicago, met Bertozzi during a seminar visit Bertozzi made to Chicago when Krishnan was a recent immigrant and young professor. Noticing that Krishnan had yet to feel at home in the chemical biology community, Krishnan recounts, Bertozzi "with her characteristic warmth and brilliance said, 'Let's de-orphanize you!'" — and then made good on the intention.

Other trainees and mentees also lauded Bertozzi's mentorship. "She is a tireless champion for her students and a beacon for queer chemists everywhere," wrote Mireille Kamariza, who earned her Ph.D. in Bertozzi's lab. (Bertozzi is the first lesbian laureate in chemistry. She and Svante Pääbo, who received this year's prize in physiology or medicine, join a short list of openly LGBT Nobel laureates, few of them scientists.)

During the Nobel press conference, held at roughly 3 a.m. California time, shortly after she received the news, Bertozzi said, "I'm absolutely stunned. … I'm still not entirely positive that it's real, but it's getting realer by the minute."

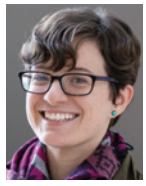
She may have been surprised, but many in the field had predicted this prize would come someday. Bertozzi is widely regarded as a leader in the field of chemical biology, and several public polls of chemists — for instance, one run by Nature editor Susan Cantrill — predicted a win for bioorthogonal chemistry.

Bertozzi noted in the press conference that she was glad the prize will draw attention to the field of chemical biology and added that it made her "reflect on how fortunate I have been" to work with talented colleagues, students and postdocs over the years.

Those colleagues emphasize that Bertozzi's inventive thinking was key to her success.

"She threw caution to the winds and approached biology with an inventor's mindset," Krishnan wrote. "Suddenly her work made chemists look at biology a little differently — (as) a complex living playground to integrate new chemistries and understand a little more."

Laurel Oldach (loldach@asbmb.org) is a science writer for the ASBMB. Follow her on Twitter: @LaurelOld.

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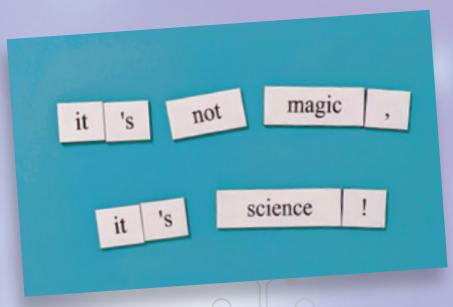
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POWERED BY COFFEE
AND MITOCHONDRIA
POWERED BY COFFEE
AND MITOCHONDRIA

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2022 HOLIDAY GIFT GUIDE

Compiled by Allison Frick

Happy holidays! We hope these suggestions will help you check some of your favorite scientists off this year's gift list.

1. 250 mL Beaker Drinking Tumbler & Reusable Straw Set ($34.99) **2.** Future Scientist Lab Coat Onesie ($19.99) **3.** Science Basics Word Magnets ($13.95) **4.** Air Plant Terrarium Kit ($34) **5.** Chemistry Playing Cards ($17.50) **6.** Powered by Coffee and Mitochondria Classic T-shirt ($18.88) **7.** Mini Animal Cell Pendant Necklace ($30.40) **8.** Microbes Super Twirler Dress ($39) and Adult Microbes A-Line Dress ($70)

You can find direct links to each of these items (and more) at asbmb.org/asbmb-today.

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We asked, you delivered

This annual meeting is packed with workshops. Can we ask one more favor?

By Kirsten Block

Over the summer, we asked you, the members of the American Society for Biochemistry and Molecular Biology, to help us create an annual meeting experience at Discover BMB 2023 that includes opportunities not just to learn the latest research but also to sharpen skills, identify new strategies to implement in classrooms and labs, expand science outreach efforts and support a more diverse, equitable, accessible and inclusive scientific workforce.

While research talks are a perennial staple, scientific conferences are also perfect venues for professional development. ASBMB members agree, and from the workshop submissions we received, we've created a meeting that showcases the many facets of being a scientist. Workshops at our meeting in Seattle will span a range of topics — something for nearly everyone.

As we offer a sneak peek of the workshops on tap for #DiscoverBMB, be on the lookout for one more big ask, specifically about the first workshop listed. In our call for proposals, we highlighted DEAI as a priority topic area. A strong scientific workforce benefits from all voices participating, and in that spirit, Neena Grover has asked us to help her identify additional leaders engaged in anti-racist classroom practices to be part of her session.

Diversity, equity, access and inclusion

- **Anti-racist classroom practices, led by Neena Grover, Colorado College.** The goal of this workshop is to provide actionable strategies to create a more inclusive and equitable classroom space that enables all students to be successful. In support of this goal, Grover hopes to engage additional faculty to share anti-racist practices they have incorporated into their classrooms. If you plan to attend #DiscoverBMB and you use anti-racist practices in your classroom, please contact us at education@asbmb.org so we can connect you. And if you're not already engaged in these practices but want to learn, be sure to add this workshop to your meeting schedule.
- **Incorporating anti-racism, social justice and equity themes into biochemistry courses, led by Rou-Jia Sung, Carleton College.** If you're looking to move from inclusive practices to inclusive course content, join Sung and her colleagues for this workshop. Attendees will explore strategies and activities to integrate the historical, racial and social impacts of biochemistry into the scientific concepts being taught. You'll walk away with an individual action plan and a network of support to implement that plan.

Science communication

- **Developing scientific writing courses for different stages of STEM training, led by Karin Musier–Forsyth, Ohio State University.** In this workshop, Musier–Forsythe and colleagues will explain how they've built scientific writing courses for both undergraduate and graduate training. The bulk of the session will include examples from these courses. Whether you're looking to build a similar course at your institution or seeking strategies to improve your own scientific writing, this workshop has you covered.
- **Building science communication training into your classrooms, training programs and large-scale grants, led by Melissa Rowland–Goldsmith, Chapman University.** The ASBMB's own science communication course, the Art of Science Communication, will be the focus as you learn from facilitators how this online course can be adapted for classrooms, research training and grant-funded research centers to help scientists improve their ability to disseminate research to general audiences. We hope educators and program directors will consider using this ASBMB resource to enhance their training efforts.

Science outreach

- **Outreach for all ages: How to build an outreach program targeted to an appropriate audience, led by Michael Wolyniak, Hampden–Sydney College.** Are you unsure where to start when engaging in science outreach? Workshop participants will learn how to identify whom you want to reach with your outreach efforts and how to design an activity that meets your audience's needs.

■ **Building partnerships to bridge STEM outreach to the real world, led by Shyretha Brown, Building Bridges Inc., and Christina Swords, University of Wisconsin–Madison.** Brown, Swords and others will share tools and strategies to establish and sustain strategic community partnerships, with an emphasis on connecting your outreach activities to inspiring and empowering future scientists. This workshop will include a hands-on outreach demonstration to inspire you to take your science from the lab out into the real world.

Education

■ **Capturing student attention by escaping traditional pedagogy, led by Antonio Mele, University of Central Florida.** Active learning is the name of the game in this workshop, where you'll find out how to use escape rooms to facilitate deeper learning. Attendees will try an example escape room, so stop by if you're in the mood for some game-based learning.

■ **Basics of the iCN3D program: A user-friendly tool for biomolecular modeling, led by Kristen Procko, University of Texas at Austin.** If you want to learn how to increase student understanding of structure–function relationships, look no further. Procko and colleagues will show attendees how to use this freely available resource in hands-on demonstrations. Be sure to bring your laptop.

■ **Using open-source molecular docking and visualization tools to explore protein–ligand interaction in the undergraduate classroom, led by Roderico Acevedo, Westfield State University.** Building from the Biochemistry Authentic Science Inquiry Laboratory, or BASIL, curriculum, Acevedo and colleagues will host another computer-intensive workshop, in which attendees will explore several tools, such as SwissDock and PyMOL, to predict protein–ligand binding and visualize results. If you're interested in integrating biomolecular modeling into your instruction, whether at the introductory or advanced level, don't miss this session.

■ **Enzyme function initiative genomic enzymology tools web resource, led by John Gerlt, University of Illinois, Urbana–Champaign.** In this workshop, attendees will walk through four freely available tools to explore sequence–function space in protein and enzyme families. Whether you're looking to use these resources in the lab or the classroom, this workshop will get you started.

Skill-building

■ **Building professional relationships, led by Erica Gobrogge, Van Andel Institute.** Consider this workshop if you're hoping to expand your network for the purpose of landing a job or establishing a collaboration. You'll receive tools and strategies to identify your networking goals and effectively initiate and maintain relationships.

■ **Seconds to impress, led by Kimberly Beatty, Oregon Health and Science University.** Learn how to make your CV stand out in a competitive job market. You'll get a behind-the-scenes glimpse of how hiring managers review CVs and walk away with strategies to identify how best to communicate your skills and qualifications. Whether you're on the job market now or planning to look for a job soon, don't miss this opportunity to give yourself a competitive edge.

■ **National Science Foundation — funding opportunities for research and broader impacts, led by Manju Hingorani, NSF Molecular and Cellular Biosciences Division.** Looking to learn more about funding opportunities at the NSF? Join Hingorani and other MCB program directors for an insider's perspective on the review process. You'll have a chance to talk to them about your research ideas.

(Workshop names and descriptions may be modified and updated before the 2023 meeting.)

Kirsten Block (kblock@asbmb.org) is the ASBMB's director of education, professional development and outreach. Follow her on Twitter: @kfblock.

Inspiring the next generation of scientists

High school students are guests of honor on Community Day at Discover BMB

By Christina Swords

Do you remember the first time you attended a big science conference? Most of us were undergraduates or graduate students, maybe presenting a poster with our advisor or telling a national audience about our research for the first time. Few of us had a chance to attend a meeting when we were still in high school.

This year, the American Society for Biochemistry and Molecular Biology Science Outreach and Communication Committee will invite Seattle-area high school students into the conference space at Discover BMB 2023 — the first time the ASBMB will offer local high schoolers an opportunity to experience the society's annual scientific conference.

This event, called Community Day at Discover BMB, will take place March 28 from 1:30 to 4 p.m. The committee expects to welcome 30-75 high school students and their teachers, including a number from underresourced communities, to join us in the exhibit hall for an afternoon of science engagement and exploration.

Early engagement in science is an important aspect of diversifying and retaining interest in the BMB fields. The more we do now to inspire the next generation of scientists, the stronger our fields will be. Community Day at Discover BMB will introduce these students to at least three key conference experiences.

Science talks are a major part of any scientific meeting. On Community Day, we'll invite the high school students to attend and judge the annual "Science in a Flash" competition (see box). The students and their teachers will hear short live talks by scientists who are challenged to distill their research down to its essence and make it accessible to the nonexpert listener.

Walking through an exhibit hall at a big meeting can be exciting (or nerve wracking, depending on how introverted you are). We'll give the high schoolers a chance to explore the hall, locating specific vendors who will showcase interactive demonstrations of basic research activities such as looking through a microscope, investigating a model and learning how a centrifuge works.

Finally, what conference would be complete without a healthy dose of networking? Many young people never have met a professional scientist, so we'll offer our special guests that opportunity with a dedicated area where they can engage with ASBMB members and ask questions about their research, careers and day-to-day lives.

Inspiring the next generation of scientists is a core part of the ASBMB's mission to "advance the science of biochemistry and molecular biology and to promote the understanding of the molecular nature of life processes." Through this Community Day event, we will show these high school students that support for careers in biology and molecular biology exists outside the classroom. If you are wandering the exhibit hall at Discover BMB on March 28, keep an eye out for these young scientists!

Odaelys Walwyn–Pollard, Matt Koci and Jelena Lucin contributed to this article.

The Science Outreach and Communication Committee develops science communication training and facilitates outreach activities for the society. The committee provides resources and professional development opportunities for ASBMB members to get involved with informal education in their communities. If you're interested in getting involved, email outreach@asbmb.org.

Christina Swords (christina.swords@fammed.wisc.edu) holds a Ph.D. in chemistry from the University of North Carolina at Chapel Hill. She is a graduate medical education coordinator at the University of Wisconsin–Madison and chair of the ASBMB Science Outreach and Communication Committee. Follow her on Twitter: @cmarvin67

Science in a flash

A three-minute talk competition

Imagine you had three minutes and a single slide to tell people about your amazing research.

Science in a Flash, an annual competition organized by the ASBMB Science Outreach and Communication Committee, does just that. Selected presenters are challenged to distill their research to its essence creatively and make it more accessible to the nonexpert audience in short live talks.

The first in-person competition was held at the 2019 ASBMB annual meeting in Orlando. The success of that pilot event was repeated in 2020 and 2021 in a virtual setting adjacent to the society's annual meetings.

Each year, the committee selects up to 10 grad student and postdoc annual meeting travel awardees to present their work. Presenters are judged by a panel of committee members for the judges' choice award and by competition attendees for the audience choice award. This means that an audience of scientists usually watches, judges and provides feedback.

This year, the competition returns to an in-person setting at Discover BMB 2023, with a new twist: Presenters will be challenged to boil their research down to its essence in front of an audience that includes students and teachers from Seattle-area high schools.

— **Jelena Lucin**

Brought to you (mostly) by and for women

The ASBMB's Women in Biochemistry and Molecular Biology Committee has big plans for Discover BMB

By Ciearra Smith

The American Society for Biochemistry and Molecular Biology's Women in Biochemistry and Molecular Biology, or WiBMB, Committee, formed in 2019, is the society's newest committee, and it also might be among the most active. The group, chaired by Susan Baserga, has hosted numerous events in support of gender equality, and it has plans to continue the conversation at Discover BMB in March in Seattle.

"Balancing opportunities" at dinner

Women scientists often are assigned what are known as non-promotable tasks, or NPTs, that can hold them back from advancing in their careers by taking time away from tasks that could help them win promotion. Many women have difficulty developing strategies to avoid being saddled repeatedly with these tasks.

Over the summer, the WiBMB Committee led a virtual book club to discuss "The No Club: Putting a Stop to Women's Dead-End Work" by Linda Babcock, Brenda Peyser, Lise Vesterlund and Laurie Weingart. During the book club session, participants discussed strategies for when and how to say no to non-promotable tasks. Weingart also presented a WiBMB Committee–sponsored webinar on Oct. 26.

And just as it is important to know when and how to say no, it is equally important to know when to say yes to an opportunity.

The Women's Networking Dinner at #DiscoverBMB will include a panel titled, "When to say no and when to say yes: Balancing opportunities."

Gira Bhabha of New York University Langone Health, winner of the society's Early-Career Leadership Award, and Kerry-Anne Rye of the University of New South Wales, winner of the Mid-Career Leadership Award and co-editor-in-chief of the Journal of Lipid Research, will take part in the panel.

Attendees will be encouraged to weigh in with their experiences and questions during the discussion.

A wellness walk

The WiBMB Committee hosted its first wellness walk at the 2022 annual meeting, allowing attendees to tour Philadelphia, exercise, network and get some much-needed sunshine.

At the 2023 meeting in Seattle, it will host another wellness walk during which participants can connect with other members of the ASBMB community and get their steps in. Let's explore Seattle together!

Ciearra Smith (csmith@asbmb.org) is the ASBMB's manager of diversity, equity and inclusion programs. Follow her on Twitter: @CB_witha_PhD.

Advocacy at #DiscoverBMB

By Sarina Neote

The Public Affairs Advisory Committee and public affairs department of the American Society for Biochemistry and Molecular Biology have been busy advocating on behalf of ASBMB members in 2022 (see details of our work this year on page 51 of this issue), and we will continue to push many of these policy efforts in 2023. Our advocacy efforts are all focused on four issue areas:

1. Addressing the rising cost of conducting science.
2. Supporting the next generation of scientists.
3. Increasing diversity, equity, inclusivity and accessibility in the research enterprise.
4. Supporting international collaboration and international researchers.

One of our priorities for 2023 is to communicate clearly the importance of basic scientific research to policymakers; without basic research, the innovation pipeline in science would collapse. But policymakers don't hear enough from scientists and science organizations about the importance of basic research. We're hoping you, as members of the ASBMB, can help us change that.

Not sure how to be an advocate for science? At Discover BMB 2023, we'll help with that. Here's what we're planning.

Advocate for basic scientific research

Come to the Advocacy Town Hall and learn how the ASBMB public affairs department and members of the Public Affairs Advisory Committee advocate for ASBMB members to policymakers at federal agencies and on Capitol Hill. During the second half of this event, committee members and staff will help you craft an email detailing the importance of basic scientific research to send to your representatives in the House and Senate.

How to engage in science advocacy

Not a letter writer? Many other avenues exist to advocate for sound science policy. Come learn what you can do at an ASBMB panel discussion with Public Affairs Advisory Committee members, delegates from our 2022 Advocacy Training Program, and science and technology fellows. We'll talk about how you can spend a lot or a little time advocating for the scientific community, and you'll get a chance to learn about how the ASBMB advocates for you. We welcome your questions and feedback.

Sarina Neote (sneote@asbmb.org) is the ASBMB's director of public affairs. Follow her on Twitter: @SNeote.

We welcome you

The MAC reception is always fun

Both great science and great food will be on the menu at the welcome reception hosted by the American Society for Biochemistry and Molecular Biology Maximizing Access Committee, or MAC, at Discover BMB 2023 in Seattle.

Each year, the MAC provides funds for underrepresented students to travel to the society's annual meeting through the Graduate Student Diversity, Equity and Inclusion Award. Recipients of the 2023 awards will share their research in a poster presentation at the reception and meet the career mentors assigned to them as part of the award program.

The ASBMB welcome reception, also known as the MAC reception, is a longtime staple at ASBMB annual meetings. Many members look forward to it as an opportunity to reconnect with colleagues they haven't seen in a year and to make new connections. Don't miss the MAC reception at Discover BMB — a time to connect and reconnect, and learn about interesting research from the next generation of scientists.

— **Ciearra Smith**

Publishing pros at your disposal

The ASBMB's editorial team will hold a workshop at #DiscoverBMB to help you prepare, revise and share your work with the world

By Angela Hopp

The editorial team at the American Society for Biochemistry and Molecular Biology works with researchers to disseminate their findings pretty much all day every day. Editors, reviewers, writers and others on the team know the ins and outs of data acquisition and presentation, wordsmithing, and promoting findings to the scientific community and beyond.

At Discover BMB, the ASBMB annual meeting, in Seattle in the spring, the editorial team will present a 60-minute workshop designed to give authors a competitive advantage — and preserve the integrity of the scientific record.

Scientific and technical editors and other staffers who support the Journal of Biological Chemistry, the Journal of Lipid Research, and Molecular & Cellular Proteomics will offer advice for (a) collecting, storing and presenting data; (b) editing text for clarity and reach; and (c) sharing your work.

Figures first

The workshop will begin with a presentation of best practices for data acquisition and presentation. While purposeful figure manipulation makes headlines, it's important to us to help curb honest mistakes. After all, your — and our — reputation is on the line.

First you'll learn about the software and settings you should use to capture the data you wish to present in your paper. If you want your data to be unassailable, you need to be fastidious from the very start. You'll learn about tools available, image resolution, file types and more.

Then you'll learn what not to do to your figures during preparation. It's tempting to want to publish a figure with zero imperfections, but some touchups simply aren't acceptable, because they can be misleading if not outright dishonest. You'll find out what's OK to polish and where to draw the line.

Stirring words

Your experiments are elegant and your findings are significant, so don't shortchange your paper by telling your story poorly. The ASBMB wordsmithing pros will demonstrate how to create compelling and accessible text that will draw in readers and increase your impact.

This segment will include examples that need a little improvement and show how to fine-tune them.

You'll get tips on organizing an abstract, finding the right words to convey precisely what you mean, writing tightly, inserting keywords that will extend your manuscript's reach, and avoiding passive voice, which proliferates in academic writing.

Post-publication promotion

Once your paper is published, your job isn't done. You have to make sure people know about your findings. The final part of the workshop will cover ways to share your work with colleagues and with the public.

Maybe you've been putting off creating a Google Scholar profile or dipping a toe into Twitter. Maybe you're interested in working with your institution's communications office to alert reporters of your discoveries. Maybe you're thinking you'll just stick to LinkedIn. Maybe you don't know the first thing about social media.

The ASBMB team will discuss creating a narrative, coming up with visuals and getting over the idea that it's wrong to give yourself a pat on the back. The work you do is important, and people should know about it.

We look forward to seeing you at #DiscoverBMB and helping you get the recognition you deserve.

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

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The f-word (failure) in research: When good plans go bad

By Paris H. Grey & David G. Oppenheimer

The following is an edited excerpt from "Life and Research: A Survival Guide for Early-Career Biomedical Scientists," a book that "started as a tweet," according to its authors. It was published in October by the University of Chicago Press.

Every researcher experiences failure, regardless of their professional title, skill level, or whether their primary workspace is a wet lab, dry lab, field or clinical environment. Failure isn't fun; nevertheless, it will be part of your research experience because failure in research is a universal experience.

A setback might test your resilience, discipline and motivation. At your lowest moments, you might even consider quitting research or reevaluating your entire career path. As disheartening as this seems, if you truly embrace the reality that failure is common and expect it to be a part of your research experience, you'll be more resilient when it happens. You also might be open to sharing your research disappointments with lab mates, colleagues and mentees, which helps reaffirm that failure is common and often unavoidable.

In research, failure can happen for numerous reasons, but three common ones are:

1. **The parameters of an experiment or procedure haven't been worked out.**
2. **Bad luck.**
3. **Operator error (a polite euphemism for the researcher having made a mistake).**

Success often is thought of in terms of "I collected the data I need for my paper, so I don't have to do the experiment again!" Yet the definition of failure isn't as straightforward, because, in part, science is personal, and how an individual researcher feels about redoing an experiment or research procedure influences whether they classify a setback as a failure or an inconvenient challenge.

For example, although you might be unfazed by redesigning your experimental strategy after several months of failed experiments, your motivation might be crushed by a nullified pet hypothesis. Yet a lab mate might feel the opposite way in similar circumstances.

It's how you handle it that matters

When a research failure happens, for whatever reason, it's OK to feel frustrated. Actually, it's a good sign if you care enough to be temporarily disappointed when something doesn't work or you experience a setback. After all, your research is personal — it requires effort and diverts time from other parts of your life, and (we hope) you feel connected to why your project matters.

How you handle failure and what you learn from solving problems are far more significant than a few mistakes or setbacks are likely to be. Research is hard, and experiencing failure or making a mistake isn't indicative of your ability to do science or think critically. But learning from failure and mustering the determination to move forward is true resilience and essential for achieving all your goals — in and out of the lab.

One more important idea to embrace is that you deserve happiness in your personal life even when you're struggling through a research failure. When managing a rough phase of a project, it's unhelpful and unhealthy to punish yourself further by denying yourself the things that make you happy, and doing so will only make it harder to reignite motivation. So, as you manage a failure, particularly a big one, tap into both your professional and your personal support networks, and don't neglect self-care as a punishment.

Three steps for managing research failures

1. Be kind to yourself.

When experiencing failure in research — whether it's beyond your control or the result of an operator error — immediately remind yourself that failure happens to

everyone, and you'll find a way to solve the problem.

Experiencing failure or making mistakes is not an indication of how successful you'll be in your career, but your resilience when faced with setbacks will be. (And that, too, is a skill that you might need to develop.) No good will come from making yourself feel worse about a research failure, but punishing yourself might prevent you from thinking clearly, believing that you belong in science or finding the determination to solve the problem.

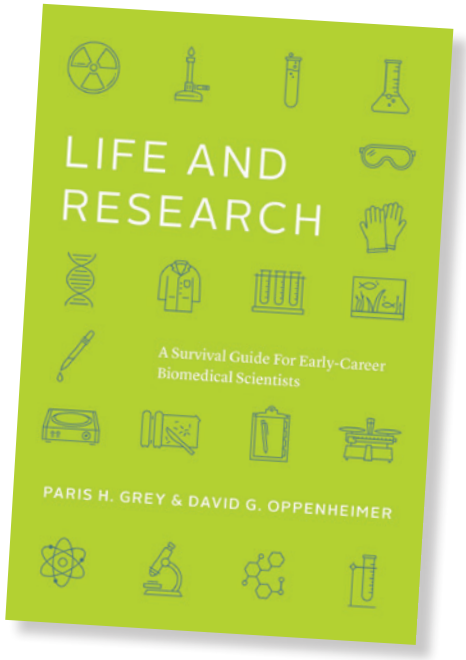
Paris Grey: In my research career so far, I've experienced plenty of failure at the bench. For example, there was the time when the thermostat in a tissue culture chamber failed and baked hundreds of my first-generation transformants, or when a flood from the lab above covered my RNA experiment with dirty water, or when a lab guest increased the speed on a shaker where my samples were incubating and destroyed my three-month isolation experiment a few days before a proposal update deadline.

But I've also managed to ruin a few experiments all by myself — such as the time I attempted to isolate a protein only to have nothing to show for it when I ran my gel. As I sat in my office, utterly confused about how a straightforward, easy-to-do procedure that I had done 50 times had failed, I was embarrassed to realize that I had mistakenly isolated it with the wrong column — essentially nullifying the procedure early in the day.

With the protein isolation experiment, as annoyed with myself as I was, I also knew that this mistake was not an indication of my abilities as a scientist or my overall qualifications. It was simply the consequence of cutting a corner — in this case, relying on my memory instead of taking two minutes to confirm which column I needed for the procedure. I made a mistake. But focusing on the error and my wasted effort would have ruined my day without changing the result. Therefore, instead of dwelling on my mistake, I worked on a different project and started fresh bacterial cultures before heading home.

2. Make a plan.

All researchers experience failure. What experienced researchers don't do, however, is dwell on the negative for too long before making a new plan and getting back to work. When you hit a stumbling block in research,



the solution you need will be influenced by the type of failure that you're experiencing. A failure from a blatant operator error is relatively straightforward to resolve. For example, after the aforementioned protein isolation experiment failure, Paris redid the work, of course, but she did more than that —going forward, she implemented a color-coding system for the proteins she used the most often to help her avoid making the same kind of mistake again.

On the other hand, a technique that fails intermittently for no obvious reason might require several rounds of troubleshooting. For some failures, the best first-round approach is to redo the technique or experiment a second time without changing anything.

For other failures, using that approach would waste your time and the lab's resources. Often, making an in-depth analysis of the situation, consulting with lab mates or your PI, and then choosing a new plan is the most effective strategy.

3. Manage a frustrating project — don't avoid it.

It's essential that the fear of more failure doesn't stop you from working through a series of research challenges. Learning to channel your disappointment into productivity is essential for completing the responsibilities of your research position and developing personal resilience to frustrating situations. So if your research project enters a particularly difficult phase, don't stop coming to the

lab or start dodging your PI's emails.

Instead, make an appointment with your PI to discuss why you're stuck, what you've tried and possible solutions.

Before you go into the first appointment, however, it's important to understand that a single meeting with your PI won't always be enough to solve a research problem. Sometimes getting unstuck requires a series of discussions — often interspersed with bench work, reading copious amounts of current scientific literature and a few additional rounds of failure in between.

Science is messy. It doesn't care if you fulfill your dreams or make it home in time for dinner. As gut-wrenching as they can be, negative results and nullified hypotheses mean that science is working. Beautiful things come from discovering something new and adding information to the universe — even if what you discover isn't what you had hoped it would be.

Paris Grey and David Oppenheimer created the blog UndergradInTheLab.com to help researchers navigate the hidden curriculum in STEMM research and to help mentors address emerging issues before small matters turn into big problems. They are also co-authors of "Getting In: The Essential Guide to Finding a STEMM Undergrad Research Experience."

Paris H. Grey (phgrey@ufl.edu) is a lab manager in the biology department at the University of Florida, a writer, a molecular biologist and a lab mentor. She has written articles on strategies for early-career researchers in the journals Nature, Lab Manager and Science. Follow her on Twitter: @TheLabMentor.

David G. Oppenheimer (oppenhe@ufl.edu) is an associate professor of biology at the University of Florida. A cell biologist and geneticist, his research program focuses on the proteins that control cytoskeleton dynamics and how this influences plant cell shape. Follow him on Twitter: @cell_biology.

Advocacy successes in 2022

By Sarina Neote

The American Society for Biochemistry and Molecular Biology Public Affairs Advisory Committee and public affairs department have recently had several policy recommendations included in appropriation bills, laws and federal agency policies, and we'd like to share our successes with you.

Here's what we've been up to.

Strengthening security, protecting collaboration

Over the past several years, the ASBMB has advocated strongly against racial profiling of Asian and Asian American scientists and urged science federal funding agencies to uphold scientific integrity. This was born out of concerns about racial profiling within the Department of Justice's China Initiative, which was partly focused on cases of suspected grant fraud and economic espionage by federally funded scientists.

The ASBMB submitted written testimony for Congressional hearings on the importance of international collaboration. We also pushed the White House Office of Science and Technology to reform research security policies on preventing foreign influences in federally funded research while maintaining openness, transparency and international collaboration. The OSTP is now in the process of reforming research security policies, and the DOJ has officially ended the China Initiative.

Improving NIH fellowship review

The ASBMB PAAC made five recommendations to the National Institutes of Health Center for Scientific Review on Jan. 23 to strengthen and improve the National Research Service Award fellowship review process so that it would support scientists whose work has been and continues to be affected by the COVID-19 pandemic; ensure that women in science, technology, engineering and mathematics are given fair and equal opportunities; and promote diversity in the STEM pipeline. The center incorporated several of the ASBMB's policy recommendations, such as eliminating grades as an evaluation criterion since grades are not an accurate measurement of success.

Modernizing national labs; support for training

In August, President Joe Biden signed into law the CHIPS and Science Act, which authorized funding and policies to bolster research and development across the country. This bipartisan bill combined multiple legislative efforts to increase American competitiveness in science and technology research and enhance research security policies. During the ASBMB's 2022 Capitol Hill Day, members of the Public Affairs Advisory Committee advocated for provisions within this bill that would modernize the infrastructure of the national labs, strengthen the bioeconomy and support training programs for the next generation of scientists. Many of the provisions we supported and endorsed have now become law.

Addressing sexual harassment

In a letter sent May 25, the ASBMB asked Senate and House appropriators to include language in the fiscal year 2023 appropriations bill that would require the National Institutes of Health to establish a strategic plan and a timeline to address and mitigate harassment within the NIH's Intramural Research Program. The Senate Labor, Health and Human Services, Education and Related Agencies subcommittee included the ASBMB's requested language, which will go a long way to address sexual harassment in the science, technology, engineering and medicine fields.

Keep up with the work of the PAAC and the ASBMB policy team at asbmb.org/asbmb-today/policy.

Sarina Neote (sneote@asbmb.org) is the ASBMB's director of public affairs. Follow her on Twitter: @SNeote.

'Keep developing your expertise'

By Martina G. Efeyini

Anand Balakrishnan talked to ASBMB Today about his work as principal scientist specializing in biochemistry at Enanta Pharmaceuticals Inc., a company that focuses on antiviral drug discovery. Balakrishnan has been with the company for more than four years.

1 What made you want to pursue an industry career?

During my postdoc, I was working in infectious diseases — on Mycobacterium tuberculosis, which causes tuberculosis disease. A part of my project was working on drug discovery, as there's a lot of unmet medical need. I joined the infectious disease research group at Novartis, as I thought it was a good overlap of interest because my goal was to continue working in infectious diseases drug discovery.

2 What do you, as a principal scientist at Enanta, do?

I am a biochemist and enzymologist by training. I lead a biochemistry group supporting all the virology projects — for example, developing enzyme assays, doing biophysical studies, and structural biology. My group has been involved in studies on respiratory syncytial virus, SARS-CoV-2 and hepatitis B virus.

3 What does a typical day look like for you?

Usually my mornings are spent in meetings for mentoring group members or managing collaborations. I spend afternoons in the lab running experiments. We collaborate with biology and medicinal chemistry colleagues on a daily basis. As a biochemist, you get to learn a lot because you're working across various diseases.

Anand Balakrishnan

CURRENT POSITION
Principal scientist at Enanta Pharmaceuticals

EDUCATION
Ph.D. in chemistry from Rutgers University and postdoctoral fellowship in microbiology and immunology at Weill Cornell Medicine

FIRST JOB OUTSIDE OF ACADEMIA
Investigator II at Novartis Institutes for BioMedical Research

FAVORITE MOLECULE OR PROTEIN
"It's actually this whole pathway of thiamine diphosphate biosynthesis, because it's very elegant chemistry and is important for all organisms."

4 What are the top skills that have helped in your career?

I'm speaking as a drug-discovery biochemist. I think a strong understanding of the basics of chemistry and biology is important. Our role sometimes involves being translators between chemistry and biology, and we have to understand both languages. The ability to listen well to people, especially when you are part of a team where everybody is basically in a different field, is also needed.

My Ph.D. research was in enzymology. I gained in-depth expertise in the area and learned infectious disease drug discovery during my postdoc and in industry. So, from a career perspective, start in one area of science and keep developing your expertise. This is your core strength. People will actually need you for that.

As you progress, I would say, writing, speaking and presentation skills also become important. You actually end up writing a lot, running project teams, and presenting data at internal and external meetings. So, whenever you get a chance, practice those skills.

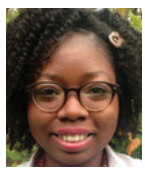
5 What is your advice to someone interested in a similar career path?

Planning is the most important career advice. Know where your passion is, and develop a plan to make a career in that field.

Next, I would say networking — trying to learn more about your chosen field and trying to connect with people to learn about their career paths. Start early when you are in graduate school or when you're about to graduate.

(This interview has been condensed and edited. To read a longer version, go to asbmb.org/asbmbtoday.)

Martina G. Efeyini (mefeyini@gmail.com) is a science communicator and STEM education advocate, and a careers columnist for ASBMB Today. Follow her on Twitter: @mefeyini.



American Society for Biochemistry and Molecular Biology

Discover BMB | 2023

SEATTLE | MARCH 25-28

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