



Vol. 20 / No. 10 / November 2021

ASBMB TODAY

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

A very delicate balance

Could blocking PIKfyve slow neurodegeneration?

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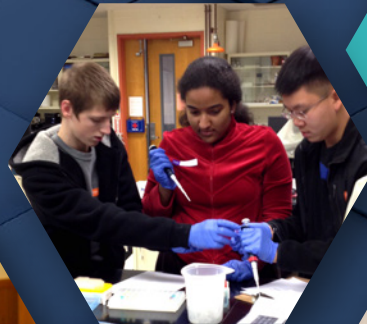
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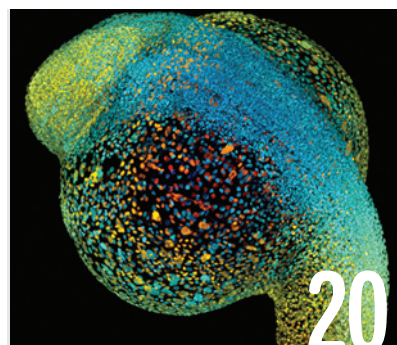
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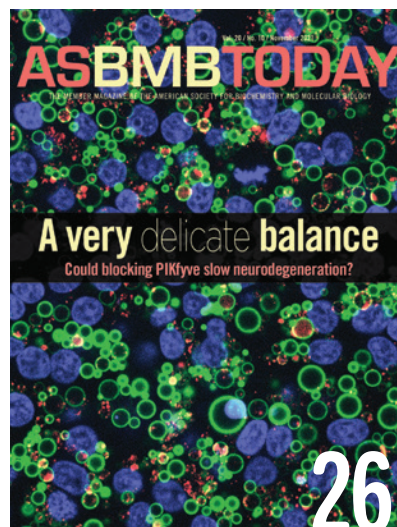
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rebuttal noun

re-but-tal | \ ri-'ba-tl \

: the act of **rebutting** especially in a legal **suit**
also : argument or proof that **rebut**s

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PRESIDENT'S MESSAGE

Come together

By Toni M. Antalis

It's hard to believe the 2022 ASBMB Annual Meeting is only a few months away. It's even harder to believe it's been so long since our community last met in person. The annual meeting in April in Philadelphia promises to be special, and I hope every single member of the society will seriously consider attending.

You might have heard that #ASBMB2022 will be the last time the society meets at the Experimental Biology conference. Yes, after many years of cooperation and coordination, the ASBMB and its sister societies are parting ways in 2023. So, if you enjoy interacting with colleagues studying physiology, pharmacology, pathology and anatomy in one place — you won't want to miss this event.

I've been to many ASBMB meetings over the years, and it's hard to say which parts I enjoy most because there are so many.

As president, I value having the opportunity to interact with the people who elected me — and who are driving our field forward. Whether those interactions are at the ASBMB booth, during a reception or even just in passing, they inform my decision-making and seed new initiatives that serve our members.

As a scientist, I am inspired by the stories told at lecterns, in workshops and at posters. I am continually impressed by this community's tireless pursuit of answers and creative problem solving. Hearing

how others have overcome scientific and personal challenges reminds me that we are not alone in our endeavors. I am particularly excited about the 2022 award lecturers. You can read about them in this issue.

As a lab leader, I look forward to meeting students and postdoctoral fellows who will propel my own research program forward. Hands down, the ASBMB annual meeting is the event at which to recruit talent! You can feel the buzz of possibility on the exhibit floor during the poster sessions. And the annual undergraduate poster competition is top notch. I hope you'll encourage your students to submit abstracts and apply for ASBMB travel awards to help cover their expenses.

I know that we're living in a time of great uncertainty, and some of you might be reasonably apprehensive about attending a large in-person meeting as the COVID-19 pandemic

CONTINUED ON PAGE 3

Important dates

Registration

Feb. 7: Early registration ends

Feb. 8: Advance registration begins

April 1: Advance registration ends

April 2: On-site registration begins

Abstracts

Nov. 30: Abstract submission deadline

Dec. 15: Last-chance abstract submissions open

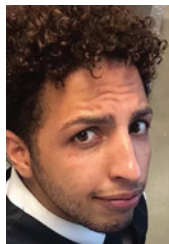
Jan. 27: Last-chance abstract submission deadline

Travel awards

Dec. 7: Deadline for applications

Morrison, Villegas among new Gilliam fellows

The Howard Hughes Medical Institute announced in July its new class of fellows in the Gilliam Program, which supports doctoral students and their advisers in an effort “to ensure that students from groups historically excluded from and underrepresented in science



MORRISON

are prepared to assume leadership roles in science and science education.” Two of the 50 new fellows are graduate student members of the American Society for Biochemistry and Molecular Biology.

Evan Morrison is a Ph.D. student in the lab of Olivia Rissland at the University of Colorado–Anschutz Medical Campus. The lab studies molecular mechanisms that regulate mRNA stability, including how translation elongation can affect mRNA decay, how maternal gene products are removed in the

zygote, and the structure of mRNA decay machinery in diverse model organisms, such as the human pathogen giardia, which has RNA processing systems with limited similarity to yeast and humans.

Alejandra Villegas, of the University of Georgia, works with advisor Vasant Muralidharan on understanding the proteins involved in escape from red blood cells by the malaria parasite *Plasmodium falciparum*. In collaboration with labs in the complex carbohydrate research center, she focuses on a glycosyltransferase. Villegas is also the president of the University of



VILLEGAS

Georgia’s Cellular Biology Graduate Student Association and works with the student science policy group.

The Gilliam fellowships provide up to \$50,000 annually to adviser–student pairs for three years. The next round of applications will open in October 2021 for a September 2022 start date.

Brennan takes home CoSIDA honors

Savannah Brennan, now a grad student at the Florida Institute of Technology working toward a master’s degree in biotechnology, was recog-



BRENNAN

nized as a Florida Tech undergraduate for her combined athletic and classroom performance by the College Sports Information Directors of America, which named her to

its 2020-21 Academic All-District Women’s At-Large Team.

Brennan majored in biomedical science and genomics and molecular genetics, held a GPA of 3.97 and was captain of the women’s swim team. She served as secretary of the American Society for Biochemistry and Molecular Biology Student Chapter at Florida Tech and as president of the school’s chapter of the National Biological Honor Society.

Brennan holds schoolwide records in six individual and, with her teammates, four relay swimming events.

CONTINUED FROM PAGE 2

persists. I want to assure you that the ASBMB and its sister societies are prioritizing your health and safety. All attendees will be required to provide proof of vaccination. The organizers will make a final ruling about masks closer to the meeting date and in accordance with federal, state, local and venue guidelines.

Finally, I want to thank the meeting co-chairs — Vahe Bandarian of the University of Utah and Martha

S. Cyert of Stanford University — and the entire program planning committee for the immense amount of work they’ve put into this important event.

Vahe and Martha quite succinctly encapsulated, in their formal invitation last month, why we are compelled to gather: “Scientists are not accustomed to the spotlight, but meetings made us feel like stars, if only briefly.” So true!

I hope to see you all in Philadel-

phia. It’s your time to shine, and your community will be there to cheer you on.

Toni M. Antalis (TAntalis@som.umaryland.edu) is a professor of physiology at the University of Maryland School of Medicine, where she is also the associate director for training and education for the Greenebaum Cancer Center and the director of the graduate program in molecular medicine. She began her term as the ASBMB’s president in July 2020.



MEMBER UPDATE

She has been named Sunshine State Conference Female Scholar–Athlete of the Year for the past two years, the first swimmer and third Florida Tech student to receive the award since it was established in 1996. A native of Oviedo, Florida, she also was named 2020-21 Outstanding Student of the Year for Florida Tech's Department of Biomedical and Chemical Engineering and Sciences.

Peterson becomes special adviser to LSU president

Cynthia Peterson, the dean of Louisiana State University's college of science, has been named special adviser on science to the university's new president, William Tate IV.

Peterson, a biophysicist, has been dean of the college of science since 2014. Her laboratory studies the bi-



PETERSON

physics of proteins involved in blood clotting, focusing on serine protease inhibitors, or serpins. Serpins are part of a complex signaling cascade that modulates homeostasis between

bleeding and clotting. Peterson's lab is interested in how the serpin plasminogen activator inhibitor 1, or PAI-1, interacts with other proteins and copper atoms to affect plasminogen activation and, ultimately, the breakdown of blood clots.

Peterson earned her bachelor's degree at LSU and her master's and doctoral degrees in biochemistry from the LSU Health Sciences Center in Shreveport, Louisiana. She was a postdoctoral fellow at the University of California, Berkeley, where she studied enzymes involved in pyrimidine biosynthesis.

She was a professor and depart-

ment chair in biochemistry at the University of Tennessee, where she also became an associate dean, before returning to the main LSU campus in Baton Rouge in 2014 to become dean of its college of science. According to an LSU press release, enrollment in math and science departments has grown under her leadership.

Among Peterson's professional honors are recognition as a Vision and Change Leadership fellow by the Partnership for Undergraduate Life Science Education; inclusion in the Baton Rouge Business Report's list of most influential women in business in 2018; and fellowship in the American Association for the Advancement of Science.

Sparks becomes interim state chemist for Mississippi

Darrell Sparks, associate state chemist and associate professor at Mississippi State University's department of biochemistry, molecular biology, entomology and plant pathology, has been named interim state chemist, a title for the director of the Mississippi State Chemical Laboratory.

The lab, housed on the campus of Mississippi State University and funded by the state, writes regulatory guidelines for and performs quality assurance analyses on chemical products sold in the state including animal feed, pesticides and fertilizers, petroleum products and food commodities.

Sparks, who earned his bachelor's and Ph.D. at Mississippi State University, has been a professor there since 2010. He recently was recog-



SPARKS

nized with Teacher of the Year and Excellence in Teaching awards.

Hall awarded Vallee visiting professorship

Michael Hall, a professor at the University of Basel's Biozentrum, was appointed as one of three Vallee visiting professors this year.

Hall studies cell growth and target of rapamycin, or TOR, signaling. He



HALL

discovered the TOR kinase in yeast in the 1990s and since has been a leader in the field that has grown in describing the kinase's key role in adjusting growth and metabolism in response to nutrient

availability. TOR and its mammalian homolog, mTOR, integrate signals about a cell's nutrient reserves and phosphorylate substrates involved in protein synthesis, ribosome production and cell growth. Hall's lab discovered that TOR belongs to two protein complexes termed TORC1 and TORC2, which have different rapamycin sensitivity and, later research showed, signaling activity.

Born in Puerto Rico, Hall grew up in Venezuela and Peru and then moved to the continental U.S. to pursue his studies. He earned his Ph.D. from Harvard University and completed postdoctoral fellowships at the Pasteur Institute in Paris and the University of California, San Francisco. He joined the Biozentrum at the University of Basel in 1987. In 1995, he started the first of three three-year terms as chair of the university's division of biochemistry; he also served for nine nonconsecutive years as the vice director of the Biozentrum.

Hall is a member of the National Academy of Sciences and a recipi-

ent of the Breakthrough Prize in Life Sciences, the Gairdner Award for Biomedical Research and the Albert Lasker Award for Basic Medical Research. He serves on the scientific advisory boards of several pharmaceutical companies and the editorial boards of numerous journals.

Vallee visiting professorships are sponsored by the Vallee Foundation, a private fund designed “to promote a collegial community of international scientists” and advance research. Bert and Natalie Vallee, a Harvard professor of medicine and a Lesley College professor of biology, respectively, started the foundation in 1996 to bring visiting scholars to Bert’s crystallography lab. Today, Vallee visiting professors receive a \$25,000 honorarium and take a one-month sabbatical at a research institution anywhere in the world. Past recipients who belong to the American Society for Biochemistry and Molecular Biology include Lewis Cantley, Emmanuelle Charpentier and Elaine Fuchs.

Beverley receives endowed chair

Stephen Beverley, a professor at Washington University School of Medicine and former head of the school’s department of molecular microbiology, is now a distinguished professor in that department. The new chair was named for the late Ernest St. John Simms, a WUSM professor who did groundbreaking research in genetics and immunology.

Beverley earned his bachelor’s degree at the California Institute of Technology and a doctorate at the University of California, Berkeley. As a postdoc at Stanford, he began to study gene amplification in *Leishmania*, a protozoan parasite transmitted by sand flies that can attack either the

skin or internal organs including the spleen and liver.

When he was an early-career professor at Harvard, Beverley developed genetic tools for studying *Leishmania* and collaborated on studies of its surface glycoconjugates, important virulence factors and potential vaccine targets. He moved to Washington University in St. Louis to head its department of molecular microbiology in 1997 and served in that capacity until



BEVERLEY

2018. He also directed the university’s Center for Infectious Disease Research.

Beverley co-founded a company, Symbionics, that aimed to treat lysosomal storage diseases using biotechnological tools borrowed from *Leishmania*, which make their homes within the lysosome. The company was bought by BioMarin in 2010 and renamed Zystor.

These days Beverley’s lab balances research on *Leishmania* reproduction, biology and genetics with studies of how the parasite interacts with the human immune system. They also have a line of inquiry into how endogenous viruses lead to increased virulence.

A former member of the editorial board of the *Journal of Biological Chemistry*, Beverley is a member of the National Academy of Sciences and a fellow of the American Association for the Advancement of Science, American Academy of Microbiology and American Society of Tropical Medicine and Hygiene. He received the Peter Raven Lifetime Achievement Award from the St. Louis Academy of Sciences in 2017.

JBC | JOURNAL OF BIOLOGICAL CHEMISTRY

**100 years
and
counting
of
powerful
science**

World's oldest Nobel laureate dies

By Laurel Oldach

Edmond H. Fischer, widely known as Eddy, an emeritus professor at the University of Washington School of Medicine in Seattle, died in late August. He was 101 years old and, at the time of his death, the world's oldest Nobel laureate, renowned for his foundational work on enzyme regulation through reversible phosphorylation.

Born in Shanghai in 1920 to European expatriates, Fischer attended boarding school in Switzerland from the age of 7 onward. He studied biology and chemistry at the University of Geneva during World War II, graduating in 1943, and continued as a doctoral student with Kurt Meyer, the head of the university's organic chemistry department. The lab was focused on the structure of complex polysaccharides such as starch and glycogen; as a doctoral student, Fischer conducted enzymology research on proteins involved in polysaccharide breakdown, focusing on amylase. He earned his Ph.D. in 1947.

Fischer continued to work with Meyer in Geneva until 1953, when Meyer's sudden death coincided with Fischer's receipt of an immigration visa to the United States. He arrived in the country intending to work as a postdoctoral fellow at Caltech but received a number of job offers from American universities and instead joined the faculty at the University of Washington as an assistant professor. Part of the decision, he later said, was because Seattle's mountains and lakes reminded him and his wife, Nelly Gagneux, of Switzerland. Gagneux



Edmond H. Fischer

died young, in 1961; Fischer later married an American, Beverly Bullock, who died in 2006.

At Washington, Fischer met Edwin Krebs, who would become a lifelong friend and collaborator. The two began to investigate the role of enzyme cofactor adenosine monophosphate in the activity of a phosphatase that regulates the breakdown of glycogen in muscle cells to supply glucose. While trying to understand why some purified forms of the enzyme were active and others inactive, they found, unexpectedly, that phosphorylation and dephosphorylation of the kinase itself regulate its activity. They published a series of articles on this line of inquiry in the *Journal of Biological Chemistry*.

"These were very exciting years when just about every experiment revealed something new and unexpected," Fischer wrote in his Nobel

biography. "We worked so closely together that whenever one of us had to leave the laboratory in the middle of an experiment, the other would carry on without a word of explanation."

The pair shared the 1992 Nobel Prize in physiology or medicine for the work, which established the importance of reversible protein phosphorylation to regulation of enzyme activity and other biological processes. In a JBC remembrance of Krebs after his 2009 death, Fischer wrote, "We often have been asked whether we realized, at the beginning, that we were dealing with a ubiquitous and, therefore, very fundamental process. Absolutely not. We stayed with this system because we felt it was an exciting and obviously important one, but we could never have predicted the incredible developments that were to follow."

Throughout his career, Fischer continued to work on the role of reversible protein phosphorylation in various signal transduction pathways, helping to sketch the widespread



Edwin G. Krebs and Edmond H. Fischer shared the 1992 Nobel prize in physiology or medicine. In Fischer's Nobel banquet speech, he quipped that "two 'Eds' are better than one."



Eddy Fischer (center) dances with former ASBMB President Susan Taylor and then-student Bradley Genovese at the ASBMB centennial bash in 2006.

importance of this reaction. His lab extensively characterized glycogen synthesis, which is important in metabolism; they also studied mitogen-activated protein kinases, or MAPKs, and signal transduction cascades involved in B and T cell activation. Fischer achieved full professorship in 1961 and continued at the University of Washington until his retirement in 1990.

Friends and colleagues on social media recalled Fischer's courtesy and sense of humor — qualities typified by remarks he made at a Stockholm banquet when he and Krebs received the Nobel Prize. Remarking on his pride in their students, Fischer said, "We owe our success to them, and also to the fact that, as the saying goes, two 'Eds' are better than one."

In addition to the Nobel, Fischer's professional honors include election to the American Academy of Arts and Sciences in 1972 and the National Academy of Sciences in 1973. He was a member or foreign associate of the

Spanish Royal Academy of Sciences, the Japanese Biochemical Society, the Korean Academy of Science and Technology, the European Academy of Sciences, and the Royal Society, in addition to being an honorary professor at numerous universities around the world. He joined the American Society of Biological Chemists (later the American Society for Biochemistry and Molecular Biology) in 1955 and served on its leadership Council from 1989 to 1993.

In later years, Fischer volunteered with other organizations, serving on the board of directors of the Vallee Foundation, a scientific philanthropy, and as honorary president of the World Cultural Council from 2007 to 2014. He was a lifelong music lover; having been admitted as a young man to the Geneva Conservatory of Music, he considered pursuing piano professionally but later wrote that he concluded it was "better to keep music purely for pleasure." His most recent public piano performance was just

this June at a virtual Lindau meeting. He also learned to fly an airplane.

In honor of Fischer's 100th birthday in April 2020, the department of biochemistry at the University of Washington threw a virtual seminar last October. It was attended by many of Fischer's former advisees and mentees and also by his granddaughter Elyse Fischer, a doctoral student in structural biology at the University of Cambridge. "Eddy gave me my love for science, research and discovery," the younger Fischer tweeted. "He always supported my career as a scientist even before I knew I'd become one."

Fischer is survived by his two sons and stepdaughter and three other grandchildren.

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



Teruko Tamura



Teruko Tamura, an influential cancer biochemist, died May 23 in Hannover, Germany. She was 71 years old.

Born July 12, 1949, in Tokyo, Tamura studied veterinary medicine at the University of Tokyo. She never worked as a veterinary doctor but began doing research at the university. She moved to Germany in 1979 to join the institute for medical virology at the Justus Liebig University Giessen. In 1992, she became the third woman in the history of the university to complete a habilitation, Germany's rigorous postdoctoral degree. Seeing how difficult it was to make a career as a woman in research, she started an initiative to support other talented women throughout their scientific careers. Tamura's lab always included scientists from countries around the world.

Tamura made major contributions to several studies related to cancer research, focusing on the Src and FMS-like tyrosine kinases and signal transduction, gaining a worldwide reputation in the field. In 1999, she discovered a protein, a new cell-fate decision factor termed FMIP/THOC5, and began the second part of her scientific journey. This novel protein is a substrate of oncogenic tyrosine kinases and a member of the mRNA export complex. Her later work on the function of THOC5 revealed the novel connection between oncogenic signaling and mRNA export.

In Giessen, Tamura met Hans-Heinrich Niemann, whom she later married. In 1996, the couple moved to Hannover to work at the Medizinische Hochschule Hannover. Both biochemists, they worked together until Niemann's death in 1999.

Tamura was diagnosed with lung cancer in January 2019. She continued her scientific work with the help of medicine and her longtime friend Thomas Bürger, whom she married in March 2021.

In addition to science, Tamura loved hiking in the mountains and classical music. She was a good piano player.

She is survived by her second husband, Thomas Bürger; her stepson, Steffen Niemann; niece and nephew, Ryoko and Ritzu Watanabe; and her research team.

Stephen Prescott



Stephen Michael Prescott, a former associate editor of the *Journal of Biological Chemistry* and president of the Oklahoma Medical Research Foundation, died May 28 at age 73. He had cancer.

Born February 22, 1948, in Bryan, Texas, Prescott earned a bachelor's degree from Texas A&M University in 1969 and an M.D. from the Baylor College of Medicine in 1973. He completed his training in internal medicine and cardiology at the University of Utah and pursued research training at Washington University School of Medicine in St. Louis. He later returned to the University of Utah as a professor of internal medicine, where he founded and directed a research program in human genetics.

For seven years, starting in 1999, Prescott served as executive director of the Huntsman Cancer Institute. He founded Lineagen, a biotechnology company that provides accessible genetic testing for children with autism spectrum disorder and developmental delay.

Prescott was president of the Oklahoma Medical Research Foundation for 15 years, raising \$100 million for the largest campus expansion in OMRF's history. Under his leadership, the foundation discovered three drugs that now are used worldwide to treat sickle cell disease, certain rare blood disorders and protein C deficiency.

In his lab, Prescott studied diacylglycerol kinases, or DGKs, enzymes that phosphorylate diacylglycerol to form phosphatidic acid. His team discovered a mechanism by which the zeta isoform of DGK stimulates the activity of a phosphate kinase and ultimately helps regulate actin polymerization, which is important in cytoskeleton remodeling. He also helped invent a method of screening for agents that regulate the shedding of membrane-bound proteins by enhancing or inhibiting the activity of DGK-delta, as well as methods of regulating inflammation and cell growth and division by applying these agents, which can be useful for treating cancer.

A JBC associate editor from 1993 to 1998, Prescott also served on advisory committees for the National Institutes of Health and American Cancer Society. His many scientific awards included the Sol Sherry Prize from the American Heart Association.

— Jessica Desamero

CALL FOR SUBMISSIONS



Meeting Connections

Have you made a connection, forged a collaboration, gleaned insight or had another meaningful experience at a scientific meeting? If so, tell us about it.

We invite you to write about your own meeting connection in 300–500 words.

We will publish the best stories in the March issue of ASBMB Today.

Email your submission to asbmbtoday@asbmb.org with the subject line “Meeting connections.”

Deadline: Dec. 1.

And there will be prizes:

FIRST PLACE: Free ASBMB membership, free registration to the 2022 ASBMB annual meeting and a \$100 Amazon gift card

SECOND PLACE: Free registration to the 2022 ASBMB annual meeting and a \$50 Amazon gift card

THIRD PLACE: \$25 Amazon gift card

ASBMBTODAY

CALL FOR SUBMISSIONS

ASBMBTODAY



DISABILITY EMPLOYMENT AWARENESS

ASBMB Today welcomes essays, interviews, opinion pieces and other articles relating to disabilities and doing science.

We encourage submissions from people with disabilities, employers/managers, researchers, allies and others.

Email submissions to asbmbtoday@asbmb.org with the subject line “Disability Employment” or use the Submit link at asbmb.org/asbmb-today.

Deadline: Dec. 31

Student Chapter applications and renewals due Nov. 30

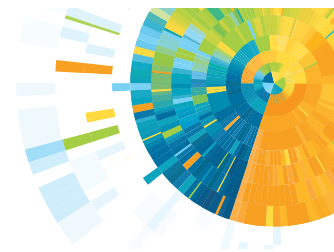
Join a national community of undergraduate students and faculty members promoting BMB research, education and outreach. Chapter students are eligible for a number of benefits, including travel awards to support attendance at the ASBMB annual meeting, summer research funding and selection for the ASBMB Honor Society, XΩΛ. Chapters also can apply for funding to organize regional meetings or support outreach initiatives. Renewals and applications for new chapters are due Nov. 30 to be eligible for Student Chapter travel awards to attend the 2022 ASBMB annual meeting. Learn more about this and other Student Chapter benefits at asbmb.org/education/student-chapters.



Annual meeting abstracts due Nov. 30

The No.1 reason people attend the ASBMB annual meeting is to present their work, so the society pulls out all the stops to make that possible for as many people as possible.

- **Share your results on your own terms:** When you submit an abstract, you can tell us if you want to give a talk or poster-only presentation.
- **Eliminating barriers:** ASBMB members save nearly 50% on registration. Plus, the society gives more than \$270,000 in travel grants. Visit asbmb.org/annual-meeting.



Public affairs

In August, the White House Office of Science and Technology Policy published a blog on their plans to develop implementation guidance for federal agencies on policies for research security and researcher responsibility. The ASBMB submitted policy recommendations urging harmonization of conflict-of-interest and conflict-of-commitment policies, transparency on violations of research integrity, and ensuring that research violation investigations do not fuel racial profiling of any group. Read the letter at asbmb.org/advocacy/letters.

New content available for members only

Visit the American Society for Biochemistry and Molecular Biology's collection of on-demand webinars. Learn about recent scientific discoveries, navigating life as a postdoc, applying for SBIR grants, ensuring that your data are solid and secure, and more. Visit asbmb.org/meetings-events/on-demand.

Give the gift of ASBMB membership

Give a colleague, student or friend a full year of exceptional resources and enriching experiences. Visit asbmb.org/gift-membership.



Data integrity leader exits

Chad McCormick, the ASBMB's data integrity manager, has taken a new position with the federal government. McCormick will be a scientist-investigator for the Office of Research Integrity at the U.S. Department of Health and Human Services. We wish him the best of luck in his new position.





JLR virtual issue: Focus on China

Scientific researchers in China have helped define and direct numerous research fields in recent years, and lipid science is no exception. We've collected a snapshot of Journal of Lipid Research papers from Chinese authors in this virtual issue. See the collection at jlr.org/focus-on-china.

New marketing manager

The ASBMB marketing department welcomed



Sarah Ornstein to the team in early October. Ornstein has an extensive

background in digital marketing and scientific associations. She previously worked at the American Association for the Advancement of Science. You can reach her at sornstein@asbmb.org.

JBC 100+ years

For more than 100 years, the Journal of Biological Chemistry has brought significant, enduring research and scientific discovery to the field via papers that contribute new and important mechanistic insights and/or novel methodologies that span the spectrum of biological chemistry.

We are delighted to share a collection of significant research published in JBC during the past century and beyond. See the collection at jbc.org/jbc-100+yearsofscience.

Mass spectrometry-based proteomics and disease

In the first installment of the ASBMB Publications Technique Talks webinar series, our speakers delved into different mass spectrometry approaches with a focus on



GARCIA

proteomics and disease. **Benjamin Garcia** of Washington University School of Medicine in St. Louis discussed developing novel mass spectrometry-based approaches for proteomics and understanding of histone post-translational

modifications in disease. **Matthias Mann** of the Max Planck

Institute of Biochemistry delved into several applications of mass spectrometric methods when studying signal transduction, biomarkers, metabolic diseases and more applications. **Michael Snyder** of Stanford University School of



MANN

Medicine explained how his was the first lab to perform



SNYDER

large-scale functional genomics and since has developed many proteomics techniques involving mass spectrometry. Register to watch the free webinar on demand at asbmb.org/meetings-events/on-demand/science.

Diversity, equity and inclusion updates

The ASBMB is part of the inaugural cohort of the National Science Foundation-funded ACCESS+ initiative. (ACCESS+ is short for Amplifying the Alliance to Catalyze Change for Equity in STEM Success.)



The society will collaborate with experts from scientific professional societies and other organizations recognized for national STEM diversity, equity and inclusion leadership to evaluate strategically the current state of DEI in the society. Representatives from the ASBMB, along with other scientific societies, attended a September ACCESS+ event at which results from an equity environmental scanning tool were discussed, DEI strategies were shared, immediate action steps were created and a community of practice was launched. Learn more about the vision of ACCESS+ at accessplusstem.com.

Ten Sewer scholarships announced

By ASBMB Today Staff

The American Society for Biochemistry and Molecular Biology's Marion B. Sewer Distinguished Scholarship for Undergraduates has doubled its reach this year.

The ASBMB's Minority Affairs Committee created the Sewer scholarship in 2016 to support students who excel academically and are dedicated to enhancing diversity in science. This year the MAC and the Student Chapters Steering Committee were able to select up to 10 undergraduate students instead of the usual five to receive up to \$2,000 toward tuition, thanks to a donation to the scholarship fund from New England Biolabs.

The scholarship honors Marion B. Sewer, who was an ASBMB member and past chair of the Minority Affairs Committee when

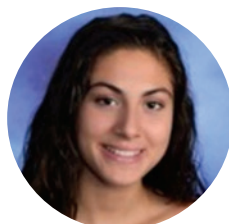
she died in January 2016 at age 43. Sewer was a principal investigator on projects devoted to increasing participation among underrepresented minorities and furthering student training. She also wrote about issues that URM scientists face, such as impostor syndrome. Sewer's work reflected her commitment to diversity and inclusivity of underrepresented minorities in science, technology, engineering and mathematics.

2021 recipients

The latest 10 recipients of the Sewer scholarship share their personal goals and how they promote diversity. Their statements have been edited.

Alyssa Cortes

Cortes plans to attend medical school after graduating with a B.A. in molecular biology and biochemistry from Wesleyan University. She is uncertain where she will complete her residency, but she is leaning toward pediatrics or emergency medicine, or even both. Following residency, and possibly a fellowship, Cortes plans to work in a hospital setting. She also plans to take multiple trips throughout her training and career to underserved countries to share her medical knowledge in village clinics. She particularly wants to go to South America and Caribbean islands to connect to her Hispanic roots.



Cole Davis

Davis is a rising senior at Duke University with a double major in chemistry and neuroscience and a minor in biology. After graduating, he plans to take a gap year and then apply to medical school to become a physician. As a young scientist, he understands the importance of research and appreciates how the scientific method can contribute to the field of biomedicine, so he plans to continue research throughout his career, depending on what medical specialty he pursues. His current interests include pharmacogenomics, clinical genomics and improvement of both life span and health span. Eventually, he hopes to find himself at the forefront of integrative biomedicine, conducting patient-focused research.



After completing her B.S. at Bates College, Duffy plans to work at an institution in Boston such as the Dana-Farber Cancer Institute or Massachusetts General Hospital to gain greater technical experience in a research-intensive setting. She intends to earn her Ph.D. in molecular oncology and operate a research lab at an R1 university to investigate genetics and metastasis formation. She wants to develop a supportive environment where researchers will feel comfortable as their authentic selves, because everyone should feel they have a place in science, technology, engineering and mathematics. She has been fortunate to have wonderful mentors in science throughout her life and would love to fill that role for other young women.

Emily-Claire Duffy

After completing her B.S. at Bates College, Duffy plans to work at an institution in Boston such as the Dana-Farber Cancer Institute or Massachusetts General Hospital to gain greater technical experience in a research-intensive setting. She intends to earn her Ph.D. in molecular oncology and operate a research lab at an R1 university to investigate genetics and metastasis formation. She wants to develop a supportive environment where researchers will feel comfortable as their authentic selves, because everyone should feel they have a place in science, technology, engineering and mathematics. She has been fortunate to have wonderful mentors in science throughout her life and would love to fill that role for other young women.



Justin Kim

Kim is majoring in biochemistry and molecular biology with a minor in Spanish at the University of Georgia. As soon as he finishes his undergraduate degree, he hopes to attend medical school to become a doctor of emergency medicine. His long-term career goals include providing health education in his hometown of Macon, Georgia, an area where a fourth of the population is known to have low health literacy. By advocating for his neighbors and through his rapport with the community as a doctor, he believes he will be able to boost this statistic. This increase in his community's understanding of personal health will help them make better health decisions and reduce their time in hospitals overall.



Natalie Labbe

After graduating from the Rochester Institute of Technology, Labbe plans to attend graduate school to pursue a Ph.D. in biochemistry. In the future, she hopes to teach at the collegiate level and perform biochemistry research of her own. One area of research that she has a personal connection to and would be interested in studying is the cause of Alzheimer's disease and possible prevention methods or cures. In her research, she wants to work with a team of diverse students to encourage women and minority students to pursue higher education and research in the sciences. In her career, she hopes to continue to encourage and mentor women and other minority students to become involved and excel in chemistry-related disciplines, whether through teaching, research or other mentorship opportunities.



Randy Le

Le's research experiences thus far have influenced his decision to pursue an M.D.–Ph.D. dual degree program and work toward becoming a physician–scientist. He is interested in the virology and neurology fields, with specific interests in developing new therapies and identifying targets that will improve overall health. He hopes to learn more about human



diseases and integrate his knowledge into practice that is aimed specifically at disadvantaged populations. One goal is to develop and implement programs that aim to better assist underserved communities, specifically programs that are about health care access, leadership within minorities, and empowerment in science, technology, engineering and mathematics. Coming from a low-income background himself, he hopes to improve the resources available for this community by leading a team that shares his interest in health care disparities.

Marvin Miller

Miller hopes to achieve stellar results in his career through effective teaching and scientific innovation. As a graduate student, he intends to study human metabolism in the aging population, where metabolic inflexibility is a player in health and disease. Nearly 40% of Americans age 51 and older are overweight, and 24% are obese. Among those 65 and older, 25.9% have Type 2 diabetes. Miller's grad school objective is to propose a remedy to metabolic inflexibility with a focus on aging. Graduate school will also prepare him for a teaching career as a professor where he hopes to inspire academic excellence in college learners. He looks forward to imparting expertise, experience and education in classrooms filled with passionate students. In summary, he aims to be a well-trained researcher and professor, molding students not just in for classroom and career but also for the intricacies and challenges of life.



Isaac Paddy

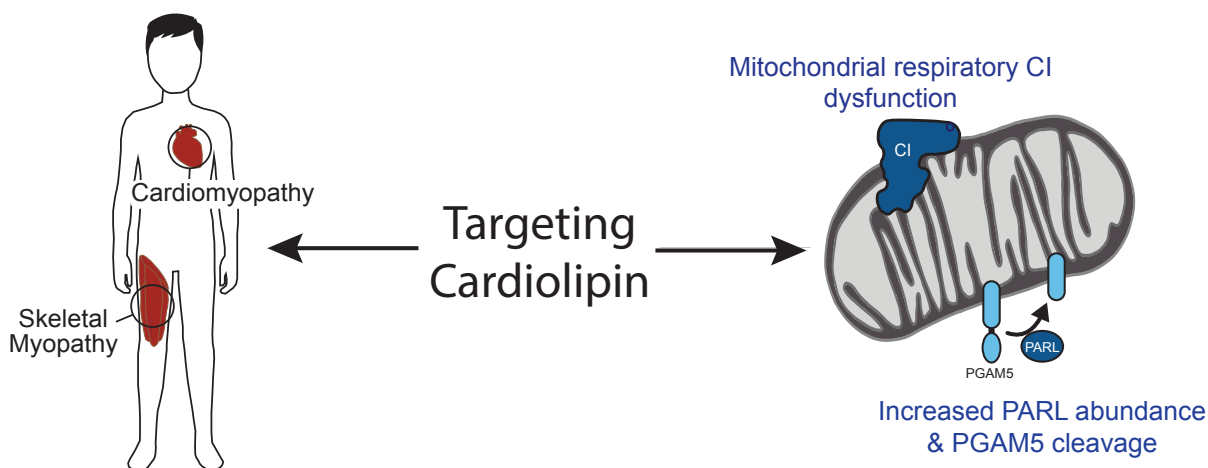
Paddy is a senior at Brandeis University studying chemistry with a specialization in chemical biology. He plans to obtain a Ph.D. in chemical biology with the goal of becoming a research scientist at the interface between chemistry and biology. He wants to investigate complex biological systems at the level of atoms and bonds and create ways to explore these systems using molecular tools. A great challenge in the science, technology, engineering and mathematics fields is making the



CONTINUED ON PAGE 15

Targeting cardiolipin modification in a genetic disorder

By Arianna F. Anzmann, Olivia Sniezek & Hilary J. Vernon



LIPIDNEWS-HVERNON.PDF

Targeting cardiolipin in TFAZZIN deficiency has shown promise in improving cellular defects in an HEK293 model of TFAZZIN deficiency and clinical problems seen in Barth syndrome, including cardiac and skeletal muscle dysfunction.

Barth syndrome, an X-linked disorder that primarily affects males, is characterized by weak skeletal muscles, cardiomyopathy and low neutrophils (the white blood cells that fight bacteria), among other medical concerns. The symptoms can be treated, but no disease-specific therapies have been approved. This rare and serious lipid metabolism disorder is caused by pathogenic variants in the gene TFAZZIN.

TFAZZIN encodes for an enzyme involved in the final remodeling step of cardiolipin, a key phospholipid localized to the mitochondrial inner membrane. TFAZZIN deficiency results in abnormal mitochondrial cardio-

lipin quantity and composition and subsequent mitochondrial dysfunction. Whereas researchers have known the primary biochemical defect in Barth syndrome for several decades, two important questions have remained unanswered: What molecular pathways are impacted by TFAZZIN deficiency and contribute to resultant mitochondrial dysfunction? And why does deficiency of an enzyme that affects a molecule present in every cell in the body affect such a specific set of tissues? Answering these questions is key to developing treatments for Barth syndrome.

Combined proteomic, me-

tabolomic and functional studies in a CRISPR-edited TFAZZIN knockout HEK293 cell model recently have offered insight into these questions. Among the molecular abnormalities that researchers at the Johns Hopkins School of Medicine identified in this cellular model were defects in the expression, assembly and function of complex I of the mitochondrial respiratory chain. The researchers also found increased expression of presenilin-associated rhomboidlike protein, a protease localized to the inner mitochondrial membrane, and abnormal cleavage of its downstream target, phosphoglycerate mutase 5. Thus, TFAZZIN deficiency affects

mitochondrial respiratory chain function and quality control.

The researchers found that both elamipretide, a molecule that binds to cardiolipin, and bromoenol lactone, which inhibits nascent cardiolipin deacylation, partially remediate these mitochondrial defects. Determining if these pathways are differentially impacted in spared versus affected tissues may help researchers understand what causes the

pleiotropic effects of TFAZZIN deficiency and suggest therapeutic approaches.

In addition to demonstrating the effects of cardiolipin targeting in cellular models of TFAZZIN deficiency in the lab, this approach has shown clinical promise. In a recent study published in the journal *Genetics in Medicine*, clinical researchers at the Johns Hopkins School of Medicine described results of a placebo-

controlled, crossover clinical trial to investigate the role of elamipretide in 12 patients affected by Barth syndrome. The study participants showed improvement in multiple clinical parameters, including muscle strength, exercise tolerance and cardiac stroke volume, after 48 weeks of treatment.

Together, these studies show the translational potential of cellular disease modeling and pathway targeting in lipid metabolism disorders.

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CONTINUED FROM PAGE 13

community more inclusive and accessible to those who are most underrepresented. While scientists conduct innovative research, they also have a platform to inspire and connect with a new generation of scientists. Paddy's mission and goal is not only to increase diversity in the science community but also to improve retention of those members of underrepresented groups through collective efforts to establish an inclusive community and foster meaningful mentorship opportunities.

Paulina Rios

Rios is majoring in biological sciences with a biomedical concentration at the University of Texas at El Paso. She currently is doing research in Chuan Xiao's structural biochemistry laboratory, where she studies proteins. After graduating in December 2022, she plans to attend graduate school to earn a Ph.D. in biochemistry or molecular biology. Her long-term goal is to work in a



biopharmaceutical or biotechnology company where she can improve human health through biomedical research. Her motivation is her family, and she is proud to be a Mexican–American woman in science.

Erykah Walton

Walton's career goal is to become a physician who both treats patients and is active in research. Conducting research as an undergraduate has opened her eyes to the lack of diversity in tissue and gene databases, which mostly contain samples from people of European descent. She will attend medical school and continue research to serve Black, Latino and other underrepresented populations and help expand their inclusion in research databases. She is optimistic that serving as a liaison between patients of color and medical research institutions can help advance science with greater consideration of all people in mind.



Finding a third form of fat

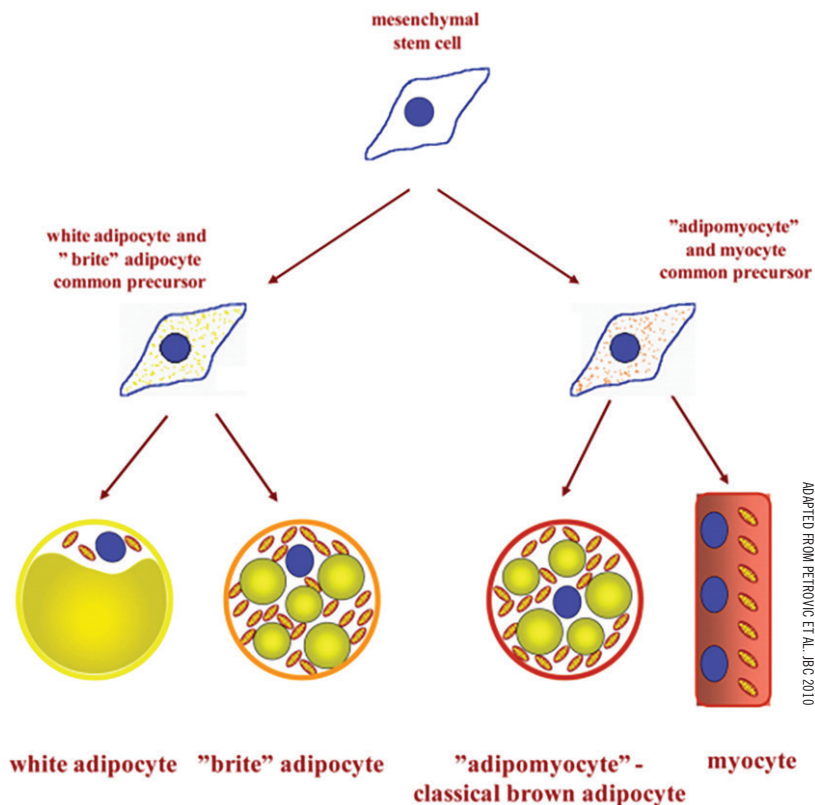
By Laurel Oldach

When brown fat was discovered in human adults in the early 2000s, it came as a surprise.

The tissue showed up as an annoying background in positron emission tomography scans, which use a radiolabeled glucose tracer to detect metabolic activity, often to ferret out metastatic cancer cells. Around the neck and shoulders, and sometimes in pockets surrounding the heart, kidneys and spine, there was a persistent signal of high metabolic activity too symmetrical to be cancerous.

“The radiologists were most interested in getting rid of the signal so as to better see metastases,” said Natasa Petrovic, a research scientist in molecular biosciences at the Wenner-Gren Institute in Stockholm. But when the observation made its way into the metabolism literature, it was an exciting finding. It meant that adult humans possessed brown adipocytes, which researchers had thought were found only in newborns.

Most fat cells, or adipocytes, are white, their cytoplasm almost completely occupied by a lipid droplet filled with triglycerides, which stores energy. In contrast, brown adipocytes are rich with mitochondria and much smaller lipid droplets. They warm the body without shivering by directly converting food energy into heat. This high metabolic activity caused them to appear in PET scans.



A figure adapted from the classic JBC article shows the lineages of brown, white and brite adipocytes. Mitochondria-rich brown adipocytes share a precursor with myocytes, or muscle cells, while white adipocytes, which contain a large lipid droplet and few mitochondria, have a different precursor. Petrovic and colleagues showed that mitochondria-rich brite adipocytes are related more closely to white than to brown adipocytes.

Because unwanted fat gain is a widespread health concern, finding brown adipocytes in human adults led researchers to ask whether they could make more of them. Brown and white adipocytes come from distinct cell lineages; either type of tissue isolated from a mouse and grown in culture generates distinct offspring cells, indicating that both phenotypes are cell autonomous. White fat cells long have been known to descend from fibroblasts. In 2007, researchers including

Petrovic reported that brown adipocytes share an origin with muscle cells.

These distinct lineages left out one very interesting group of cells. In animals exposed to cold or stress, metabolically active adipocytes expressing some signature brown-cell proteins proliferated in their white adipose tissue. How did these brownlike cells arise? Did they descend from myogenic precursors that had been lurking in white adipose depots, or were they converted

from white adipocytes? Either way, could researchers reverse unwanted weight gain by finding a way to convert white adipocytes to brown?

In a **Journal of Biological Chemistry** paper published in 2010, Petrovic and colleagues offered an answer, reporting that these cells had their origin in white adipose tissue but had a phenotype distinct from both white and brown adipose cells. They were a new type of cell.

Petrovic started on the project by accident, trying to coax white adipocyte progenitor cells in culture to mature more completely.

“PPAR gamma is a central regulator of adipogenesis,” Petrovic said. Therefore, it surprised her that when she treated preadipocytes with a PPAR gamma agonist, the stimulation also yielded a subset of cells that shared features with brown adipocytes.

The cells expressed a key signature of brown adipocytes, mitochondrial uncoupling protein 1, or UCP1. This transmembrane protein lets protons flow from the mitochondrial intermembrane space back into the matrix, generating heat instead of ATP. After norepinephrine treatment mimicking cold stress, the cells also contained more mitochondria and expressed more PGC1 alpha, which links stimulation of PPAR gamma to mitochondrial biogenesis.

The brownlike cells in white cell culture recalled the question about the developmental origin of brown cells in white depots. Petrovic and colleagues had established that brown and white fat cells are from different precursors. How were they both showing up in her culture?

To exclude the possibility that stray brown preadipocytes might

be mixed into the starting culture and growing faster than the white adipocytes, she generated hybrid cultures, mixing UCP1-knockout brown preadipocytes with wild-type white preadipocytes at varying ratios. No matter the starting ratio, there was proportional stimulation of the knockout-specific noncoding transcript from brown cells and the wild-type transcript from white cells, suggesting that the brown and white cells were stimulated to the same degree. This meant, the team concluded, that browning “cannot be explained by the overgrowth of a few pre-existing brown adipocytes in these cultures.”

Transcriptomic analysis showed that PPAR gamma could induce, and norepinephrine could boost, numerous brown fat–related transcripts. However, other signature genes of brown adipocytes were never expressed in white adipocyte–derived cultures, which also continued to express many white adipocyte markers. This indicated that PPAR gamma cannot reprogram white adipocytes completely into brown.

Finally, by imaging to count mitochondria and their UCP1 expression, they observed that adrenergic stimulation turned up mitochondrial biogenesis globally but induced UCP1 expression in only a few cells.

The team concluded that brown adipocytes cannot be conjured from white precursors by turning on UCP1 expression — but a specific pool of white precursors can develop into a brownlike thermogenic cell type. “Importantly,” they wrote, “these cells are molecularly and developmentally distinct from the classic brown adipocytes.”

But what should they be called?

“I remember very clearly our numerous and long discussions attempting to coin the most appropriate and catchy name for the novel cell type — one of my suggestions was ‘brownies,’” Petrovic said. She cannot recall whose idea it was, but the lab settled on the name brite, short for brownlike-in-white. After an unrelated study called the same tissue type beige for its mixture of brown and white characteristics, that name also stuck.

Later research found that brite/beige adipocytes exist in humans as well as mice and showed that, like classical brown adipocytes, brite cells can contribute modestly to an organism’s heat production. Researchers also have found that white adipocytes’ browning competence decreases with age.

Ten years on, Petrovic said, the field still is trying to understand the heterogeneity of fat tissues. “Adipocytes are so far classified as white, brown, and beige/brite,” she said. “However, I would say that this classification is an oversimplification of the real situation.”

Petrovic has continued to study the brown–brite distinction in mice, unraveling the functions of specific genes expressed in both types of thermogenesis-competent cells to understand their differences.

Meanwhile, other researchers continue to search for pharmaceutical approaches to stimulate white-to-brite conversion in humans as a potential way to tackle obesity.

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Flipping the switch

How the structure of the Rag GTPases regulates mTORC1

By Courtney Chandler

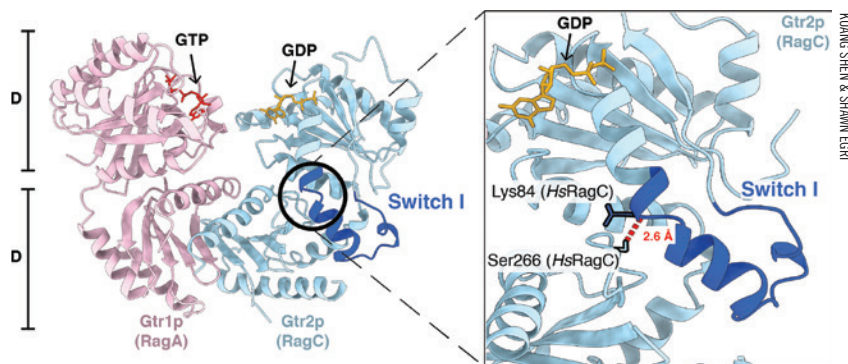
Eukaryotic cells must balance multiple factors to grow. The mechanistic target of rapamycin complex 1, or mTORC1, pathway senses and responds to environmental cues, such as nutrient availability, to control protein synthesis and cell growth.

The RagA–RagC GTPase heterodimer is required to activate mTORC1. Depending on amino acid availability, the RagA and RagC subunits will be oppositely loaded with either guanosine triphosphate or guanosine diphosphate, known as GTP and GDP.

When concentrations of amino acids in the cell are high, RagA is bound to GTP, and RagC is bound to GDP — this structural conformation facilitates mTORC1 interaction and activation of protein synthesis at the lysosomal surface. The reverse GTP/GDP loading leads to inhibition of mTORC1 and release from the lysosomal surface into the cytosol.

Until recently, researchers did not understand clearly how RagA and RagC maintain their oppositely nucleotide-loaded state to regulate mTORC1. In an article in the *Journal of Biological Chemistry*, a team from the University of Massachusetts Chan Medical School describes the molecular mechanism behind this regulation and the consequences of disrupting this balance.

Kuang Shen, an assistant professor at UMass and senior author on the article, described the RagA–RagC complex as a complicated light switch that controls mTORC1 — only when



A single hydrogen bond (in red in the box on the right) ensures the Rag GTPase complex can switch appropriately between the on and off states to regulate mTORC1 signaling and protein synthesis.

one switch is up and one switch is down will the mTORC1 lightbulb turn on.

“We were curious about the mechanism of regulation, because for us it’s like a black box and we didn’t understand how it worked,” Shen said.

To peer into the black box, graduate student Shawn Egri used enzyme kinetics, structural biology and chemistry tools to probe the mechanism behind the regulation. Egri said he purified between 30 and 40 RagA–RagC mutants with individual amino acid differences and tested their activity one by one.

Eventually, the researchers identified mutants that eliminated normal RagA–RagC activity. They found that one interdomain hydrogen bond is all it takes to keep the switch in one position or the other and prevent it from spontaneously flipping between the two states.

“It was really amazing that just one hydrogen bond has this profound of an impact,” Shen said.

They next introduced those mutants into cells. They observed that

with the interdomain hydrogen bond abolished, the GTPase subunits could not maintain their original nucleotide-loaded states in cells, leading to distorted responses to amino acid availability and altered mTORC1 interactions.

“It was surprising to us that our results (with purified proteins) translated so strongly in cells,” Egri said. “The phenotype was very clear even in wild-type cell background.”

In the future, Egri and Shen want to lock the complex in the on and off positions to see how that affects interactions with upstream regulators and downstream effectors of the mTORC1 pathway. This could help piece together a better idea of the signals and pathways that regulate the essential processes of protein synthesis and cell growth.

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KUANG SHEN & SHAWN EGRI

A hormone's guide to healthy living

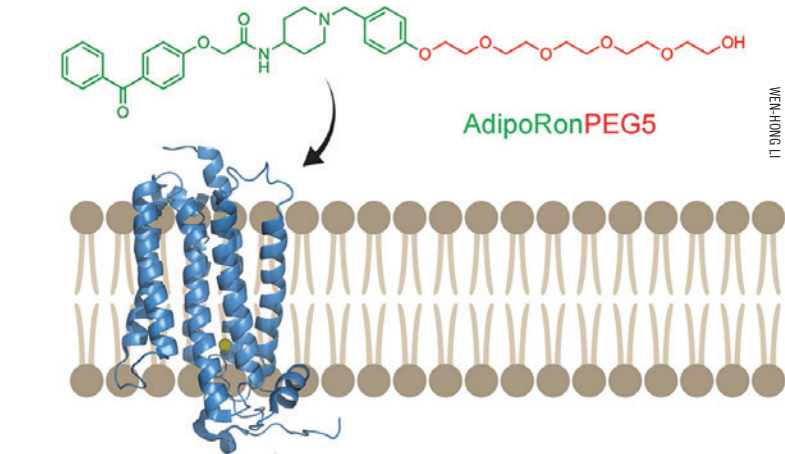
By Himanshi Bhatia

Research in the 20th century showed us the ill effects of our lifestyle choices. Countless studies demonstrated that smoking and drinking were gateways to cancer and other diseases. Scientists now are finding that the modern-day way of life — a sedentary lifestyle and a high-calorie diet — can have equally disastrous health impacts. The constant obsession with screen time has affected our metabolism in a way that makes us more susceptible to developing insulin resistance, thereby leading to Type 2 diabetes.

On the other hand, the human body can synthesize molecules that keep our metabolism in check and prevent it from going awry. These molecules, called adipokines, are hormones secreted by fat cells (and other metabolic organs in the body) and serve as the body's defense mechanism against metabolic anomalies.

A team of researchers in Philipp Scherer's and Wen-hong Li's labs at the University of Texas Southwestern Medical Center takes a special interest in the physiological effects of adipokines. Toshiharu Onodera, a postdoctoral fellow, said, "We have had a longstanding interest in pancreatic islets with respect to the relationship between adiponectin and the health and functionality of insulin-producing cells because there is a substantial presence of adiponectin receptors in pancreatic beta cells."

In a study published recently in the **Journal of Lipid Research**, Onodera, Ebrahim Zadeh and their team evaluated the effects of a modified version of an adipokine, adiponectin, on



PEG linker enhances bioavailability and improves receptor binding.

glucose and lipid metabolism.

"Adiponectin is a multifaceted protein with beneficial effects on many organs, such as the liver, pancreas, muscles, heart and kidneys," Onodera said. "These effects are mediated by adiponectin receptors."

While different ligands (also called adipokine agonists) can activate adiponectin receptors, none of them are clinically useful. One such agonist, AdipoRon, is limited further by its poor solubility and bioavailability.

"In our study," Onodera said, "we expand on the protective effects of AdipoRon by generating a series of AdipoRon analogs containing amphiphilic ethylene glycol chains."

In studies of mice that were genetically altered to have low insulin and fed a high-fat diet, the researchers found that their bodies absorbed one of these analogs, AdipoRonPEG5, better than the others, and it effectively reduced toxic lipid species in organs, resulting in dramatically improved therapeutic effect on diabetes and fatty liver disease. After administration of AdipoRonPEG5, the mice had improved blood glucose

levels, decreased lipotoxicity in the pancreas, reduced fibrosis in adipose tissue and reduced gluconeogenesis in the liver.

"We believe that we made substantial progress towards the improvement of an existing molecule of importance for diabetes and fatty liver disease," Onodera said.

Although AdipoRonPEG5 has longer half-life in circulation than its un-PEGylated form, the team was concerned about its frequent dosage, so they administered the agonist to mice twice a day for five days to observe a protective effect. "The next step is to generate longer-acting versions of these adiponectin receptor agonists," Onodera said.

These findings could present a novel mechanism for the design of diabetes-combating drugs.

DOI: 10.1016/j.jlr.2021.100095

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WEN-HONG LI

A new way to ID protein interactions

By Nivedita Uday Hegdekar

Understanding protein interactions and how proteins are organized in cellular compartments is essential to understanding their function. Since 2012, researchers have been using a technique called enzyme-catalyzed proximity labeling to study spatial and interaction characteristics of proteins in living cells.

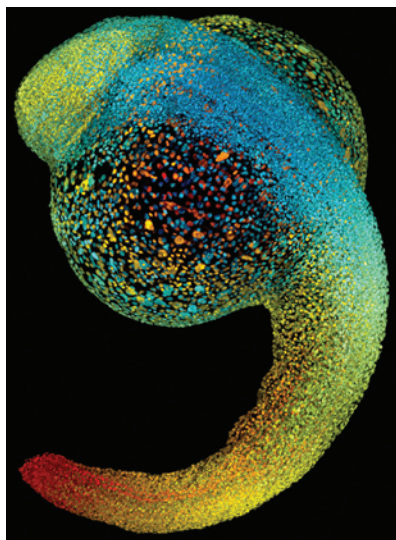
In this technique, an enzyme, usually biotin ligase, also called BioID, is fused to a protein of interest, or bait protein, and exogenously introduced into cells. The cells are then supplemented with substrates that cause the biotin ligase to add biotin tags to other proteins in proximity of or interacting with the target protein. These biotinylated proteins can then be enriched, isolated and identified using liquid chromatography coupled with mass spectrometry.

Anne-Claude Gingras' research lab at the University of Toronto was one of the earliest adopters of enzyme-catalyzed proximity labeling.

"My lab has extensively used the BioID enzyme to label different proteins in living cells and report on their organization in cells and identify new components of organelles and protein binding partners," Gingras said. "However, like many other researchers using proximity labeling, our studies have been limited to cells in culture."

Studies assessing proximity labeling in animal models, including vertebrates such as zebra fish, have been limited.

Ian Scott is also a researcher at Toronto; his lab uses zebra fish to study early cardiac and vascular develop-



PHILIPP KELLER ET AL/HOWARD HUGHES MEDICAL INSTITUTE

Just 22 hours after fertilization, a zebra fish embryo already is taking shape. By 36 hours, all of the major organs will have started to form.

ment. "Zebra fish embryos develop outside the mother's body, and most of their organs appear within 36 hours of fertilization," Scott said. "This makes them an ideal model for studying early development."

As a first-year graduate student at the university, Shimon Rosenthal pursued research rotations in both Gingras' and Scott's labs. For his doctoral research, he was interested in using genetic and proteomics tools to study cardiac development in animal models.

"We were interested in establishing a proximity labeling approach in the zebra fish model," Rosenthal said. "The project really interested me, and I welcomed the opportunity to be co-mentored by (Gingras and Scott)."

It turned out that the widely used BioID enzyme was not effective for proximity labeling in zebra fish embryos. Eventually, two mutants

of BioID — TurboID and miniTurbo — developed by Alice Ting's research group at Stanford University demonstrated effective proximity labeling in zebra fish embryos.

Rosenthal successfully developed and optimized TurboID and miniTurbo labeling in early zebra fish embryos. In addition, he demonstrated the versatility of his methodology through commonly used methods of exogenous protein introduction into cells. The methodology was recently published in a paper in **Molecular & Cellular Proteomics**.

"We not only proved that our protocol works, but that it is just as effective as the proximity labeling technique in cultured cells," Rosenthal said.

By generating transgenic zebra fish lines, Rosenthal was also able to study protein-protein interactions in specific tissues. Gingras and Scott will use this approach to check protein-protein interactions in diseases such as cerebral cavernous malformations, a disorder characterized by abnormal vessels in the brain's vasculature that are prone to leak blood.

"In addition," Scott said, "we hope to perform some experiments in mutant zebra fish models and understand how getting rid of one protein affects protein-protein interactions."

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From the journals

By Inayah Entzminger, Sarah May & Laurel Oldach

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

Glycogen storage turbocharges mice

Energy storage and release are important for performance in endurance exercise. Glycogen, a highly accessible glucose storage form, is typically the

first energy source used during activity; an animal's endurance capacity may depend in part on the extent of its glycogen stores. Mammals store glycogen in liver and muscle cells. While depletion of muscle glycogen is known to cause fatigue, researchers know less about how liver glycogen contributes to endurance capacity, although lengthy exercise is known to lower liver glycogen.

In a recent article in the **Journal of Biological Chemistry**, Iliana López–

Soldado and a team at the Barcelona Institute of Science and Technology describe their study of mice overexpressing a gene that drives glycogen synthase activation in liver cells. They tested the animals' ability to sustain a low-intensity run, which they compared to marathon training in humans. Animals with this modification maintained higher glycogen in their livers after exercise and showed longer endurance. They also were less sensitive to a

How psoriasis changes skin lipids

Psoriasis is an inflammatory disease affecting the outer layer of the skin, or epidermis, which serves as a critical barrier against infection, chemicals and loss of nutrients and water. Psoriasis compromises skin barrier function and causes epidermal skin cells to proliferate, forming raised plaques and scales on the skin.

While skin lipids — fatty acids, ceramides and cholesterol — are essential for maintaining a healthy epidermis, researchers do not yet know the exact composition of skin lipids in healthy and disease states. As the epidermal skin barrier is formed, ceramides must be oxidized by lipoxygenase enzymes, or LOXs. Mutations of these LOX enzymes disrupt the skin barrier so that the skin loses water and becomes dry, red and scaly. Despite this, researchers have not fully characterized the products of LOX oxidation of ceramides and their roles in maintaining the skin barrier.

Victoria J. Tyrrell and colleagues at Cardiff University used new mass spectrometry–based methods to characterize the LOX pathway ceramides present in the human epidermis and determine how these lipids change in psoriasis. Their results, published in the **Journal of Lipid Research**, demonstrate that substrates of the LOX ceramide pathway are elevated in psoriatic patient skin, even in the absence of plaque, whereas oxidized ceramide products are reduced. They also found that psoriatic le-



ALESEI SIMONENKOV/SHUTTERSTOCK

Psoriasis sends skin cell production into overdrive, causing buildup and shedding of dead skin cells.

sions had more oxidized free fatty acids than nonlesion or healthy skin, but the implications of this are unknown. In psoriasis, many genes were upregulated in the LOX ceramide oxidation pathway, which is required to form the epidermal barrier, possibly as an attempt to repair barrier function. Using network analyses, they identified a potential master regulator of these genes as the zinc finger transcription factor ZIC1.

While ZIC1 stimulates proliferation of some tumor cells, it had not been associated previously with skin cell proliferation during psoriasis. The authors state that ZIC1 is a potential new drug target for psoriasis.

DOI: 10.1016/j.jlr.2021.100094

— Sarah May

reduction in performance while fasting than wild-type mice. The results indicate that liver glycogen is an important source for supplementary energy to power endurance activity. DOI: 10.1016/j.jbc.2021.100976

Nonstructural protein 3 in coronaviruses

SARS-CoV-2, the virus that causes COVID-19, is the third highly infectious strain of human coronavirus to emerge in two decades. Nonstructural protein 3, or nsp3, is an enzyme found in all three of these strains — SARS-CoV, SARS-CoV-2 and MERS-CoV — as well as in the common-cold coronaviruses hCoV-229E and hCoV-OC43. Researchers have yet to analyze thoroughly the function of this enzyme so, in a new study in the journal **Molecular & Cellular Proteomics**, Katherine M. Almasy, Jonathan P. Davies and colleagues at Vanderbilt University investigated nsp3 in these five coronavirus strains.

Nsp3, a large multidomain protein, can enzymatically break down other proteins, perform cleavage reactions on itself and perform other important regulatory reactions. The Vanderbilt researchers divided the protein into three fragments based on known domains: the N-terminal, middle and C-terminal fragments. They analyzed protein interactions of each using liquid chromatography with tandem mass spectrometry.

The researchers found that nsp3 has divergent targets in each of the coronaviruses despite similar domains. One important discovery was that the N-terminal portion of the protein could block a cellular stress response called the unfolded protein response that normally is activated by the virus during infection. The team intends to investigate how nsp3 interacts

with two other nonstructural proteins known to coordinate to form double-membrane vesicles out of the ER to replicate coronaviruses. They also believe it may be important to study variations in protein interactions among emerging SARS-CoV-2 variants.

DOI: 10.1016/j.mcpro.2021.100120

It doesn't take guts to secrete PCSK9

Too much low-density lipoprotein, or LDL, cholesterol clogs the arteries so they can no longer pump enough blood. This can cause a heart attack or stroke. LDL cholesterol is cleared out of the bloodstream by the liver LDL receptor — unless the receptor has been degraded.

The latest cholesterol-lowering drugs prevent LDL receptor degradation. These drugs target proprotein convertase subtilisin/kexin 9, or PCSK9, a protein that escorts the LDL receptor along the path to degradation. PCSK9 is highly expressed by the liver and intestines, but only the liver is known to secrete PCSK9 into the bloodstream — where it controls liver LDL receptor expression. Researchers are debating whether the intestines secrete PCSK9.

In a study in the **Journal of Lipid Research**, François Moreau, Aurélie Thédrez and colleagues at the University of Nantes report that human intestinal explants and mature human intestinal Caco2 cells do not secrete PCSK9. In mice lacking liver PCSK9, they detected no PCSK9 in the portal vein — a conduit between the intestines and liver — ruling out the possibility that it transports intestinally secreted PCSK9 to the liver LDL receptors. This study emphasizes the role of PCSK9 secreted by the liver in regulating cholesterol homeostasis. DOI: 10.1016/j.jlr.2021.100096

Blocking hormone synthesis to block cancer

A subtype of cytochrome P450, P450 17A1, catalyzes two steps in the production of androgens: hydroxylation of steroid precursors to androgens and glucocorticoids and a second oxidation reaction that is specific to testosterone and other androgens. Human physiology depends on glucocorticoids, so blocking the cytochrome's second oxidation activity without affecting the hydroxylation is a goal for treatment of androgen-dependent prostate cancer.

In a recent article in the **Journal of Biological Chemistry**, F. Peter Guengerich and colleagues at Vanderbilt University write that they investigated inhibition mechanisms of drugs that block steroid hormone synthesis, which were designed as a treatment for hormone-dependent cancers such as prostate cancer. They found that all five of the compounds they tested bound to the cytochrome without a need for further changes and inhibited both types of reaction. The finding indicates that more work will be needed to develop a compound that can block one activity and not the other.

DOI: 10.1016/j.jbc.2021.100969

Anchoring NOD2 on the plasma membrane

Crohn's disease causes chronic inflammation of the digestive tract. Possible triggers include changes in the gut microbiome and genetic factors. One of the strongest risk factors for Crohn's disease is mutation of an immune system protein called nucleotide-binding and oligomerization domain protein 2, or NOD2.

Within a cell, NOD2 senses peptidoglycans — the basic unit of the bacterial cell wall — that bacteria

shed during infection. Then, NOD2 activates the host immune response, which requires its attachment to the cell membrane. Two cysteine residues on NOD2 can be linked to the fatty acid palmitate, thus anchoring it to the membrane.

In a new Images in Lipid Research publication in the **Journal of Lipid Research** providing further evidence for a study published in the journal *Science* in 2019, Charneal Dixon and Gregory Fairn at the University of Toronto show how they performed metabolic labeling experiments in HCT116 human colon cancer cells and showed that wild-type NOD2, but not a double cysteine mutant, was labeled with a palmitate mimetic. Additionally, the double cysteine mutant failed to reach the cell membrane. Knowing these cysteine residues are linked to palmitate, the researchers inferred that the surface of NOD2 interacts with the cell membrane. Defects in NOD2 membrane recruitment, which is critical for its ability to sense and respond to bacterial pathogens, are associated with inflammatory disorders, including Crohn's disease.

DOI: 10.1016/j.jlr.2021.100097

Hub proteins associated with oral cancer

Oral squamous cell carcinoma, or OSCC, makes up over 90% of all head and neck cancers that involve the upper layer of the epithelium. A major factor in determining patient outcome for these cancers is metastasis to the lymph nodes in the neck. This can decrease already-low survival rates to below 50%. OSCC has paired human primary tumor cells and lymph node metastasis cells, making it a prime target for extracellular vesicle, or EV, analysis



The ion channel TRPV1 opens in response to capsaicin from hot peppers, and to heat — a discovery recognized with the 2021 Nobel Prize in physiology or medicine.

How a TRP channel tells “hot” from “pot”

Transient receptor potential V1, or TRPV1, is an ion channel that performs double duty, recognizing both high heat and a range of small molecules that includes both the spicy compound capsaicin and peptide toxins found in venom. The receptor, which is expressed in pain-sensing neurons, is responsible for translating all these stimuli into pain.

But TRPV1 also binds endocannabinoids, lipid signals that are not usually noxious. And although it is not their major receptor, TRPV1 also responds to active compounds found in cannabis. This is a bit odd since, unlike other TRPV1 ligands, endo- and exogenous cannabinoids are generally not a noxious signal. The receptor is not a primary mediator of cannabinoid signaling — but could it nonetheless be linked to the anti-pain properties of endocannabinoids and their herbal counterparts? Although structures of TRPV1 have been solved, researchers do not understand fully yet how it interacts with its diverse ligands.

In a recent article in the **Journal of Biological Chemistry**, Yanxin Li, Xiaoying Chen and colleagues at Zhejiang University School of Medicine and Qingdao University Medical College write that they used molecular docking to investigate how endocannabinoids bind to TRPV1 and patch-clamp recording to determine the effects of interaction on channel opening.

They found that the general orientation in which endocannabinoids such as anandamide bind to TRPV1 is similar to that of other compounds such as capsaicin. However, cannabinoids engage a crucial tyrosine residue within the protein that does not participate in binding to capsaicin. The authors conclude that the channel's mechanism for opening differs between the two types of ligand, perhaps explaining the different effects of these compounds on pain sensation.

DOI: 10.1016/j.jbc.2021.101022

— Laurel Oldach

A target for triple-negative breast cancer

Triple-negative breast cancer, or TNBC, is an aggressive form of breast cancer. It tests negative for the three main targets of hormonal and protein receptor therapies: estrogen receptors, progesterone receptors and HER2 protein. This lack of targets for therapy limits treatment options. Patients with TNBC have a poorer chance of recovery than those with other forms of breast cancer.

A new study in the journal **Molecular & Cellular Proteomics** characterizes the functions of CD151, a protein that researchers have found to be significant in TNBC. The study also establishes the importance of studying

proteins that leave cancerous cells for noncancerous targets within the body as possible therapeutic targets. Sipeng Li and Xinya Li of Peking University and a research team in China reviewed literature establishing extracellular vesicles from TNBC as key players in cancer progression before focusing on the proteins transferred within those vesicles.

The researchers used liquid chromatography with tandem mass spectrometry analysis to fully profile the serum of healthy donors and patients with TNBC. They found increased expression levels of ITGB1, a known prognostic marker for cancer, and the protein CD151 in TNBC serum samples. This suggests that increased CD151 expression in patient serum could be a diagnostic marker for TNBC.

CD151 is a scaffolding protein that interacts with integrin receptors. Researchers previously have demonstrated that CD151 can activate extracellular signal-related proteins as well as the intercellular signaling cascade Akt/PKB, which promotes nontumor mammary cell replication. The research team headed by Li and Li generated cells lacking CD151 to interrogate its function. They determined that CD151 regulates the intracellular trafficking of proteins as well as regulating when the cell secretes these proteins using extracellular vesicles. The researchers intend to develop effective small molecules to block CD151 packaging and secretion via extracellular vesicle as a method of TNBC therapy.

DOI: 10.1016/j.mcpro.2021.100121



Early detection of breast cancer via mammography also can determine the cancer subtype. Mammograms of triple-negative breast cancer often reveal round, oval or lobulated masses with indistinct margins.

— Inayah Entzminger

and for the search for molecular targets for the disease.

A recent paper in the journal **Molecular & Cellular Proteomics** outlines how Ariane Fidelis Busso-Lopes from the Brazilian Biosciences National Laboratory and a team from Brazil and the U.S. identified 11 hub proteins that were significantly deregulated at metastatic sites, seven of them with a potential application as prognostic markers. The researchers examined every molecule of EVs released by the primary site tumor cells and absorbed into paired lymph node metastatic cells, or LN1. They found that OSCC-derived EVs contained specific cargo associated with metastasis. The researchers identified an upregulation of a set of integrins in LN1 EVs originating from the site of metastasis that differed from a set known to be involved in distant metastasis, providing targets for regional metastasis therapy. Eleven hub proteins in total were downregulated in LN1 EVs when compared to primary site tumor cells, indicating that low protein concentrations were associated with an aggressive, metastasizing OSCC phenotype.

DOI: 10.1016/j.mcpro.2021.100118

Proteins poised to battle pathogens

Researchers studying a channel-forming protein that works as a weapon against parasitic protists have found that the protein's homologs may be geared toward other types of pathogen.

Apolipoprotein L1, first found in a small subset of high-density lipoprotein particles, is involved in immune signaling and upregulated during infection. Apolipoprotein L1 can integrate into lipid bilayers, forming cation channels that even-

tually kill cells. This makes it a useful weapon against extracellular eukaryotic parasites like trypanosomes; after ApoL1 breaches their membranes, cations flow into the cell, and osmotic swelling and lysis ensue.

Humans and other primates express five more apolipoproteins homologous to ApoL1, called ApoL2-6, whose channel-forming properties have not been studied. In the **Journal of Biological Chemistry**, Jyoti Pant and colleagues at the City University of New York report on a study of whether ApoL 2-6 are able to puncture membranes the same way that ApoL1 can. They found that some of the proteins can, when overexpressed, cause cells to swell and release lactate dehydrogenase; others cannot. The six apolipoproteins tend to be expressed in different cellular compartments, suggesting that they might protect against pathogens not just outside the cell, such as trypanosomes, but also internal pathogens.

DOI: [10.1016/j.jbc.2021.100951](https://doi.org/10.1016/j.jbc.2021.100951)

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Upcoming ASBMB events and deadlines

NOVEMBER

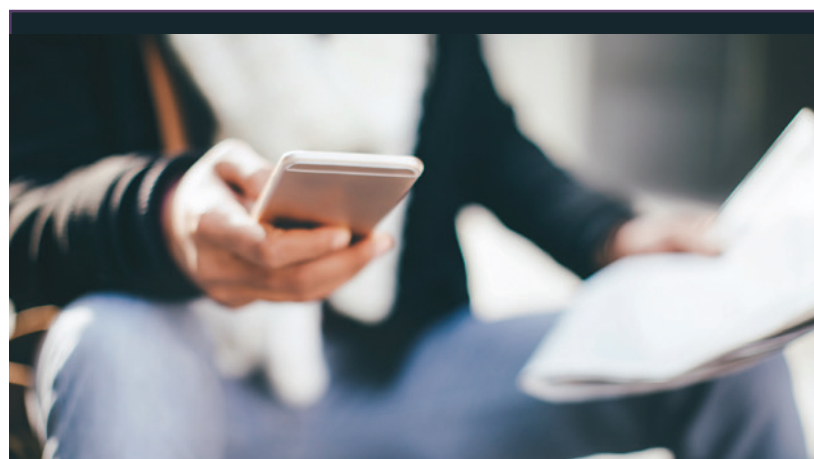
- 8 National STEM Day
- 10–13 Annual Biomedical Research Conference for Minority Students
- 12 ASBMB fellows nomination deadline
- 18 LGBT in STEM Day
- 20 Student Chapters renewal deadline
- 27 Student Chapters Travel Award Deadline
- 30 ASBMB 2022 annual meeting abstract deadline

DECEMBER

- 6 DEUEL early registration deadline
- 7 ASBMB annual meeting travel award deadline
- 15 ASBMB annual meeting last-chance abstract submissions open

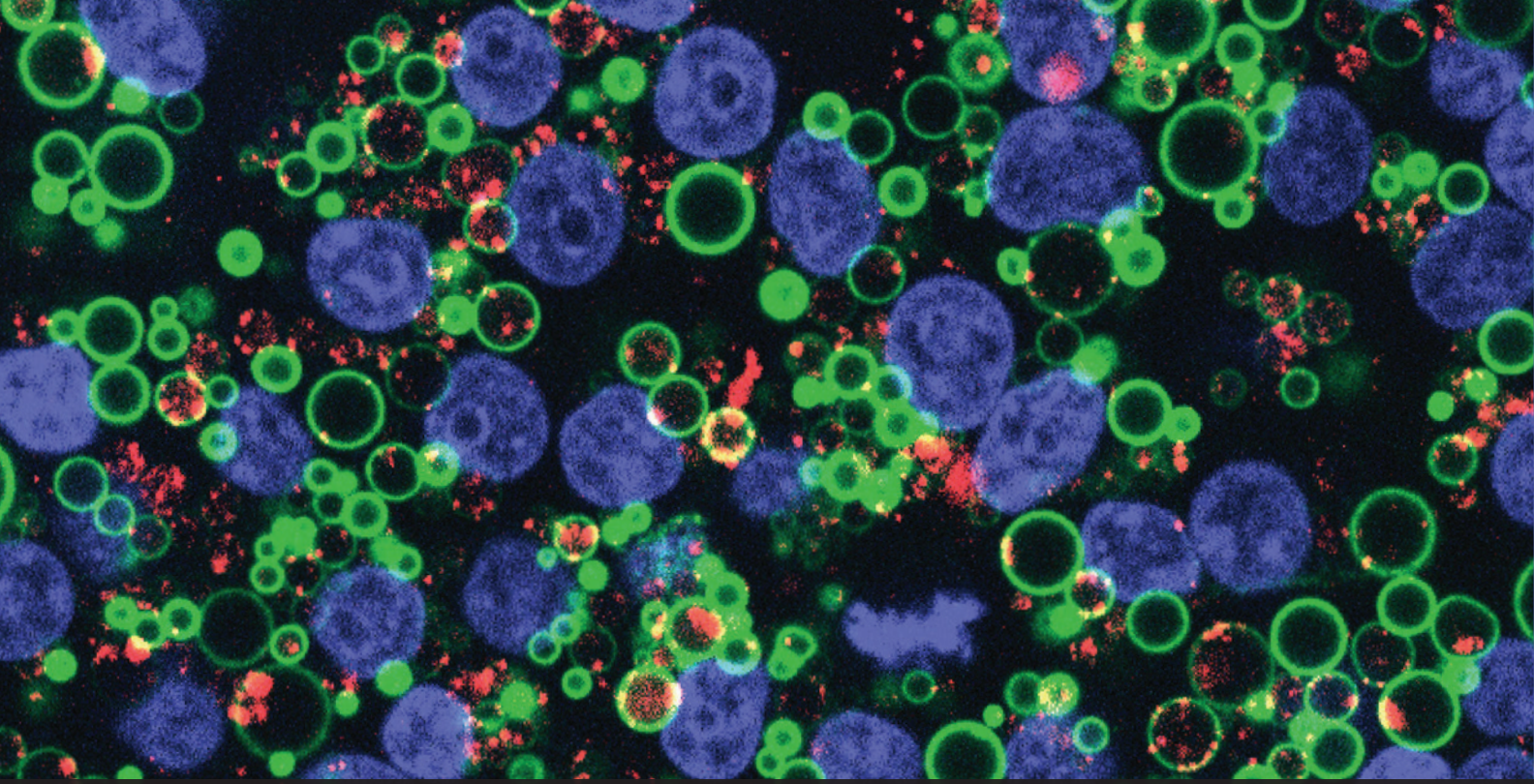
JANUARY

- 10 DEUEL abstract deadline
- 27 ASBMB annual meeting last-chance abstract deadline
- 31 ASBMB Honor Society nominations deadline

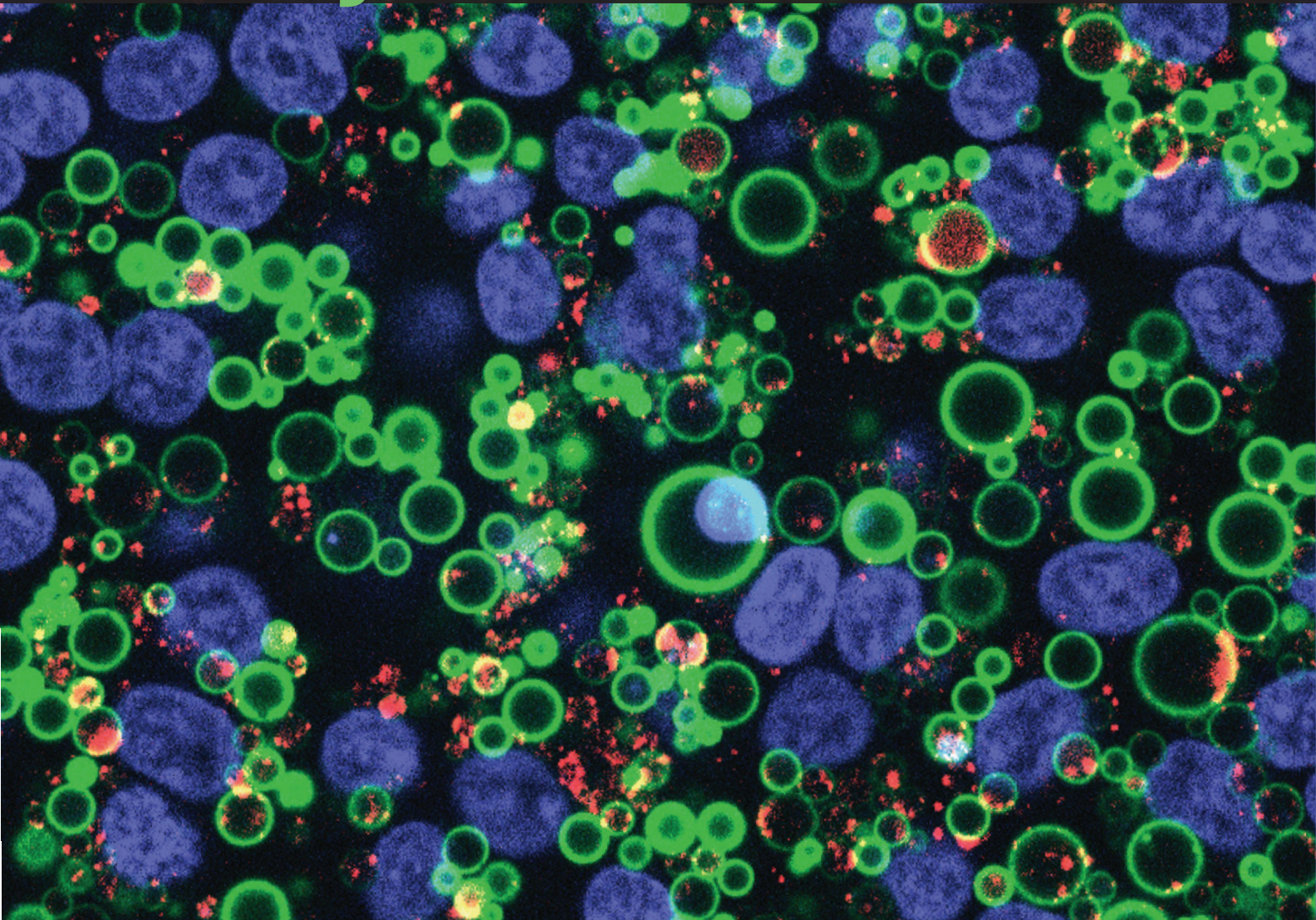


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A very delicate **balance**



Could blocking lysosomal gatekeeper PIKfyve slow neurodegeneration?

By *Laurel Oldach*

Earlier this year, the U.S. Food and Drug Administration approved the drug Aduhelm for Alzheimer's disease. Its manufacturers say Aduhelm blocks aggregation of the protein amyloid beta in the brain. But evidence that the drug can help patients requires a very hopeful eye; clinical studies were so inconclusive that the agency's advisory panel recommended against clearing the drug for marketing to patients. FDA leaders' willingness to override that recommendation speaks to patients' unmet need.

Whether the symptoms are the loss of mental clarity due to Alzheimer's disease, the loss of physical control caused by Lou Gehrig's or Parkinson's disease, or another pattern of infirmity, neurodegenerative disease is a terrible diagnosis. Treatment options are limited, often restricted to managing symptoms with no effect on the slow advance of the underlying pathology. These diseases are estimated to affect about 6.5 million Americans today, and, as the population ages, that number is expected to rise.

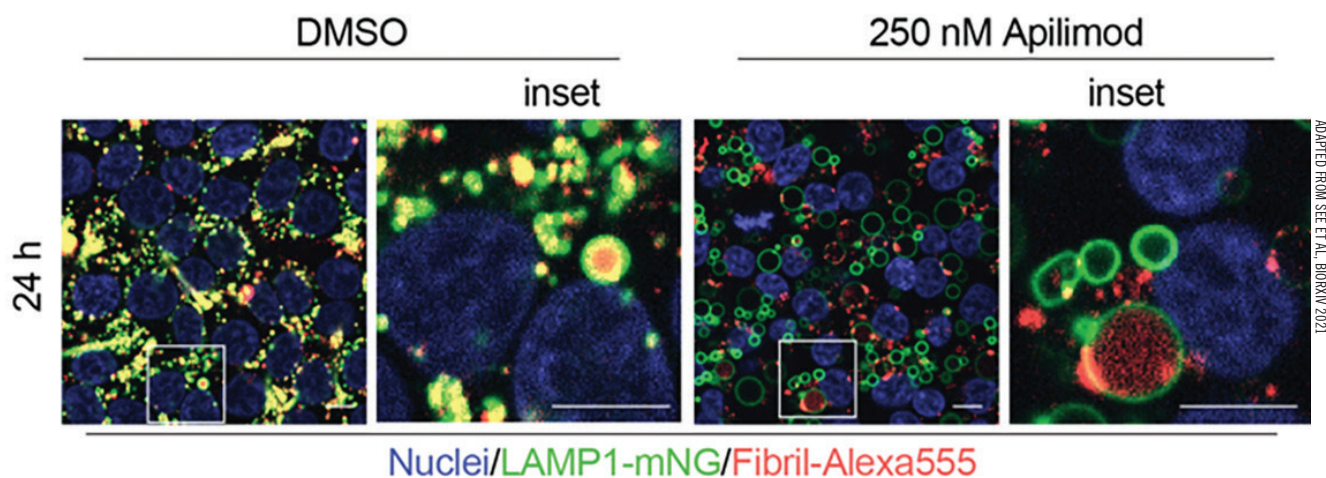
Many neurodegenerative diseases share a feature: accumulation of misfolded proteins that neurons struggle to get rid of. Researchers are testing many possible ways to slow or reverse this aggregation, including using monoclonal antibodies such as Aduhelm that bind

the offending proteins, reducing the activity of enzymes that produce them or boosting pathways that clear them. A few labs are investigating the possibility that a little-known enzyme called PIKfyve might offer another way to alter the course of aggregation and therefore disease. PIKfyve has an obscure role in cell biology, generating phospholipid species that are a vanishing minority of all the lipids in the cell. Yet the kinase seems to act as a gatekeeper to the lysosome, a key organelle in cellular waste disposal.

PIKfyve has been receiving attention from disparate sources recently, as the gene that encodes it turns up repeatedly in screens for genes affecting neurodegenerative disease. Researchers have found roles for the kinase in the development of Alzheimer's, Parkinson's and amyotrophic lateral sclerosis, or ALS — and they're looking for ways to target it. The enzyme maintains a delicate homeostatic balance, and researchers in academic and corporate laboratories are eager to determine whether it can be manipulated safely.

But some researchers argue that we don't know enough about PIKfyve to drug it successfully and that cutting off access to the lysosome could do more harm than good. The complex discussion is a case study in why it's so difficult to develop new treatments for neurodegenerative disease.

Opposite page: Cells (blue nuclei) treated with an inhibitor of the lipid kinase PIKfyve show enlarged lysosomes (green, LAMP1) that co-localize with alpha-synuclein fibrils (red). Researchers are investigating whether the kinase could become a drug target for several neurodegenerative diseases.



Part of a figure panel from Stephanie See and colleagues' preprint on alpha-synuclein seeding shows the effect of PIKfyve inhibition on seed trafficking to the lysosome. In an untreated cell (left two panels), synuclein fibrils labeled in red and lysosomes in green show a high degree of yellow overlap 24 hours after seeds are added. After treatment with apilimod (right two panels), they are separate.

Seeds and lysosomes

Belgian graduate student Alberto Soares wasn't looking for lysosome regulators in 2015 when he started a study of cell-to-cell transmission of tau fibrils in Alzheimer's disease, but the lysosome turns out to be important for how fibrils spread.

Fibrils, tough and durable structures formed when misfolded monomers of the protein tau glom together, make up the intracellular tangles that appear in brains with Alzheimer's. The tangles spread from one part of the brain to another as the disease progresses, following known routes of neuronal connection. Researchers believe that misfolding of tau may be transmissible — that a misfolded copy of tau can, upon encountering a properly folded peer, propel it into the misfolded conformation. The disease-causing proteins called prions are well known to behave this way. In Alzheimer's disease, tau and amyloid beta accumulate; other diseases have been linked to aggregates of other proteins that also seem to spread. The model, sometimes called proteopathic seeding, is an increasingly prevalent and well-supported hypothesis.

Researchers still are investigating exactly how clumps of aggregated proteins kill neurons — whether by

blocking normal function or through some directly toxic pathway. The proteopathic seeding model also raises questions about how a fibril that starts inside one cell can gain access to properly folded proteins inside another.

Wim Annaert, a group leader at the Katholieke Universiteit Leuven in Belgium, is Soares' research mentor. "If you can understand the mechanism of spreading and you can interfere with it," Annaert said, "you might start looking at disease-modifying drugs that delay or even stop spreading."

Annaert's lab and collaborators in a lab at Janssen, the research arm of Johnson & Johnson, set out to understand whether a protein called clathrin, which is involved in endocytosis, helped to pick up the problem fibrils and introduce them into the cytoplasm. They found that it did not — but by the time they published early this year in the *Journal of Biological Chemistry*, that was almost an afterthought, eclipsed by something they came across accidentally.

After adding an inhibitor of a protein downstream of endocytosis, Soares noticed different results depending on the dye he had used to label fibrils. Pursuing the discrepancy, he found that inhibition of the kinase PIKfyve prevents seeds a neuron has

picked up from reaching the lysosome. This prevented fibrils tagged with acid-sensitive dyes from fluorescing. More importantly, the team found, it stopped fibril seeds from spreading.

To touch off a misfolding chain reaction throughout the cell, misfolded tau proteins first must gain access to the cytoplasm. To do that, they have to pass through the lysosome, which functions like the stomach of a cell: more acidic than the cytoplasm at large, it is filled with enzymes that break down complex molecules.

Proteopathic seeds give the lysosome a bad case of indigestion. When they're delivered, for reasons that researchers do not yet understand, lysosomes tend to burst, letting seeds infiltrate the cytoplasm.

Louis De Munnck is a Janssen scientist who co-mentored Soares. "If you prevent the seed itself from ending up in the lysosome, you get less aggregation," De Munnck said. "It's not every day that we stumble upon these nice observations."

PIKfyve, a lipid kinase, helps to give lysosomes and late endosomes their unique identity within the cell. Without the phosphoinositide species PIKfyve generates, endosomes and autophagosomes fail to fuse with lysosomes. And if tau fibrils never reach the lysosome, they never can escape from it.

The phosphoinositide code

Organelles are many and motley, filled with contents that differ from one compartment to the next. But from the cytoplasmic side, those components are obscured by a membrane wrapping. You might imagine the membranes of different organelles as closed doors to mysterious rooms.

Almost like paint color, the composition of each membrane can convey

information about what's behind each door. Subcellular membranes are composed of lipids that determine their fluidity, acidity, curvature and surface properties. Through different binding domains, lipids also help to determine which proteins are recruited to an organelle's surface.

Phosphatidylinositol, or PI, lipids are particularly important in giving each organelle membrane its character. Their head group, inositol, is unusually large, a sugar that can be phosphorylated at any — or all — of three hydroxyl groups. The combinations

PIKfyve pleiotropy

PIKfyve phosphorylates PI3P, generating PI(3,5)P₂. On this much, everyone agrees.

In mammalian cells, PIKfyve contributes to levels of PI5P, which is phosphorylated at just one location. But scientists have yet to reach consensus — and rumors fly about major meeting arguments — over whether PIKfyve generates PI5P directly, by phosphorylating PI, or indirectly, by raising the amount of PI(3,5)P₂ that phosphatases can act on.

Whether direct or indirect, said University of Pittsburgh lipid biochemist Gerry Hammond, "The controversy comes from the fact that there are so many experimental observations that would agree with both models."

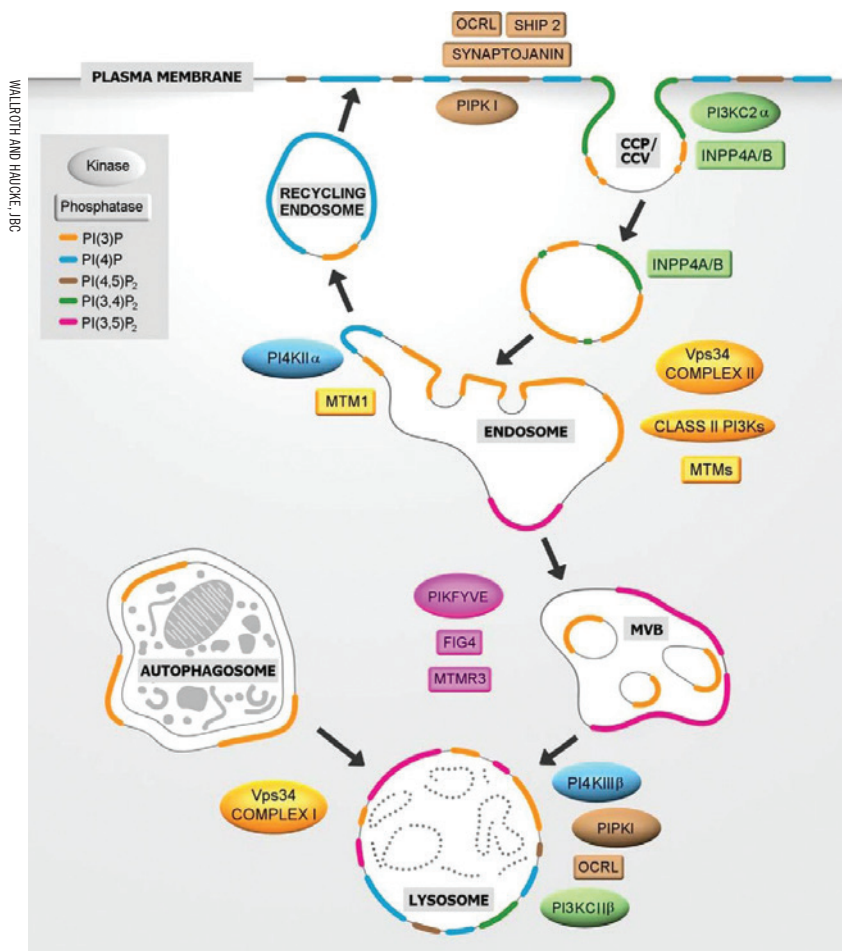
In addition, PIKfyve activity may slightly lower the level of its abundant substrate PI3P, which could contribute its own effects to overall cell biology. As with many metabolic pathways, Hammond said that it's very difficult to disentangle the lipids' contributions when PIKfyve is inhibited.

Those effects, he added, depend on more than just the presence of specific phosphorylated lipid species. "There's kind of two parts of the story," Hammond said. "There's the biochemistry to figure out the enzymes that are involved in making these lipids. But then there's a class of effector proteins."

"With PI(3,5)P₂ we don't have a very complete list yet of bona fide effector proteins," Hammond added. It is likely that those effector proteins — whatever they are — govern many of the downstream effects of PIKfyve activity, which are thought to include lysosome acidification, fusion between endosomes and the lysosome, and perhaps also fission.

A similar mystery hovers around where, exactly, the lipids in question are most effective. "We do think that more than one compartment is affected by PIKfyve inhibition," Martin Kampmann said. His lab and Lois Weisman's have observed PIKfyve in cellular neighborhoods other than the lysosome.

"When people would inhibit something with apilimod, then they'd see these huge swollen lysosomes," Weisman said. "That was the most striking phenotype. ... But then, you have to wonder: is that all PIKfyve does?"



A figure published as part of a JBC review on the phosphoinositide code shows the distribution of phosphorylated phosphoinositides on membranes in the endolysosomal system, and the enzymes that produce them.

give a total of seven different phosphorylated species. Phosphorylated PIs are a small but influential subset of a cell's total lipid species. Each is thought to be enriched at some stages of the endomembrane system, the network of organelles that starts with endocytosis and often terminates in the lysosome.

According to Scott Emr, a Cornell University professor who studies the roles phosphorylated PIs, or PIPs, play in membrane trafficking, it has become clear that the so-called organelle lipid code, in which one PIP species is enough to give a membrane its identity, is not an absolute. "That is, you don't only find one PIP species on each organelle. However, each PIP is highly enriched on specific organelles," he said, adding, "This preference in quantity on different

membranes still supports the lipid code model."

PIKfyve plays a key role in encrypting this code as the only kinase that can make the phosphatidylinositol species $PI(3,5)P_2$, which is phosphorylated on the third and fifth positions of inositol. It also makes — whether directly or indirectly is hotly debated — the lipid $PI5P$. (See "PIKfyve pleiotropy.")

Lois Weisman, a University of Michigan professor who has studied PIKfyve and its yeast homolog, Fab1, for decades, compared PIKfyve to the metabolic enzyme mTor, a well-studied protein kinase that conducts a metabolic symphony from its perch on the surface of the lysosome. PIKfyve, she said, regulates just as many processes. "Why PIKfyve isn't as famous has nothing to do with its importance, in my opinion. It's because measuring $PI(3,5)P_2$ is next to impossible."

Such measurements, which rely on high-performance liquid chromatography, are finicky and don't give much information about cellular location. Thus far, efforts to develop a fluorescent sensor to visualize $PI(3,5)P_2$ in cells have produced probes that probably bind other lipid species too.

Still, you don't need a biosensor to see the most dramatic result of PIKfyve inhibition: enormous, numerous lysosomes.

Assia Shisheva, who identified and named PIKfyve in human cells soon after Emr and colleagues described its yeast homolog, also has worked on the kinase for many years. Shisheva, a professor at Wayne State University, was among the first to generate and express a mutant of the kinase that lacked enzymatic activity. "Initially when we were looking at these cells, we were saying, 'Wait a minute. Why

are the cells having this (appearance) — kind of like they're taking a bubble bath? Is it something that we screwed up, the serum or something?"

But the cells expressing the wild-type enzyme were perfectly healthy, and the result appeared reliably in subsequent trials. The phenotype Shisheva observed was real; when PIKfyve was blocked, the cells gradually filled with vesicles that looked a little like soap bubbles.

Some effect of PIKfyve inhibition — whether the absence of PI(3,5)P₂ or PI5P, or perhaps an excess of PI3P — closed the door to the lysosome. And strangely, when Shisheva and other researchers knocked out a phosphatase called Fig4 that reverses PIKfyve activity, they saw the same effect.

A marriage of opposites

Karin Reinisch, a Yale structural biologist who recently published on the structure of PIKfyve and its binding partners, said she was drawn to study the enzyme in part because paradoxes abound in the literature about it.

For starters, biochemists gradually had established that PIKfyve and the phosphatase Fig4 travel in tandem in the cell along with a third protein, Vac14. Given that the two enzymes have opposite effects, the observation didn't make much sense. Reinisch said, "Nobody understood how you could have these two things in the same complex — how come they're not just burning up ATP?"

In addition, it was unclear why knocking out Fig4 activity had the same effect as knocking out PIKfyve. "Why would you need to have phosphatase activity to have an active kinase?" Reinisch said.

"Nobody understood that either."

Last year, researchers in Reinisch's lab reported on a structure of the complex that helped clarify matters a little. The tentpoles of the complex are made of a star-shaped pentamer of the protein Vac14 cupped like a hand over the membrane. This five-pointed framework binds one copy of PIKfyve and one of Fig4. Based on the shape of the complex, Reinisch said, it's likely that only one enzyme's active site can gain access to the membrane at any moment, preventing wanton waste of ATP.

While PIKfyve and Fig4 have opposing effects on the phosphorylation of their lipid substrate, each one also acts on proteins — and here, they help each other out. When PIKfyve is active, it autophosphorylates, inhibiting its own lipid kinase activity. Meanwhile, Fig4 can dephosphorylate the kinase, which increases its activity.

"The interactions between the three proteins are very, very complex," Shisheva said, pointing out that her lab previously had described the counterintuitive effect of Fig4 on PIKfyve activity.

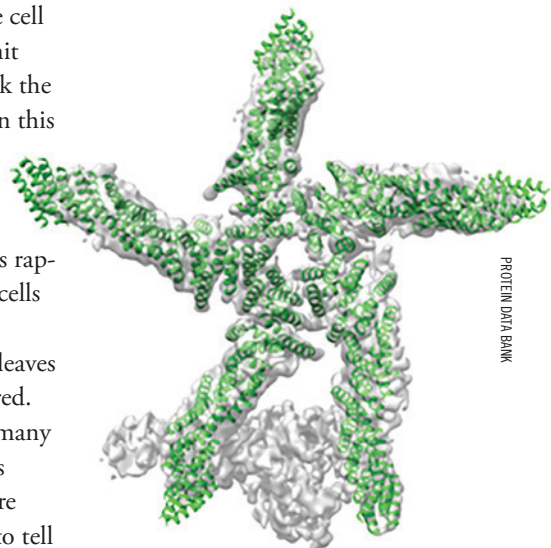
According to Weisman, the complex, almost Rube Goldbergian interaction could give the cell numerous ways to open or limit access to the lysosome. "I think the cell needs a way to acutely turn this pathway on and off," she said, noting that in yeast cells under acute osmotic stress, PI(3,5)P₂ concentration surges rapidly and then drops off as the cells adapt to their new conditions.

Reinisch said the structure leaves numerous questions unanswered. PIKfyve is phosphorylated at many additional sites, and the effects of those other modifications are unclear. In addition, it's hard to tell from the cryo-electron microscopy

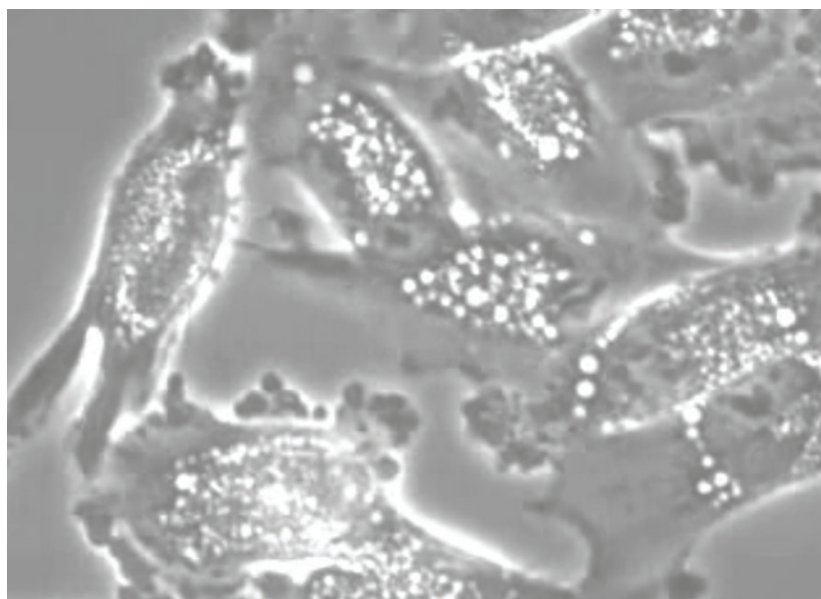
“It's kind of easy to break a system. But if you can inhibit something and decrease the pathological phenotype, that's really, really cool.”

Stephanie See

A structure Karin Reinisch's lab solved using cryo-electron microscopy shows the scaffolding protein Vac14 (green) in complex with the kinase PIKfyve and phosphatase Fig4 (gray).



PROTEIN DATA BANK



Still from a timecourse video showing how cells from a glioblastoma line respond to treatment with a molecule later described as a PIKfyve inhibitor.

WIKIMEDIA/EVERETT ET AL. MOLECULAR CANCER 2011

the ALS-related protein C9Orf72, and driver mutations in thousands of patients with neurodegenerative disorders. In addition, Fig4 mutations have been known for decades to link to a subtype of the degenerative nerve disorder Charcot–Marie–Tooth disease.

“Not that many people are interested in (PIKfyve), but, because these disparate groups are, it makes you think maybe something’s really there,” Weisman said of the emerging trend in the literature.

Stephanie See, a postdoc at the University of California, Berkeley, said, “I think it’s very possible that it’s sort of a universal mechanism ... important for controlling the spread of many aggregating proteins.”

As a graduate student, See worked in Martin Kampmann’s lab at the University of California, San Francisco. In a recent preprint, she and colleagues reported that using a CRISPR loss-of-function screen to remove some enzymes in the phosphatidylinositol pathway could slow the spread of alpha-synuclein fibrils in human embryonic kidney cells. In follow-up experiments using various specific inhibitors for phosphatidylinositol-regulating enzymes, See found that a PIKfyve inhibitor had the most dramatic effect, reducing aggregation almost completely.

“From a therapeutic standpoint, that was really interesting for us,” See said. “It’s kind of easy to break a system. But if you can inhibit something and decrease the pathological phenotype, that’s really, really cool.”

Many researchers have considered attacking proteopathic diseases by turning up autophagy, the cell’s system for directing bulk waste to the lysosome. But inhibiting PIKfyve should do the opposite.

Justin Ichida’s lab at the Univer-

structure exactly how PIKfyve inhibitors might fit into the protein’s structure.

“We’ve been contacted by several people (to ask) could we crystallize the kinase with the inhibitor,” Reinisch said. Thus far, that has been impossible because “the molecule is very big, with many domains, and it’s breathing and it’s moving around, so we can’t get to a higher resolution.”

PIKfyve and neurodegeneration

The researchers asking Reinisch about the inhibitor probably are intrigued by the number of independent high-throughput screens, using different methodologies and investigating different diseases, that recently have pointed to PIKfyve as a promising drug target.

In addition to the JBC study on tau, researchers have identified PIKfyve in screens for regulators that control the aggregation of alpha-synuclein in Parkinson’s disease, modifiers of the deterioration of neurons with mutations in

sity of Southern California posted a preprint in 2019 showing that in cultured neurons with mutations linked to ALS and frontotemporal dementia, inhibiting PIKfyve had a neuroprotective effect. “It was really puzzling when we first found it,” Ichida said. “Why would blocking something that blocks autophagy be helpful here? It was kind of counterintuitive.”

In the studies from Ichida’s and Kampmann’s labs, as in the JBC study that focused on tau, the bubble-bath phenotype that arises after inhibiting PIKfyve seems to be important in helping cells. “By blocking PIKfyve, you trap the fibrils in early endosome compartments,” See said. “They can’t get to the place where they can break out of the endosome and cause problems.”

But for some researchers, vacuole-filled cells have ominous implications. Asked about blocking PIKfyve to treat neurodegenerative disorders recently, Adriano Aguzzi, a neuropathologist at the University of Zurich, answered quickly and emphatically. “No, no, no. Don’t do that. It will kill you.”

Aguzzi calls the phenotype spongiosis. “It’s so characteristic and so unique that, as a pathologist, if you look at the brain and see spongiosis, you know within a fraction of a second that there is a prion disease.”

His lab reported in a paper published in July that after deliberate prion infection in cultured neurons or in mice, PIKfyve vanishes. “The moment the mice are really terminally sick, there is no PIKfyve detectable in the brain anymore,” Aguzzi said. “This was one of the very first times in my life where a result coming out of a blot genuinely surprised me.”

Following up the observation with mechanistic biochemistry, the researchers found a causal chain from an unfolded protein response to PIKfyve destabilization to the bubble-bath phenotype. In samples from a brain biobank, they observed that patients with more dramatic loss of PIKfyve had succumbed to prion disease earlier.

Weisman said the Aguzzi lab’s findings “broadly fit with our own earlier finding that mouse mutants deleted for Vac14 or Fig4, or with a hypomorphic mutation in PIKfyve, exhibit spongiform brains.”

Aguzzi is less sanguine than many colleagues about inhibiting PIKfyve to prevent the spread of proteopathy from one cell to the next. “I think it’s a very delicate equilibrium between PIKfyve and Fig4 and the amount of spongiosis,” he said, “and I would be super scared of touching that.”

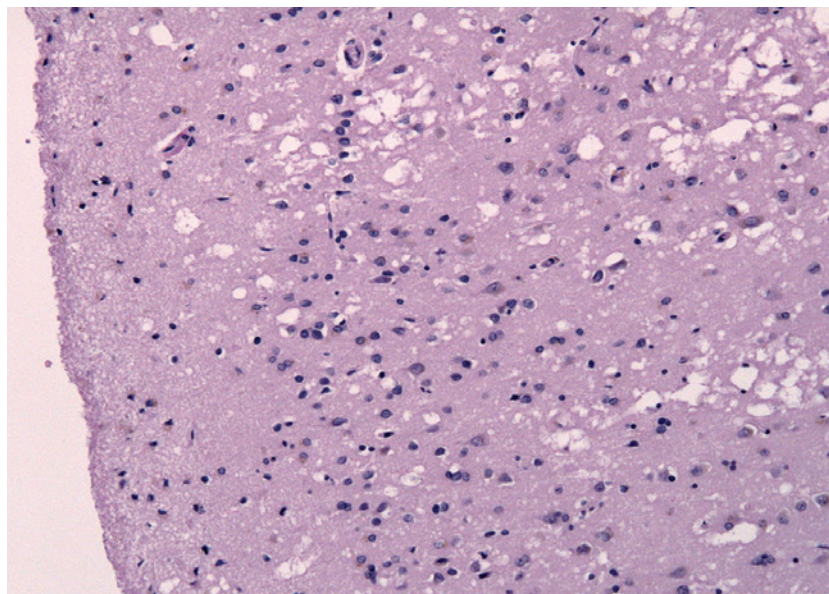
Drugging PIKfyve

Despite the concerns, preliminary results from numerous studies of as-yet-untreatable diseases of

“It’s so characteristic and so unique that, as a pathologist, if you look at the brain and see spongiosis, you know within a fraction of a second that there is a prion disease.”

Adriano Aguzzi

A histological slide shows spongiosis in cortical tissue from a brain affected by prion disease.



JENSLORIAN/WIKIMEDIA COMMONS

The many lives of apilimod

When the molecule now called apilimod first was reported in 2006, researchers believed it acted by inhibiting interleukin production in T cells; its inventors figured that this might be useful for the treatment of Crohn's disease. It took several years before another pharmaceutical team reported that the molecule actually inhibits PIKfyve and that PI(3,5)P₂ was part of an intermediate step in the T-cell signaling that leads to release of some interleukins.

In 2017, cancer researchers at AI Therapeutics reported that non-Hodgkin's lymphoma cells are highly sensitive to PIKfyve inhibition, dying when exposed to a low concentration of apilimod. The cells, the authors concluded, were more dependent on autophagy and the downstream lysosome activity than ordinary cells. Partial data from a clinical trial testing apilimod for safety in people with non-Hodgkin's lymphoma are available. Meanwhile, the company appears to have pivoted from using apilimod for oncology and now is testing it as a small-molecule antiviral against SARS-CoV-2 in phase 2 preliminary efficacy trials.

protein aggregation have piqued drug developers' interest in PIKfyve.

"There's a lot going on in the PIKfyve therapeutic development world," Ichida said. "Our company, Acurastem, is making an antisense therapeutic for PIKfyve; Verge Genomics is making a small-molecule inhibitor; AI Therapeutics is moving forward their small-molecule inhibitor; then there are other large companies that are trying to either develop their own programs or license other programs."

The most advanced of these drug development programs, at AI Therapeutics, was conceived as a way to kill cancer cells, not to save neurons. (See "The many lives of apilimod.") But the company announced early in 2020 that, while doing large-scale data mining, it had linked PIKfyve to ALS and that collaborators in Ichida's and other academic labs had found that ALS-model neurons survive better in culture when treated with AI's PIKfyve inhibitor, apilimod.

Apilimod already has made it through the first phase of drug development, clinical safety testing,

While some study participants suffered nausea and vomiting at high doses, lower doses seemed to be reasonably well tolerated. Based on those safety results, Ichida and other scientists working in this area argue that there may be a therapeutic window — a dose that delivers benefits without harmful side effects — for PIKfyve inhibitors.

"Clearly, people can survive having been treated with this molecule, right?" Weisman said. "So either these vacuoles aren't arising, or maybe they are being resolved somehow."

PIKfyve optimists also cite genetic evidence. Although an embryo without PIKfyve will die very early in development, people can be born with just one functional copy of the gene. Those individuals seem to suffer no ill consequences except for a tendency to develop white flecks within their corneas that can mildly impair vision, and which upon examination turn out to be cells filled with swollen vacuoles.

Perhaps a drug could reduce PIKfyve activity enough to slow lysosome fusion, and therefore seed propagation, without halting it altogether. Ichida said that his company, Acurastem, has conducted but not yet published experiments applying its PIKfyve inhibitors to a mouse model of ALS. There, he said, "Vesicle enlargement doesn't seem to be something that's required for the efficacy or the therapeutic rescue."

Or maybe vesicles could be cleared by a mechanism that doesn't involve the lysosome. Ichida noted that even if vacuoles do develop, scientists have found that some cultured cells activate secretory autophagy when PIKfyve is blocked. He suggested that the phenomenon, which happens when autophagosomes blocked from the lysosome

dump their contents into the extracellular space, could act as an escape valve for the extra vacuoles.

Like researchers at AI Therapeutics, scientists at Verge Genomics picked up on PIKfyve as a potential target based on mining genetic data from ALS patients. Irene Choi, a senior director and head of drug discovery at Verge, said her team has not observed abnormal vesicle formation in cells treated with their lead candidate, a small-molecule inhibitor of PIKfyve. “But of course, we weren’t specifically looking for that either, at that time. We are currently exploring what potential liabilities vacuole formation imposes,” Choi said. “What we do know is that, in our model systems, we don’t see an accelerated cell death; we actually see an improvement in cell death over time.”

Like Ichida, Choi said that the lack of neurological danger signals from clinical trials of apilimod, which has been tested in hundreds of patients, some for six months or longer, was an encouraging sign that PIKfyve inhibitors might be safe to use.

The whole drug-development industry runs on this kind of bet: being the first to stake out, and patent, a therapeutic area and then making sure over time that the treatment strategy is safe for patients and achieves the desired result. It’s part of the reason so many drug candidates fail before reaching patients.

What happens now?

Researchers are left with a puzzling combination of observations to sift through. Will low-grade inhibition of PIKfyve be a useful brake on uncontrolled spreading of pathological protein aggregates, or will it kill neurons by overfilling them with

vacuoles? Is closing the door to the lysosome beneficial or harmful?

“I would like to believe that this is going to pan out,” Weisman said. Still, she acknowledged that she has her doubts. The mixed sentiment is widely held. No one is rooting for neurodegenerative diseases, but many potential mechanisms for therapy have failed over time.

Could blocking PIKfyve be therapeutic? “I think that remains to be seen,” Kampmann said. “The nice thing about the cell-based studies is we now know what to look at” during a transition into model organism studies. Kampmann added that his lab has found evidence that other phosphatidylinositol pathway enzymes are involved in the onset of neurodegenerative disease.

Even Aguzzi, the most emphatically skeptical researcher interviewed for this article, thinks studying PIKfyve could lead to useful knowledge about neurodegeneration. His lab has started to run CRISPR screens in search of modulators of PIKfyve activity that might influence vesicle trafficking.

Exploration in the pharmaceutical labs is likely to determine whether neurons in a living brain fill with vacuoles during sustained pharmaceutical inhibition of PIKfyve.

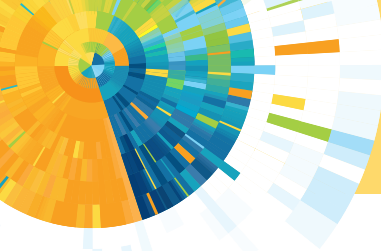
Even if PIKfyve inhibitors don’t prove to be a safe and effective way to block the spread of seeds, researchers still may be able to parlay knowledge about PIKfyve’s role into useful approaches to combat neurodegeneration. De Muyenck, the Janssen scientist, said, “We’re keeping an eye open.”

“Clearly people can survive having been treated with this molecule, right? So either these vacuoles aren’t arising, or maybe they are being resolved somehow.”

Lois Weisman

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





‘We love to see the hard work of undergraduates come to life’

By Angela Hopp

The ASBMB Undergraduate Poster Competition was conceived to attract and retain the society’s youngest members. But it ended up benefiting — and becoming a must-attend event for — scientists at all career stages.

Joycelyn Radeny, a student at Juniata College, talks at the ASBMB annual meeting with another undergraduate about her work on how lipid metabolism affects lifespan in *C. elegans*.

Over the past two decades, thousands of students have cut their science communication teeth at the undergraduate poster competition at the annual meeting of the American Society for Biochemistry and Molecular Biology.

Begun in 1997 by postdoc Catherine Drennan (now a professor at the Massachusetts Institute of Technology), the event has grown in both participation and impact.

It has helped undergrads become more competitive for graduate programs and find supportive mentors. It has helped educators connect with colleagues, launch collaborative projects and secure funding. And it serves as an annual reminder, as Drennan said, that it’s unwise to underestimate undergrads.

Phillip Ortiz, assistant provost for

undergraduate and STEM education at the State University of New York, has helped orchestrate the poster competition since the early days and said it’s his favorite part of the ASBMB meeting. “The energy in there is just so wonderful,” he said. “It has that feeling of any competition: the sort of a tingle of excitement, fear and anticipation.”

Kathleen Cornely of Providence College, chair of the poster competition committee, echoed Ortiz: “This is why it’s so popular — because you walk into the room and that energy is incredible.”

This is the first time many competitors have presented on a national stage, Ortiz said. And many, Cornely added, come with an entourage.

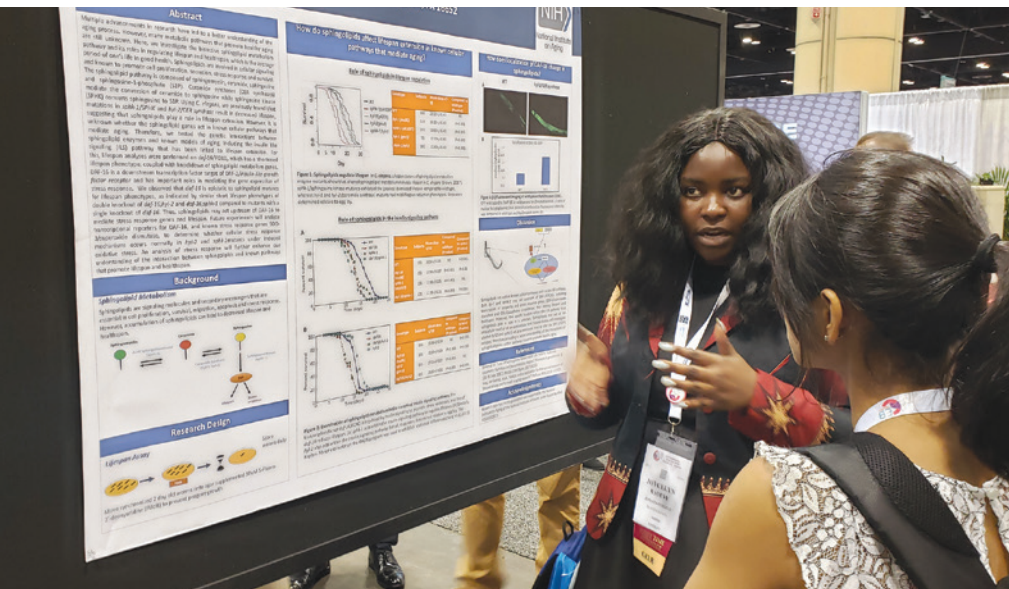
“It’s loud because there are so many great conversations being had,” Cornely said. “The students’ friends are there, so you might see a little crowd gathered around a poster.”

The judges also are revved up. Many, Cornely said, show up early.

Ortiz concurred: “For a lot of (judges), this is their primary contact with undergraduate students, so they’re getting to show their mentoring chops and talk to students who are tremendously engaged in their research.”

The society expects almost 300 students and more than 150 judges to participate during the annual meeting in April in Philadelphia.

Over the years, ASBMB Today has reported on aspects of the poster



competition, but it's never attempted to capture the big picture — until now. For this joint reporting project, we interviewed people who've made the event possible and who've benefited from their experiences — as organizers, judges, mentors and participants. We discovered that the competition has a way of getting its claws in you — enticing you to return year after year.

A seat at the table

The poster competition was conceived to achieve multiple goals, Drennan and Ortiz said. The society wanted to attract younger members and make sure they were well served.

"We've often thought of the undergraduate poster competition as a way of certainly bringing people into the society but also demonstrating that the society is not just about researchers but also about learning," Ortiz said.

The ASBMB's founders established criteria that limited membership to the most accomplished and credentialed scientists, which meant that, in the early days, young scientists, women and people from marginalized groups were few and far between.

The history book "100 Years of the Chemistry of Life: The ASBMB Centennial History" by Ralph Bradshaw and colleagues records how society leaders debated those exclusionary criteria in the 1980s and abandoned them in the 1990s, effectively converting the ASBMB "to a society embracing a much broader range of individuals with an interest in the biochemical sciences."

Aware that they needed to do more to make the society relevant to forthcoming generations of scientists and to make its membership more diverse,

From presenter to mentor

Daniel Dries chairs the chemistry and biochemistry department at Juniata College in Pennsylvania. He first attended the ASBMB annual meeting as an undergraduate at the University of Delaware under the guidance of Hal White, a previous ASBMB education award winner.

Dries helped establish the ASBMB student chapter at Juniata and serves as its faculty adviser. Every year, he said, he takes as many students as he can to the annual meeting. He noted that the society's travel grants help a lot.

"One year, after the poster competition, I remember running into Natalie Ahn with my students. (She was) the president of ASBMB at the time," he said. "Natalie had a great personal story about her experiences presenting research, what it means to be a scientist, and how to handle criticism. It was a fantastic opportunity for my students."

Dries attributes his success to the encouragement and support of his many mentors.

"Being a good mentor is having the ability to utilize your knowledge and network to guide your students to their best possible future," Dries said. "Hal taught me that education is more than being lectured at ... When I take students to the annual meeting, it changes their perspective on what a scientific community is and the importance of networking."



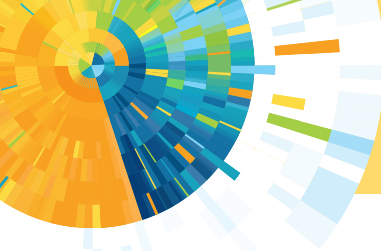
Daniel Dries earned his Ph.D. at the University of California San Diego, and joined Juniata College as a faculty member in 2013.

the leadership held a retreat in 1995 in California to do some strategic planning. Among those invited was Drennan, then a grad student.

Drennan said she doesn't know who decided it might be good to have a grad student at this meeting talking about the future of the society, "but it just became very clear to me that the ASBMB wasn't doing enough to embrace young scientists who were interested in biochemistry and that we could do a whole lot more."

She suggested a poster session to attract undergrads to the national meeting.

"People were like, 'Well, I don't really think that undergrads are going



Catherine Drennan, a professor at the Massachusetts Institute of Technology and a Howard Hughes Medical Institute investigator, founded the ASBMB Poster Competition in the late 1990s and went on to lead it for five years. Drennan is a former member of the ASBMB Education and Professional Development Committee, a past ASBMB annual meeting session organizer, and a past winner of the ASBMB–Schering–Plough Research Institute Award. She was named a member of the inaugural class of ASBMB fellows in 2021.

to necessarily come. It's such a big meeting' and all these things," Drennan said. "And I was like, 'Let's see if we can give them a reason to come.'"

Also up for debate was the timing of the session.

"Originally it was put at the beginning of the meeting, because, honestly, some people thought it would be a huge disaster and last one year," she said. "We could just stick it in the front, and they would show me that this was not going to work."

Ortiz too recalled that timing was a sticking point. "At one point it was at the midpoint of the meeting ... which was problematic because we always thought of the poster competition as a way to help students prepare for the main meeting," he said. "And then we shifted it (back) to the afternoon of the opening plenary," where it remains.

"A lot of the undergrads meet each other doing it, and then they have a buddy for the meeting," Drennan said.

Judging: Why and how

Drennan had concerns. One big worry was that not every participant would enjoy the experience.

"I had attended one meeting where my poster was in the very back — like in the last row of a giant room — and I don't think anyone made it that far. And I was like, 'I put all this work into this poster!'" she said. "I didn't want no one to look at an undergrad's poster if they put all this time into it."

Cornely agreed: "Maybe you're standing by your poster and nobody comes by ... Sometimes being at a poster during a big meeting can be a great experience, but sometimes it's not."

The solution? Judges.

"If you're at the poster competition, you know that you're going to have judges paying rapt attention to what you're saying," Cornely said.

Drennan made it a point to invite textbook authors to serve as judges, because "textbook authors are people who undergraduates have heard of."

Judy and Donald Voet — authors of the gold standard in biochemistry texts — were among the judges at the first competition in 1997.

"I went around and said, 'You see that person? That's Judy Voet of Voet and Voet,' and the students' eyes were wide," Drennan said. "And then they met Judy Voet, and she was really nice and engaged. That was just beyond exciting."

Being a participant

Some of the 2021 winners said they were nervous about the poster competition, but that nervousness was tinged with excitement.

Mlana Lore, a recent graduate of Eckerd College, is now a grad student

Tips from the 2021 competition winners

Preparation. Make sure that you can speak about all aspects of your poster. Practice giving a short presentation and prepare responses for a list of potential questions. Read the relevant literature within your field of study and practice presenting your poster to your mentor, fellow students and any additional faculty who are willing to help.

Talking to the judges. Try to have a professional and comfortable flow through your poster. Following the scientific method throughout your poster allows for your audience to get a clear idea of the thought process behind the work. As you talk, follow your poster as a reference, highlighting significant pieces of data as they come up.

General. Use this as an opportunity to understand your research techniques, learn how to write an abstract, create a fantastic poster and network with other scientists in the conference. The competition is a wonderful opportunity to showcase all the hard work you have done. Be confident and think of it as an opportunity to share ideas with other scientists. No matter the result, you will gain insights you can apply to your own research.

at the University of Colorado. She won last year's microbiology and RNA category.

"It was definitely nerve-racking ... I was used to small local conferences," she said. "Right before talking to the judges, I was anxiously double-checking my poster for mistakes but also excited to talk about the research

that I had spent the majority of my undergraduate time working on."

For Anna Corradi, a recent graduate of Bemidji State and now a grad student at University of North Dakota, the stakes felt high.

"As the time got closer to present my data, I began to feel nervous, knowing that this would be the last time I was able to present my undergraduate research project that I poured years of work into," said Corradi, who won in one of the cell biology and signal transduction categories.

As the competition went on and the students began to interact with the judges, some of their nerves began to dissipate.

Natalie Botros, a student from the University of San Diego, said that all the judges she spoke to "had a genuine interest in



Milana Lore won the microbiology and RNA category of the poster competition in 2021.



Natalie Botros won one of the protein structure, function, synthesis, degradation and enzymology categories of the poster competition in 2021.

What sets the ASBMB competition apart

While other scientific societies and organizations hold undergraduate poster competitions, there are some aspects of the ASBMB's event that make it unique.

Joseph Chihade, a professor at Carleton College in Minnesota and a member of the ASBMB Undergraduate Poster Competition committee, has been bringing his students to the annual meeting since 2005 and has served as a judge several times.

"Since I have worked exclusively at undergraduate-only institutions, every presentation that I have made at a national or international meeting includes, and is usually entirely composed of, work that was done by undergraduates," Chihade said.

He noted that while other meetings might have poster competitions, he prefers the ASBMB approach, which allows students to present their work first with other undergrads and then later in the exhibition hall with scientists at all career stages.

"The ASBMB structure seemed set up to actually educate students, while also celebrating their research accomplishments," he said. "The idea of letting students present posters both in an undergraduate-only setting and 'on the big stage' in the regular poster session is so obviously the right thing to do. The fact that the undergraduate session occurs first, so that students get practice and receive outside coaching from the poster competition judges before the regular poster session, is also brilliant."

Another committee member, Jeremy Johnson, a professor at Butler University in Indiana, agreed. He said: "Unlike undergraduate poster sessions at other large conferences, my students come away feeling valued as a scientist from (the ASBMB event). ... They are not merely patted on the back and told congratulations for completing a research project, but they are treated like a scientific colleague."

Kirsten Block, the ASBMB's director of education, professional development and outreach, said that "the reputation of the competition extends beyond the ASBMB," so much so that it's been replicated.

"In fact, it was ASBMB's competition that served as inspiration when I established a trainee poster competition for my previous organization," Block said.

my overall project, data and future research goals and were excited to learn more." Botros' poster presentation was the winner of one of the protein structure, function, synthesis, degradation and enzymology categories.

Even if it's stressful, talking to the judges is an important part of undergraduate research development.

Shawn Lin at Wesleyan University, who took the prize for the DNA,

Virtual is possible but lacks pizzazz

When the 2021 ASBMB Annual Meeting was held in a virtual format because of the COVID-19 pandemic, the Student Chapters Steering Committee provided input on reformatting the poster competition.

Jeremy Johnson, a professor at Butler University and a member of the poster committee, served as a judge.

“I got to experience the virtual poster session from the planning and implementation sides. I had lowered expectations for the virtual poster session, but I was pleasantly surprised,” he said. “For this format, the students prerecorded a shorter overview of their poster and research story, which judges were able to interact with prior to the interpersonal conversation about their poster. This format gave myself as a judge more time to examine the poster, think about the results, and then have a more informed conversation with the students about their results.”

Pamela Mertz is a professor at St. Mary’s College of Maryland and is chair of the poster committee. She noted that the virtual format benefited undergraduates who in normal years might have faced barriers to travel such as prohibitive expenses or academic scheduling issues.

Joseph Chihade of Carleton College in Minnesota, also a member of the poster competition committee, said that “having to come up with a polished, recorded elevator speech describing the poster helped develop skills that might otherwise not have been honed quite so sharply.”

Still, the people we talked to agreed that there is no substitute for the experience of attending an in-person meeting.

“Going to a big national conference, especially for an undergrad, and being able to network with different types of people and go to different types of sessions in person and seeing all those interactions — I think that’s something you can’t replace and have the same experience with a virtual conference,” Mertz said. “The enthusiasm and the energy in that room when that event is happening is not something you can mimic virtually.”

Chihade added that sometimes it’s hard to get a sense from virtual poster sessions “of the wide scope of work being done by other undergraduates.” He added: “The excitement and buzz of that crowded in-person poster session is just marvelous.”



Jeremy Johnson is a professor at Butler University in Indiana and a member of the poster competition committee.



Joseph Chihade is a professor at Carleton College in Minnesota and a member of the poster competition committee.

chromosomes and gene regulation category, reports that the judges “were all very nice and encouraging” and were “excited to meet young researchers.”

The winners all urged future competitors to remember that, even if it feels like you performed poorly, the judges might see things differently.

“I was very surprised to see that I won! I felt like my conversations with the judges went all right but not spectacularly, and two judges had independently pointed out an error in my data presentation that I didn’t have much explanation for,” said Lore.

When Corradi finished talking to three judges, she said, she felt like she did well but also recognized that she could have done better.



Anna Corradi won one of the cell biology and signal transduction categories of the poster competition in 2021.

“When the awards were announced, and I saw my name on the list I was filled with so much joy,” Corradi said.

In addition, the winners all said they felt that their participation in the poster competition will help them in their career trajectory. Corradi notes that “these events were a great point of conversation during my graduate school interviews and allowed me to develop public speaking abilities.”

The winners underscored that science communication skills are key not only for the competition but for all aspects of scientific discourse.

Botros said she thinks “it is

extremely important to be able to effectively describe and communicate the techniques and experiments performed to acquire data; this helps to promote reproducibility and understanding.

Science communication allows the individual to answer questions regarding their research and communicate new scientific knowledge.”

Who judges are and what’s expected of them

Whereas you need only be an undergraduate and first author on an abstract to compete, not just anyone can be a judge. The organizers look for faculty members who have a good understanding of teaching and who can provide constructive feedback to the competitors.

“This is a formative moment for the students. You’re not here to make the students feel bad; you’re here to help them become better scientists and better presenters,” Ortiz said.

Postdocs are welcome to apply too. However, they should be prepared to participate in a training session on how to be a mentor and how to give constructive feedback.

That feedback can make a difference in real time. If the first judge takes a few minutes to explain how the presenter could do better, the presenter can turn around and apply that advice when the second judge comes over. And if the second



Shawn Lin won the DNA, chromosomes and gene regulation category of the poster competition in 2021.

judge offers additional advice, the competitor’s next attempt will be even better. Ideally, by the time the student is at their poster on the exhibit floor with everyone else at the meeting, their presentation will be top-notch.

Importantly, feedback goes both ways. The lead judges and organizers always are listening to the back and forth during the competition.

“And if we get a report that a judge may be, you know, a little harsh or not giving appropriate feedback, we coach that judge to being a better mentor,” Ortiz said.

Pamela Mertz of St. Mary’s College of Maryland, who chairs the ASBMB Student Chapters Steering Committee, emphasized that even though it’s a competition, the environment is overwhelmingly supportive.

“Everybody who’s there is super excited about undergraduate research, wants to help mentor undergraduate research, and wants to help the students think about their projects and be able to answer questions. In other words, it’s not a hostile environment,” said Mertz.

What it’s like to be a judge

Past judges told us that the undergraduate poster competition holds a special place in their hearts.

Chris Rohlman, a professor at Albion College, has been involved since 1997, serving as an organizer, judge and lead judge. “(It) started as a lunch with Cathy (Drennan) in Claremont, California, and in the first couple of years we ran it out of the hatchback of her car,” he recalled.

One of Rohlman’s favorite memories, he said, relates to the close



Pamela Mertz is professor of biochemistry at St. Mary’s College of Maryland and chair of the ASBMB Student Chapters Steering Committee. Previously, Mertz served as a southeast regional director for student chapters from 2013 to 2020.



Chris Rohlman is a professor of biochemistry at Albion College in Michigan. He has helped organize the poster competition and has served as both a judge and lead judge.



student–faculty connections that the poster competition facilitates.

“I was sitting with longtime ASBMB colleague and friend Marilee Benore (a professor at the University of Michigan–Dearborn) waiting for a plenary session when two of my students were talking about how they really wanted Michael Cox’s autograph in their Lehninger textbook. Marilee — being Marilee — marched my students to the front row of a giant plenary session and said to him, ‘These two young ladies would really like to meet you.’ That’s an example of an experience of how people that judge the poster competition really welcome undergrads there and help them to be excited about their science.”

Kristin Fox, a professor at Union College in New York state,

is both a veteran of the organizing committee as well as a judge. For her, the competition stands out as a networking nexus not only for the students but also for the faculty. She said it attracts scientists, many repeat judges like her, who truly value undergraduate education and for whom teaching is a major part of their academic focus.

“A lot of us met at the undergraduate poster competition, judging together and having lunch together. We all care about teaching, and I mean really teaching,” she said.

This networking aspect even has resulted in active academic collaborations for Fox and colleagues, including a National Science Foundation pedagogy grant funding the Malate Dehydrogenase CUREs Community project involving protein-centric course-based undergraduate research experiences around the country.

Jeremy Johnson, a member of the poster competition committee and a frequent judge, said he also has “met ongoing collaborators, reconnected with colleagues and set up rotating seminar presentations” while at the event. A professor at Butler University in Indiana, he said he also has adjusted his in-class grading of presentations “to reflect the rigor” of the competition’s rubric.

Some judges are so psyched about participating that they even show up early, Cornely said.

“We tell them to come at 11:30 so that we can have a judges’ orientation and they can read their abstracts, and everyone comes early — sometimes

Juniata alumna Amanda Harvey (left) talks with Juniata students (from left to right) Olivia Drake, Owen Baker and Isabella Amaniera at the ASBMB annual meeting.



COURTESY OF DAN DRIES

hours early. And nobody's reading abstracts," she said. "Everyone is hugging and catching up on the joys and sorrows of the last year."

Johnson said he's one of the early birds: "I always show up early to reconnect with friends, to meet new colleagues, and to hear Phil give his speech about proper use of the scoring rubric."

Once the competition is truly under way, each judge is assigned six posters.

During the first half of the competition, students with even-numbered posters present their work. A judge observes three presentations and reports to the lead judge which of the three could be real contenders. After a lunch break, the odd-numbered presenters have the floor, and each judge observes another three and again confers with the lead judge.

The experience can be rather frantic, Cornely said, and yet the judges are exceptionally loyal: "They come back and judge year after year, even though all they get out of this is a box lunch."

Applications for prospective judges will be accepted beginning in January after the abstracts have been submitted, counted and reviewed. The number of judges selected will depend on the number of competitors, Cornely said.

Ortiz emphasized how important judges are to the success of the event.

"I think it's really important to say that it would not work if we didn't have the participation of a tremendous number of judges and organizers. And these people are volunteering their time. Without that, it would never work."

What makes a winning presentation

If you're a student reading this, you probably want to know what it takes to win. (Prospective judges might be curious as well.) There is no simple formula.

"We encourage the judges to look for content first. Is the poster clear? Is the poster coherent? Is the student able to explain the content thoroughly? Does the student have a deep understanding of what they're presenting?" Ortiz said.

Keep in mind that some of the students might be presenting the results of eight-week summer projects, while others might have worked for one or more years. Some might have conceived of the projects themselves, and others simply might have taken over someone else's project without a lot of background information.

"The students come in with a wide variety of expertise and insights. But yet, we still expect them to have an understanding of the fundamentals, the techniques, the results and the implications of those results," Ortiz said.

Fox said the students who perform well are those who "clearly articulate the research they did and weren't just following along to someone else's research plan."

For Drennan, what's important is that the presenter "tells me a really cool story about what they're doing."

She explained: "There's so much amazing science out there. But can you convey why what you're doing is important in a way that gets others excited? ... It's a great way to practice communication skills."

Sometimes she's so hooked, she



Phillip Ortiz is assistant provost for undergraduate and STEM education at the State University of New York. He has helped run the ASBMB Undergraduate Poster Competition for almost 20 years. He has served as chair of the ASBMB Minority Affairs Committee and is a former member of the ASBMB Education and Professional Development Committee. He is editor-in-chief of the journal *Biochemistry and Molecular Biology Education*, commonly known as *BAMBED*.



Kathleen Cornely is a professor of chemistry at Providence College in Rhode Island and chair of the ASBMB Undergraduate Poster Competition Committee. She directs Providence's ASBMB student chapter as well.



Kristin Fox is a professor at Union College in New York state. She directs her institution's ASBMB Student Chapter and frequently judges the poster competition at the society's annual meeting.

said, she'll ask presenters to email her to let her know how the final experiment goes. "I need to know — if it's an unfinished story — what the answer is!" she said.

Both Fox and Rohlman said one key question is at the root of the judging process: How well does the student understand the fundamentals of the research they did and why they did it? Both also emphasized a core tenet of the training for judges: It should be a positive experience for the student.

It's not just about fancy schools or equipment

You might suspect that students with access to expensive instrumentation or decorated leaders in the field fare better in the competition than those without. Drennan wondered about this too when she first started the contest.

"I looked at the abstracts and I tried to kind of guess who might have the top posters, and I was largely wrong. Because sometimes people had more help writing, and

other people, once you met with them, they just blew you out of the water."

Rohlman, a repeat judge, said that judges consistently are impressed by the quality of the undergraduates' work. "Whether they attend a small college or an R1 research institute, some undergraduate students just take their work and run, and end up working at the same level as graduate students. You can't even tell the difference between their posters," he said.

So the answer is decidedly no. You don't have to be at an elite institution or have access to the newest technologies to win.

"Some of the undergrads who are at smaller schools with fewer resources often have a lot more time with their faculty member. And that is super important," Drennan said. "Students from schools that maybe you hadn't even heard of before were just doing the most impressive work. So that's partly what I love about this — anybody can win," Drennan said.

And even those competitors who don't win prizes get to go home with written feedback. "Every student gets their judging forms back," Ortiz said.

Joseph Chihade, a professor at Carleton College in Minnesota and a member of the poster competition committee, said that "while prize money and certificates are awarded, the real goal is to celebrate undergraduate work, to provide opportunities for students to get constructive feedback and mentoring, and to bring students into a broader scientific community."

Chihade continued: "We make

Come one, come all

The 2022 ASBMB Undergraduate Poster Competition will be held on Saturday, April 2, the first day of the annual meeting. Many of the people we interviewed for this story emphasized that the competition space is open for all meeting attendees to visit and that doing so can be mutually beneficial.

Kirsten Block, the ASBMB's director of education, professional development and outreach, said: "These students are the future of the discipline. They are eager and excited for the opportunity to engage with established scientists about their work and to learn from them. The competition is a chance to help guide these students in their scientific development, and you may even be able to guide them into a future as a graduate student in your department — or your lab."

a tremendous effort and spend a lot of time worrying about being fair as we evaluate posters, but those awards are out there mostly to motivate students to do their best work, not to provide definitive judgments of what constitutes the ‘best’ science or presentation.”

Science takes a village

Daniel Dries participated in the poster competition when he was an undergrad. Today, as an associate professor and department head at Juniata College, he passes the torch year after year by taking his students to the meeting. (See sidebar “From presenter to mentor.”)

“The annual meeting is an opportunity for the free exchange of ideas: criticism, new collaborations and new questions you may not have thought to ask,” said Dries. “It is a great example of how science takes a village, and how we need to find the people within that village to advance our science and our professional goals.”

It’s not uncommon for students to return year after year, according to Johnson of Butler University.

“I have participants who I meet as a sophomore or junior and then they return as a senior. It is fun to see the progression of their research project and especially their intellectual growth as a scientist,” he said. “In addition, you see distinct students from many of the same undergraduate institutions and labs so you get to follow the progression of the research project over time.”

Drennan said she’s been glad to observe and contribute to the society’s efforts to “reach out to communities that might have felt

COURTESY OF DAN DRIES



like, when I started, a little bit left out. I’ve seen a lot of transformation, and I think the ASBMB should be really proud of what it’s done, especially when it comes to underrepresented researchers and being inclusive.”

She added that the poster competition “just shows the quality of science that’s being done everywhere, and the quality of work that undergraduates are doing. Never underestimate an undergraduate: They’re capable of so much.”

(Leia Dwyer, Lisa Learman, Nicole Lynn and Sarah May contributed to this article.)

Juniata College undergraduates meet up at the ASBMB annual meeting with school alumna Amanda Harvey at her poster. From left to right (all Juniata students unless otherwise noted): Joycelyn Radeny, Isabella Amaniera, Maria Fowler, Amanda Harvey (Philadelphia College of Osteopathic Medicine), Dan Dries (professor and chair), Hephzibah Nwanosike, Olivia Drake and Owen Baker.

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



ASBMB abstract categories

Submit your abstract to one of these topic categories before the Nov. 30 deadline for a chance to be featured in a spotlight session or present a poster during the 2022 American Society for Biochemistry and Molecular Biology Annual Meeting.

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| 2038 Proteasomes: Structure and Regulation | 2113 Membrane Proteins, Lipid Interactions and Lipid Domains |
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| 2065 Protein–Small Molecule Interactions | 2121 Glycosyltransferases and Hydrolases |
| 2066 Nanotechnology | 2122 Glycan Binding Proteins |
| | 2123 Glycans in Disease |
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| 2071 Genomics | 2171 Active Learning in the Molecular Life Sciences |
| 2072 Glycomics | 2172 Big Data in Molecular Life Sciences, Student Projects, Labs and the Classroom |
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| 2074 Metabolomics | 2174 Service Learning Initiatives, Community Involvement and Context Dependent Biochemistry Instruction |
| 2075 Computational Biology and Bioinformatics | |
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Deuel conference on lipids

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Evolution and core processes in gene expression

July 21–24, 2022 | Kansas City, Mo.

Mass spectrometry in the health and life sciences

Aug. 14–18, 2022 | Cambridge, Mass.

The interplay between epigenetic regulation and genome stability

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Transcriptional regulation: Chromatin and RNA polymerase II

Sept. 29–Oct. 2, 2022 | Snowbird, Utah

Explore all upcoming events at [asbmb.org/meetings-events](https://www.asbmb.org/meetings-events).

Pondering the power of connections in the post–COVID-19 era

By Etienne Caron

For 70 years, meetings in Lindau, Germany, have gathered Nobel Prize winners to educate, inspire and connect next-generation scientists from around the world. Through these interactions, the meetings shape the minds of future scientific leaders.

As we move out of pandemic restrictions and toward resuming in-person gatherings, I am reminded of the origins of Lindau, my own experiences at these meetings and others, and the many lessons I've learned about the value of making personal connections with my fellow scientists.

The meetings begin

After World War II, German physicians Franz Karl Hein and Gustav Wilhelm Parade addressed the isolation of scientists in their fragmented country by organizing a meeting in Lindau, a tiny, picturesque island city on Lake Constance. Their aims were to inform doctors about the latest medical developments and to promote Germany's

reintegration into the wider scientific community, as John G. Simmons wrote in a 2010 article in *Nature*. To achieve these goals, they decided to invite Nobel laureates, the best of the best, with the help of Lennart Bernadotte, a well-connected Swedish count.

The first Lindau Nobel Laureate Meeting in June 1951 brought together 400 physicians and researchers and seven Nobel winners in the disciplines of medicine, chemistry and physics. Otto Warburg described his theory of photosynthesis, William Murphy discussed pernicious anaemia and Gerhard Domagk talked about treatments for tuberculosis. Two years later, some of the younger scientists present were invited to converse with the speakers, beginning the Lindau meetings' transformation into a platform for lively exchanges between outstanding students and postdocs and Nobel laureates.

Colleagues who had been separated during the war were reunited at Lindau, including Max Born and Werner Heisenberg, who received Nobels in physics in 1954 and 1932, respectively. Before the war, Heisenberg was Born's assistant at the University of Göttingen. Together, they provided paradigm-shifting concepts in quantum mechanics. When the Nazi Party came to power, Born, who was Jewish, was suspended from his professorship and forced to leave Germany. Heisenberg stayed and led the German atomic bomb program during the war. The two reconnected at the fifth Lindau meeting in 1955 and became avid participants; Born attended 16 meetings and Heisenberg 10. Together, they advanced quantum mechanics through their long friendship and their interactions with young scientists at Lindau.

Societal and political ideas have been discussed at Lindau, with ramifications beyond the purely scientific core. In 1955, the year after the U.S. detonated a hydrogen bomb on Bikini Atoll, all Nobel laureates who worked in nuclear research were invited to the meeting. They



ARCHIVE SPANGL/LINDAU NOBEL LAUREATE MEETINGS

Werner Heisenberg, who won the 1932 Nobel Prize in physics, is surrounded by students during the fifth Lindau Nobel Laureate Meeting in 1955.



CHRISTIAN FLEMING/AMINEDIA COMMONS

issued a joint warning against nuclear weaponry and drafted an appeal to political decision-makers “to reject force as the ultimate instrument of politics” at Mainau, a garden island near Lindau where Bernadotte owned an estate. The Mainau Declaration of 1955 was signed by the 18 laureates present at the fifth meeting.

Sixty years later, 36 Nobelists signed the Mainau Declaration 2015 on Climate Change to support the decision by nations at the 2015 United Nations Climate Change Conference in Paris to take decisive actions to limit future global emissions.

Personal impact

In 2014, I was invited to participate in the 64th Lindau meeting and a satellite workshop that preceded the meeting held by the Else Kröner-Fresenius-Stiftung, a nonprofit foundation. I was in a group composed of nine Nobel laureates, nine journal editors and 14 postdoctoral scientists. We broke into smaller groups for roundtable discussions to help determine what medical field the EKFS would fund. At my table were two Nobelists, two senior journal editors, a former EKFS award winner and two other postdocs. The medical field of psychiatric disorders was selected, and three years later, the EKFS awarded a 4 million euro prize to Karl Deisseroth, a neuroscientist and psychiatrist at Stanford University and the Howard Hughes Medical Institute.

During the 2014 meeting, I also met Michal Bas-

This group photo from the 65th Lindau Nobel Laureate Meeting includes some of the laureates who signed the Mainau Declaration 2015.

sani–Sternberg, a postdoc in Matthias Mann’s group at the Max Planck Institute of Biochemistry in Germany. I was a postdoc in Ruedi Aebersold’s lab at ETH–Zürich in Switzerland. Both of us were experts in immunopeptidomics at a time when only a handful of researchers were working in the field, and opportunities to discuss our specialized discipline with scientists from other groups around the world were rare.

When I learned that Bassani–Sternberg would be attending the meeting, I emailed her, mentioning that it would be great to connect in person. She responded with enthusiasm. At Lindau we had a nonstop six-hour discussion that felt like two minutes. We started to collaborate, and in 2017 we cofounded the Human Immuno-Peptidome Project, or HIPP, an international initiative to advance the field of peptide antigen sequencing using mass spectrometry technologies, known as immunopeptidomics, under the umbrella of the Human Proteome Organization.

‘Connect with your scientific community’

Aebersold, my postdoc mentor, trained many students and postdocs, 53 of whom had formed their own academic research group. He was once asked in a conference about mentoring, “What is the trick to being so success-



COURTESY OF ETIENNE CARON AND ELSPETER

During a 2014 scientific retreat in Tschamut, Switzerland, Ruedi Aebersold (in red) converses with immunopeptidomics experts.

ful at training them?”

Aebersold answered, “I don’t really train them; they are who they are. We are also very fortunate in science to be surrounded by a lot of smart people, but I’ve noticed over the years that those that really stand out are those that are involved in the scientific community because they connect with their peers, they exchange and discuss ideas, they gain visibility and so much more.”

In other words, being smart, creative, rigorous and passionate is important, but connecting with other researchers and being involved in the scientific community — through teaching or organizing workshops and conferences — is what makes young researchers stand out from their peers.

This resonates with me because I’ve been involved in the scientific community since my graduate studies. As far as I remember, I’ve always been motivated to help people move forward in my own research field and also elsewhere, including the field of earth science, as I wrote in a 2016 article. Helping to unlock the scientific potential of someone or of a group of people by bringing them together is gratifying; it brings me happiness and the sensation of being truly alive and useful. Bringing people together also often has led to unexpected and fruitful connections to advance my own career.

As a Ph.D. student at the Institute for Research in Immunology and Cancer in Montreal, I helped organize our first Systems Biology in Immunology and Cancer Symposium in 2009. The organizing committee was composed almost exclusively of Ph.D. students and post-docs, and our goal was to provide a forum to improve communication among disciplines, to exchange results

and ideas, and to foster collaboration in cancer and immunology research.

While we were organizing this event, a colleague connected me with Hiroaki Kitano, one of the founders of systems biology, which led to a three-month internship in his group at the Systems Biology Institute in Tokyo. My project about building a comprehensive map of the mTOR signaling network was published in 2010 as a resource for the community.

Four years later, as a postdoc in Aebersold’s lab, I invited Hiroaki to give a lecture at ETH-Zürich, thereby enabling more people to interact with him and giving myself the opportunity to collaborate with his team on another project, which led to another publication in 2017.

The evolution of the HIPP

When I was in Aebersold’s group, his annual scientific retreat in Tschamut, a village in the Swiss Alps, was a perfect time and environment to brainstorm and discuss science as well as enjoy outdoor activities with colleagues. The group had four or five scientific sessions on different topics over two days, each organized and presented by small groups that had spent about a month preparing.

During my second year in the lab, I organized a session on immunopeptidomics for the upcoming retreat and invited some of my collaborators from Australia, California and Germany to help me prepare the session. I had met with them over Skype, but connecting in person further strengthened our collaborative spirit. After the retreat, that collaboration led to two community-oriented immunopeptidomics papers. The feeling of building a new research community motivated me to initiate the HIPP.

Inspired by the 64th Lindau meeting and all that followed, I decided that the time was ripe to bring together the immunopeptidomics community. I asked Bassani-Sternberg to co-organize the first international HIPP workshop. In May 2017, 40 leading scientists and industry representatives from 18 universities and nine companies convened in Zürich for the meeting, which was divided into two main activities: scientific talks by immunopeptidomics leaders and roundtable discussions that were inspired by the EKFP meeting I had attended three years earlier.

In this workshop, we set a long-term goal of mapping the entire repertoire of peptides presented by human leukocyte antigen molecules using mass spectrometry technologies and making its robust analysis accessible to any immunologist. We outlined the specific challenges to this goal and, within this framework, structured a multi-pronged program aimed at addressing these challenges and



Participants in the Human Immuno-Peptidome Project workshop held in Zürich, Switzerland, May 4 and 5, 2017, included Josh Elias, Albert Heck, Tim Fugmann, Geert Mommen, Claude Perreault, Patrick Pedrioli, Wenguang Shao, John Castle, Morten Nielson, Anthony Purcell, Arie Admon, Erin Jeffery, Paisley Myers, Roger Geiger, Heiko Schuster, Jennifer Busby, Miguel Marcilla, Jenn Abelin, Fabio Marino, Markus Müller, Nicola Ternette, Daniel Kowalewski, Hans-Georg Rammensee, Alexey Nesvizhskii, Stefan Tenzer, Toni Weinschenk, Michal Bassani–Sternberg, Amir Banaei–Esfahani, Chloe Chong, Jennie Lill, David Gfeller, Hui-Song Pak, Etienne Caron, George Coukos, Peter Van Veelen, Alessandro Sette and Ruedi Aebersold.

implementing solutions. Pillars of that program were method and technology development, standardization, effective data sharing and education, as we wrote in our 2017 article in *Immunity*.

Members of the HIPP initiative since have published Minimal Information About an Immuno-peptidomics Experiment, or MIAIPE, to standardize methods. An international summer school program was launched in 2018 to expand the community more rapidly. New public–private partnerships were discussed during the second HIPP workshop in 2019. The SystemMHC Atlas project was created to enable effective immuno-peptidomic data sharing. A new executive committee was created, and the second summer course is expected to take place in 2022.

The launch of the HIPP, catalyzed by our participation at the 64th Lindau Nobel Laureate Meeting, is likely to contribute to groundbreaking advances in precision medicine, such as the Human Immuno-Peptidome Project published in *Molecular & Cellular Proteomics*.

Making connections after COVID-19

In-person connections among researchers are important to move science and society forward. COVID-19 has disrupted those moments, and new initiative and investment will be needed to encourage science connections after the pandemic so that young scientists can

thrive. Here are a few suggestions.

Internal funds from university departments that have not been spent during the pandemic could be reinvested to encourage science connections through organizing symposiums and workshops by students and postdocs. New leadership awards could be created to support activities of talented young individuals with community-building skills.

We need to look for an event similar to the first Lindau Nobel Laureate Meeting. The Lindau doctors were bold and determined to get Germany out of isolation after World War II. As a result, the Lindau meetings continue to shape the minds of scientific leaders 70 years later. Funding organizations could support bold and creative Lindau-like scientific events in the near future.

Just as the pandemic radically changed the way we interact with each other, an unpredictable, groundbreaking event could be created to change the way we will connect and reconnect after the pandemic. This will depend on the support of funders and the strength of our collective imagination.

Etienne Caron (etienne.caron@umontreal.ca) is a principal investigator at CHU Sainte-Justine Research Center and an assistant professor in the pathology and cellular biology department at the University of Montreal.



Replying to reviewers' comments

A guide to better rebuttals

By Jon Mueller

As a scientific author, reviewer and editor, I have written a fair number of rebuttals and read even more. After receiving positive comments about my rebuttals from several colleagues, I posted my Top Tips on Twitter. Here is an extended version of those recommendations.

1. Truly engage in peer review. The rebuttal is part of the formalized communication process between colleagues; neither reviewers nor editors are any better or worse than you.

Do not apologize for anything from the old version of the manuscript. I personally would not even call a single thing in the old manuscript a mistake (a typo at most). Just do better! This rebuttal is all about the current, massively improved version. Factually state all the improvements that you have made.

2. Whatever happens, never respond in a rush. You might receive reviewers' responses at any time of the day or the week. However, apparently a lot of us receive these emails on a Friday afternoon, just before we want to head off for a long weekend. Do not respond immediately. Should the reviewers' comments stir you emotionally, let them rest for a day or two before you write a response.

If you are still fuming — feeling utterly unfairly treated — a good practice is to write a response not directly into your emailing software but in Word and to send it to yourself only. This also works wonders with other sensitive emails.

3. The rebuttal is a sales pitch. You want the editor to agree with you constantly while reading your rebuttal. So please make sure that it is ultra-clear and a joy to read. Don't use technical jargon excessively. Do not force the editor to scroll back and forth through your text.

- If reviewers 1 and 3 have a similar question, simply repeat your answer, perhaps with some paraphrasing.
- If you have to cite scientific papers (such as your own awesome new preprint somewhere else), give the

rebuttal noun

re·but·tal | \ ri-'bʌ-tl \

: the act of [rebutting](#) especially in a legal suit

also : argument or proof that [rebut](#)s

reference in full where it is needed within the text.

- Should a reviewer ask you for some exact values, please do write out those numbers — don't force the editor to look them up externally.

4. Divide and conquer. The Romans knew about this. Some reviewers provide rich and very dense text. Feel free to break down those text blocks into smaller units, maybe sentences or even phrases, so that you clearly address each and every little part. Don't provide a wordy reply to a wordy question; it smells as if you want to waffle over complex points.

5. Get the tone right. An editor might look more for the pitch of your writing than the actual response. I tend to be aggressively friendly and polite in a rebuttal but not leave any doubt at all that I actually have done something.

Do not write that you will "attempt to address" reviewer comments; address them.

Be conscious of the words you use. Have a dedicated proofing round to kill weak words. Do not use "some," "a bit" or "many"; instead, include specific numbers and values in your response.

Revised version of ms #jxyz.2021-0011

Dear Dr Smith,

Thanks ever so much for providing us with generally very positive and constructive feedback of two anonymous reviewers. Our manuscript certainly has improved a lot during this peer-review process.

...

6. Clearly display the reviewers' comments differently from your reply. Use a 10-point font shaded in gray for the reviewers' comments, but write your responses in an 11- or 12-point font in bold black writing — never the other way around.

a serious question by some reviewer

our bold response

7. Never thank reviewers for the time they spent with the manuscript. After all, peer review is about the quality of the review, not about how long it took.

I always thank them for their intellectual input and their comments and ideas. If they spot a scientific error, I am honestly grateful to them — the review process might have saved me from an embarrassing erratum or even a retraction.

8. You might want to paraphrase the reviewers' words.

Should there be something in the reviewers' comments that is very unclear or even insulting, no one is stopping you from rewording to soften, correct or reframe them in your rebuttal.

Please use this one sparingly.

I hope that these tips are useful when crafting your next rebuttal. Some might even be good to consider for your scientific writing in general. All the best with your next publications. Please feel free to share your opinions and ideas about rebuttals with me.

Jon Mueller (j.w.mueller@bham.ac.uk) teaches endocrinology and pharmacology at the University of Birmingham. His research group at the Institute of Metabolism and Systems Research studies sulfated steroids and the adrenal gland. Follow him on Twitter: @JonWolfMueller.



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“With biochemistry ... you can survive anywhere.”

By Laurel Oldach

For graduate school, Manjunath Goolyam Basavaraj traveled from his hometown of Bangalore to the Norwegian city of Tromsø, 1,400 miles from the North Pole. In the milder climate of Philadelphia, he landed industry funding for a postdoc in blood clotting. With that experience, a transition to industry was surprisingly smooth: Now, at Takeda, he continues to work on hemostasis and thrombosis. This interview has been condensed and edited.

1 You develop anticoagulants. Tell me about this kind of drug?

Blood clotting is a basically natural, healthy phenomenon. But when it happens inside the arteries or veins, it can stop blood flow to heart or brain. In this situation, physicians use anticoagulants. These drugs stop blood clots but also affect bleeding. We need novel anticoagulants, which research scientists call the holy grail, to stop clots inside the arteries but not affect the normal clotting process.

2 What got you interested in clotting?

Actually, it was personal: My father had a stroke. After my master's in India, I wanted to do a Ph.D. on stem cells. But after the stroke I felt, Why not do research with a personal connection? There were few labs in India doing this research, so I ended up going to Norway to work on thrombosis.



Manjunath Goolyam Basavaraj

CURRENT POSITION

Project lead, rare disease drug discovery, Takeda

FIRST JOB OUTSIDE OF ACADEMIA

Scientist, rare disease drug discovery, Takeda

FAVORITE MOLECULE OR PROTEIN

Tissue factor pathway inhibitor, or TFPI, a serine protease inhibitor involved in blood clotting

3 How did you transition into industry?

I was more interested in academia than industry as a postdoc. But time decides a lot of things. Becoming independent faculty is really difficult. I realized that really successful academic researchers do three or four years of postdoc, then transition. If that does not happen, that means you're not there.

The time you spend in industry is really well worth it; every year of experience adds. Whereas in academia, it sort of has diminishing or even negative returns.

4 Did having industry grants as a postdoc help you get a foot in the door?

Definitely. After getting the two grants, I had more confidence in the work I was doing. This is the first position I applied for. I was lucky; they were looking for exactly the experience I had.

It's important that the work you do as a Ph.D. and postdoc be relevant to industry. With biochemistry, protein work and enzyme kinetics, you can survive anywhere.

5 What does promotion look like in industry?

It depends on your direct manager, experience and competence. It's important to interact with people and actively participate in departmental seminars. Many people in industry change jobs to get promoted.

Before coming here, I thought industry was a completely different world — but R&D is exactly like academia. I'm doing almost the same research, using the same techniques. Compared to academia, there is no problem with funding. As faculty, you have a lot of freedom to study what you want, whereas here it's more predetermined. But as long as you really love research, it doesn't matter which work you do.

(Read a longer version of this interview at asbmb.org/asbmb-today.)

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



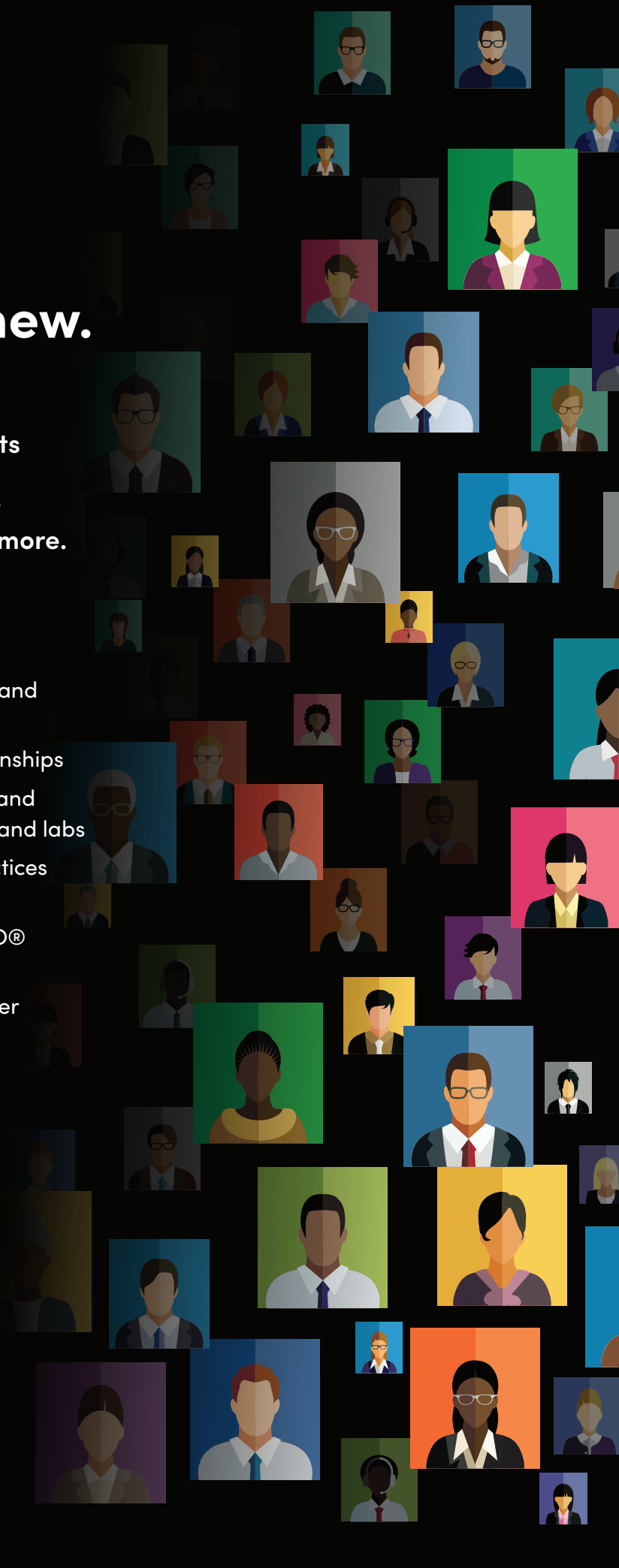
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CLASSIFIEDS

Assistant Professor

The Johns Hopkins University School of Medicine

The Department
of Biophysics
and Biophysical
Chemistry at



the Johns Hopkins University School of Medicine invites applications for a tenure-track faculty position at the rank of Assistant Professor. Scientists in the department work in a collaborative, interdisciplinary environment fostered by interactions among the nine basic science departments in the Institute for Basic Biomedical Sciences and with colleagues in clinical departments.

<https://careers.asbmb.org/jobs/view/assistant-professor/59065611/>

Scientific Data Application Developer

RCSB PDB Rutgers

RCSB PDB is looking for a highly motivated scientific developer with domain experience in structural



biology or bioinformatics or related fields. The candidate should be interested in structural biological data and enjoy engaging with other developers and scientists in a collaborative team environment.

<https://careers.asbmb.org/job/scientific-data-application-developer-at-rcsb-pdb-rutgers/59002309/>

Postdoctoral Researcher, Chemistry

Reed College

Reed College seeks an outgoing and dedicated postdoctoral research



associate for a position in biochemistry/bioinorganic chemistry under the supervision of Dr. Kelly Chacón. This research position focuses on working to characterize a novel set of proteins that may bind chalcogens. The postdoctoral researcher will further develop ways to express and characterize these novel proteins and enzymes using protein biochemistry and spectroscopy.

<https://careers.asbmb.org/job/postdoctoral-researcher-chemistry/58858256/>

Tenure-Track Faculty Position in Molecular Cell Biology

Wake Forest University

The Department of Biology at Wake Forest University



invites applications for a full-time, tenure-track faculty position in molecular cell biology, with a start date of July 1, 2022. We are seeking candidates whose research programs address fundamental aspects of eukaryotic cell biology in areas including, but not limited to, intracellular trafficking, cellular signaling, cell-cell interactions, organelle biology, cell metabolism, and gene expression.

<https://careers.asbmb.org/job/tenure-track-faculty-position-in-molecular-cell-biology/59043235/>

To see a full list of jobs, please visit careers.asbmb.org



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2022 ASBMB Annual Meeting

APRIL 2-5 | PHILADELPHIA

A place for you

When you present your research at the annual meeting, you get the recognition you've earned and the constructive feedback that you need to make your work even better.

Empowering presenters. Share your results on your own terms. If you want to give a short oral presentation at the podium, there are opportunities to do that. If you'd prefer to present a poster in the exhibit hall, that's fine too.

Eliminating barriers. ASBMB members save nearly **50% on registration**. Plus, the society gives more than **\$270,000 in travel and dependent care grants**.

Important deadlines:

Abstract deadline: Nov. 30

Travel award deadline: Dec. 7

asbmb.org/annual-meeting



The ASBMB annual meeting is held in conjunction with Experimental Biology.