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ASBMB TODAY

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

The Reimagining Issue

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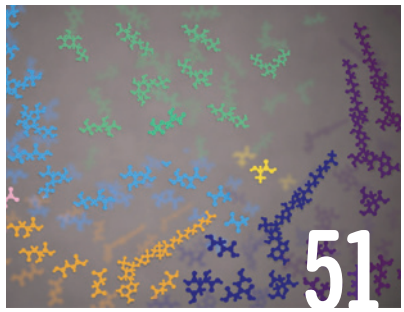
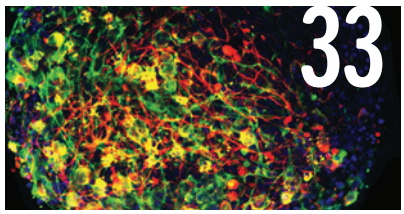
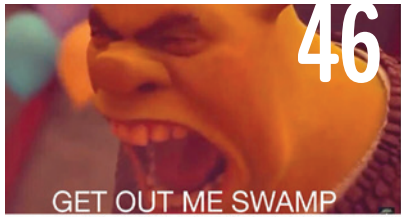
The Reimagining Issue

NEWS







ASBMBTODAY
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Reimagining a best-case scenario

By Comfort Dorn

"Worst-case scenario" is what I call a grim little mind game I play to ward off catastrophe. As the name implies, I try to think of the worst thing that could happen in a given situation. Because I have imagined it, I reason, it can't possibly happen. This system has been pretty effective. When one of my children was out late and I imagined a horrific car crash, it never happened. On the flip side, the sudden death of my father from a pulmonary embolism was something I had never thought about. Likewise, airplanes flying into the World Trade Center and a global pandemic.

Infectious disease experts have said they knew it was only a matter of time before we were hit hard by a new virus, but I was caught off guard. Even last spring, when the world was closing down, I had a hard time believing it was all true. Like most white, well-off people who have lived their whole lives in the United States, I never had experienced an event that required me to restructure my life on such a sweeping scale.

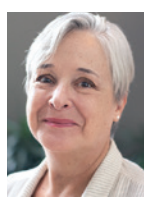
About a year ago, when we were just getting used to what everyone had started to call "the new normal," a couple of writers submitted essays to ASBMB Today suggesting that changes wrought by the pandemic might have a positive effect. As our lives were turned upside down, we suddenly could see the cobwebs under the furniture, not to mention cracks in the floor. And that led some of us to wonder if we needed all the bric-a-brac (literal and metaphorical) that surrounds us — and if our foundation was as solid as we always had assumed.

This was almost the opposite of my worst-case scenario game. We were living in the worst case, and our new existence was showing us the clutter and the weak spots in our fine old ways of doing business. So now, in this upside-down world, we could imagine something new and better once we took our masks off, ditched the hand sanitizer and went back to school/work/life in the world.

In this case, I'd like to see some of the scenarios play out.

In our reimagining issue, we present a dozen glimpses of how science and academia might change for the better. These proposals range from vast systemic upheaval to tweaks in individual mindset. As you read, I encourage you to look at your own life over the past 16 months for clues to a reimagined future.

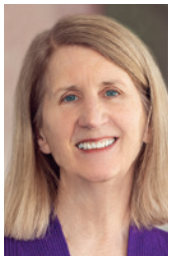
Comfort Dorn (cdorn@asbmb.org) is the managing editor of ASBMB Today. Follow her on Twitter: @cdorn56.



Protein Society honors Smith, Rosenzweig

Two members of the American Society for Biochemistry and Molecular Biology are among the eight researchers who have been honored with the Protein Society's 2021 awards. **Janet Smith** will receive the Dorothy Crowfoot Hodgkin Award, and **Amy Rosenzweig** will receive the Hans Neurath Award.

Smith is a professor of biological chemistry and biophysics at the University of Michigan, associate director of the crystallography facility at the General Medical Sciences and Cancer Institute's Structural Biology Facility at the Department of Energy's Advanced Photon Source.



SMITH

She is recognized for "exceptional contributions to our understanding of the biological function of proteins through knowledge of their 3D structures," the Protein Society stated on its website. The goal of Smith's lab is to understand biological function at the molecular level through knowledge of protein 3D structure using X-ray crystallography.

Smith earned her Ph.D. in biochemistry at the University of Wisconsin–Madison. She is a fellow of the American Association for the Advancement of Science and a member of the National Academy of Sciences. The Hodgkin award, named for a founder of protein crystallography and Nobel laureate, recognizes exceptional contributions in protein science that profoundly influence our understanding of biology.

Rosenzweig is a professor of life sciences, molecular biosciences and chemistry at Northwestern University and faculty director of Northwestern's Keck Biophysics Facility. "Her contributions characterizing the membrane-bound methane monooxygenase have inspired new ways to harness the energy of methane, a potent greenhouse gas, as an alternative liquid fuel source," the Protein Society stated. Her lab studies the active site structure and chemical mechanism of particulate methane monooxygenase, probing its function within the larger context of methanotroph physiology.

ROSENZWEIG

Rosenzweig earned her Ph.D. in chemistry at the Massachusetts Institute of Technology. She is a member of the National Academy of Sciences and a fellow of the American Academy of Arts and Sciences and of the American Association for the Advancement of Science. The Neurath award, named for a founding member of the Protein Society, recognizes recent contributions of exceptional merit to basic protein research.

The Protein Society will present the 2021 awards during its virtual 35th anniversary symposium in July.

Biochemical Society recognizes Thorner, Trost and Murphy

The Biochemical Society, the United Kingdom's professional association of biochemists, has announced its 2022 awards, which recognize research that is "fundamental to life and of transformative relevance to health and disease." Among the 11 recipients, three ASBMB members were honored: **Jeremy Thorner, Matthias Trost** and **James Murphy**.

Jeremy Thorner will receive the 2022 Centenary Award, which recognizes a biochemist of distinction from any part of the world. Thorner is an emeritus professor of biochemistry, biophysics and structural biology at the University of California, Berkeley, known for major contributions to the biochemistry of signal transduction in yeast. His lab investigated hormone maturation through the secretory system, cloned the first MAP kinase and demonstrated that MAP kinases are activated downstream of G protein–coupled receptors, among many other findings. Thorner is a member of the American Academy of Arts and Sciences and the National Academy of Sciences. He also received the 2019 Herbert Tabor Research Award from the ASBMB.

THORNER

Matthias Trost will receive the 2022 Industry and Academic Collaboration Award, recognizing an early to midcareer scientist who has contributed to cross-sector interactions. Trost is a Wellcome Trust investigator and a professor of proteomics at Newcastle University, where his team studies immune signaling driven by post-translational modifications in macrophages and phagosomes. In recent years, they have developed a mass spectrometry–based approach

TROST

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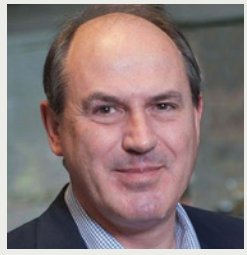
Academy names new members

The American Academy of Arts and Sciences announced in April its new class of members. The academy dates back to 1780; it was founded by political figures including John Adams and John Hancock as a way to honor accomplished Americans and involve them in solving challenges the new nation faced. Seven members of the American Society for Biochemistry and Molecular Biology were elected this year.

Ronald Breaker, a professor of molecular, cellular and developmental biology at Yale University and a Howard Hughes Medical Institute investigator, was elected into the biochemistry, biophysics and molecular biology section of the academy. Breaker's lab studies noncoding RNAs in bacteria, with particular interest in ribozymes, which catalyze chemical reactions, and riboswitches, which change conformation in response to binding of specific molecules. Breaker's lab discovered riboswitches and since has studied their ability to act as sensors and regulate translation, particularly in metabolism. Breaker was the 2016 recipient of the ASBMB–Merck Award. His other honors include election to the National Academy of Sciences and the American Association for the Advancement of Science. Breaker earned his Ph.D. at Purdue University and was a postdoctoral fellow at Scripps Research.

Axel Brunger, a professor at Stanford University and a Howard Hughes Medical Institute investigator, was elected into the academy's biochemistry, biophysics and molecular biology section. Brunger, trained as a crystallographer, studies synaptic vesicle fusion and neurotransmitter release. His group has been a leader in understanding the structures and mechanisms of synaptic protein supercomplexes involved in calcium-triggered vesicle membrane fusion. He was the 2011 recipient of the ASBMB's DeLano Award for Computational Biosciences, has received awards from biophysical and crystallographic societies, and is an elected member of the National Academy of Sciences. Brunger received his Ph.D. from the Technical University of Munich and was a postdoctoral fellow at Harvard University before starting his faculty career at Yale University.



Roger Davis, a professor at the University of Massachusetts Medical School, was elected to the academy's cellular and developmental biology section. Davis was the first to clone human cJun N-terminal kinase, or JNK, and has studied stress-activated signaling through these proteins and related signaling molecules ever since. His group seeks to understand the role of JNK signaling in inflammatory diseases and how intervening in the pathway might address a wide variety of diseases. Davis is a fellow of the Royal Society and is an elected member of the National Academy of Sciences, American Association for the Advancement of Science and the European Molecular Biology Organization. He was the editor-in-chief of the journal Molecular and Cellular Biology. He earned his Ph.D. at Cambridge University and did postdoctoral research at the University of Massachusetts Medical School; after joining the faculty at UMass, he co-founded its molecular medicine program, which he now chairs.

Sharon Dent, chair of the epigenetics and molecular carcinogenesis department at the University of Texas MD Anderson Cancer Center, was elected into the academy's biochemistry, biophysics and molecular biology section. Dent's lab studies the roles of chromatin-modifying enzymes in gene expression and genome integrity. Her lab investigates lysine methyltransferases, histone acetyltransferases and deubiquitinases to understand how developmental gene expression patterns may be reactivated in cancer. For 10 years, she served as director of the Center for Cancer Epigenetics at MD Anderson. Her other honors include election to the American Association for the Advancement of Science and an MD Anderson President's Leadership Award, which she received in 2015. She earned her Ph.D. at Rice University and did postdoctoral research at Baylor College of Medicine, followed by a senior research fellow position at the National Institutes of Health.

Carol Fierke, provost and executive vice president at Brandeis University, was elected into the academy's chemistry section. In addition to being her university's chief academic officer, Fierke is an enzymologist, running a lab that studies the role of metal ions in the active sites of metalloenzymes, focusing on histone deacetylases with additional research into other catalytic proteins and RNAs. Fierke has been a force for increasing faculty diversity in her current post and in previous roles as a professor at the University of Michigan and provost of Texas A&M University. In recognition of that work, she was the 2019 recipient of the ASBMB's Mildred Cohn Award and has received numerous other honors from the Protein Society and the American Chemical Society. Fierke earned her Ph.D. at Brandeis University and was a postdoctoral fellow at Pennsylvania State University; she started her faculty career at Duke University.

Maureen Hanson, a professor of molecular biology and genetics at Cornell University, was elected to the academy's cellular and developmental biology section. Hanson's lab studies gene expression and genome architecture in chloroplasts and the enzymatic activity of rubisco; she also pursues a separate line of research into chronic fatigue syndrome, or myalgic encephalomyelitis. Hanson is a fellow of the American Society of Plant Biologists and director of Cornell's Center for Enervating Neuroimmune Disease. She earned her Ph.D. at Harvard University and pursued postdoctoral studies there before beginning her faculty career at the University of Virginia.

Hao Wu, a professor of structural biology, biological chemistry and molecular pharmacology at Harvard Medical School, was elected to the academy's microbiology and immunology section. Wu's lab uses cryo-electron microscopy and other biophysical methods to understand molecular complexes involved in innate immunity, including signalosomes and pore-forming complexes like gasdermin D. She is a fellow of the Biophysical Society and the American Association for the Advancement of Science, a Pew scholar, and a 2015 recipient of the NIH Pioneer Award. Wu studied medicine at Peking Union Medical College, earned her Ph.D. at Purdue University and was a postdoc at Columbia University. She started her faculty career at Weill Cornell Medical College before moving to Harvard Medical School.

CONTINUED FROM PAGE 3

for label-free screening of small molecules to find enzyme inhibitors, catalyzing numerous collaborations with industry groups.

James Murphy will receive the International Award. Murphy is an associate professor and head of the inflammation division at Australia's Walter and Eliza Hall Institute in Melbourne. His research focuses on protein–protein interaction in cell signaling, with particular interest in pseudokinases, which lack catalytic activity but still can play important roles in cell biology. One pseudokinase they focus on in particular, MLKL, is an effector in necroptosis. Along with service to other journals, Murphy is a member of the editorial board of the ASBMB's Journal of Biological Chemistry.

MURPHY

All Biochemical Society awards and medal lectureships carry prize money, and all award winners are invited to submit an article to a society-owned publication. Seven awards are presented annually and the rest either biennially or triennially. The society encourages nominations that reflect the diversity of the bioscience community.

Springer receives service award

Amy Springer, a lecturer and chief undergraduate adviser at the University of Massachusetts Amherst's biochemistry and molecular biology department, has received her department's Normanly Award for Outstanding Service, which recognizes exemplary teaching and service.

Springer is recognized for her work in undergraduate biochemistry curriculum reform; she played a major role in converting the university's biochemistry lab classes to course-based undergraduate research experiences. She is also an ASBMB education fellow, having been involved in the development and scoring of the society's undergraduate certification exam since it began, and leads a faculty mentoring group for fellow lecturers in the natural sciences at her university.

SPRINGER

Springer introduces students to authentic research in an upper-level laboratory course and has published with them. She and her students currently study isoforms of malate dehydrogenase, a TCA cycle enzyme, in pathogenic trypanosomes. The work is supported by the MDH CUREs community, which supports course-based undergraduate research projects focused on malate dehydrogenases.

Springer earned her Ph.D. at Princeton University and pursued postdoctoral training at both the California Institute of Technology and the University of Washington.

Blaho, Carr share first award honoring Obeid

Victoria Blaho, an assistant professor at Sanford Burnham Prebys Medical Discovery Institute in San Diego, and **Rotonya Carr**, a physician–scientist at the Hospital of the University of Pennsylvania and a former junior associate editor at the Journal of Lipid Research, are two of three inaugural recipients of the International Ceramide Committee's Lina Obeid Award for young investigators.

Blaho studies sphingosine-1-phosphate signaling in the immune system. Carr's research focuses on the role of ceramide signaling in fatty liver disease. The award's third recipient, Doris Höglinger of the University of Heidelberg, studies Niemann–Pick disease type C, which is caused by sphingolipid accumulation.

The award is named for the late Lina Obeid, a physician–scientist and dean of research at Stony Brook University who died in 2019 at age 64. Obeid was a pioneer in sphingolipid signaling in cell death and senescence; she was the first to demonstrate a role for the lipid ceramide in apoptosis, and she conducted extensive research into bioactive lipids in cancer. She also, with husband Yusuf Hannun, directed a center for metabolomics at Stony Brook.

BLAHO

CARR

According to the International Ceramide Committee, "in addition to being a pioneering force in the sphingolipid field, Dr. Lina Obeid was a fierce advocate for women in science." Both Carr and Blaho regarded her as a mentor and friend; in a post on Twitter, Carr called the award "my highest professional award ... in honor of the late Dr. Lina Obeid; my friend and mentor who is gone too soon."

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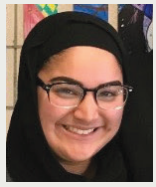
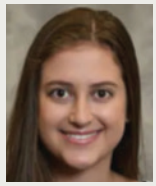
Goldwater scholars named

The Barry Goldwater Scholarship and Excellence in Education Foundation has announced the 2021 Goldwater scholars. The recipients of these scholarships are second- and third-year undergraduates from across the United States. Of the scholars in the natural sciences, the following eight are ASBMB members.



Ahlenne Abreu, a New York resident and a life sciences student at Smith College, hopes to earn a Ph.D. in molecular pharmacology and physiology and "conduct biomedical science research for a biotechnology company and eventually open my own biotech company." Abreu's mentors are Stylianos P. Scordilis, Kevin Shea and Leslie Nickerson.

Colby Agostino, a Massachusetts resident and a chemistry student at Providence College, plans to earn a Ph.D. in biochemistry and "conduct interdisciplinary research at the crossroads of chemistry, biology and computer science as a faculty member of a Research I university." Agostino's mentors are Kathleen Cornely, Seann Mulcahy and Darra Mulderry.



Zoe Behrman, a Maryland resident and a life sciences student at Salisbury University, aspires to attain an M.D.–Ph.D. in molecular microbiology and immunology and "lead a translational research laboratory producing therapeutics for patients experiencing autoimmune diseases." Behrman's mentors are Jessica Clark, Lindley Bark and Bethany Shivers.

Caleb Lines, an Iowa resident and a life sciences student at Wartburg College, hopes to earn an M.D.–Ph.D in biochemistry and "lead a cancer research team focused on developing clinical trials by conducting translational research at an academic medical center and pursue a teaching position." Lines' mentors are Shawn Ellerbroek, Suzan Turner and Derek Barchenger.

Qianyun (Lexi) Luo, an Illinois resident and a life sciences student at the University of Wisconsin–Madison, hopes to earn an M.D.–Ph.D. in cancer biology to "conduct translational research in the field of oncology studying how metabolism shapes the tumor immune microenvironment to improve cancer treatment." Luo's mentors are Randall Kimple, Alexandre Reuben and Zafer Gurel.

Paiton McDonald, an Iowa resident and a life sciences student at Iowa State University, hopes to earn a Ph.D. in immunology and infectious diseases and to "conduct immunology research and teach at the university level." McDonald's mentor is Jodi McGill.

Grace McIntyre, an Indiana resident and a life sciences student at Marian University, hopes to earn a Ph.D. in biomedical science and to "investigate the underlying molecular, cell, and integrative biology associated with how tissues communicate with each other in a university or industry setting." McIntyre's mentors are Jason Chan, Trisha Staab and Colleen Doci.

Cameron Young, a Massachusetts resident studying chemical engineering and biochemistry at Northeastern University, hopes to earn an M.D.–Ph.D. in biomedical engineering and "develop the next generation of personalized cancer therapeutics." Young's mentors are Adrienne Randolph, Giovanni Traverso and Ambika G. Bajpayee.

Each Goldwater scholar receives up to $7,500 for tuition, fees, books, and room and board each year until they graduate.

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The prize is sponsored by Cayman Chemical.

Stoddard wins mentoring award

Shana Stoddard, an assistant professor of chemistry at Rhodes College in Memphis, Tennessee, has received the 2021 Early Career Mentor Award from the Health Sciences Division of the Council on Undergraduate Research. She is one of four CUR mentoring honorees.

STODDARD

The Stoddard lab works to improve therapies for autoimmune disorders, particularly idiopathic membranous nephritis, through development of autoantibody-specific inhibitors, antigen-specific therapies and novel methods for development of antigen-specific therapies, using a combination of computational chemistry, biochemistry and cell-based assays.

Stoddard holds a Ph.D. in chemistry and biochemistry from the University of Mississippi and did postdoctoral work at St. Jude Children's Research Hospital and Rhodes College. She has mentored more than 40 undergraduate students, including those from underrepresented backgrounds. She also has nurtured connections among students and faculty of color and promoted inclusive teaching strategies on the Rhodes campus.

These CUR awards honor exceptional mentoring and advising by higher education faculty across all subdivisions of health sciences. Each consists of a cash award, a certificate of recognition and a letter of commendation.

Do recognized for his athleticism and studies

Daniel Do, a member of the ASBMB student chapter at Stockton University in New Jersey, has been named first runner-up for Arthur Ashe Jr. Male Athlete of the Year by the publication Diverse: Issues in Higher Education. Do competes as a member of the Stockton men's cross-country and track and field teams.

Do is a biochemistry and molecular biology major with a 4.0 grade point average, and he has earned his ASBMB certification. After graduation from Stockton, he plans to pursue a Ph.D. in food science at Ohio State University.

In his four years on the Stockton men's cross-country team, Do has been named three times to the New Jersey Athletic Conference first team; he has two career victories and 12 top-10 finishes in 22 races. On the Stockton track and field team, he holds school records in the indoor 3,000-meter run and outdoor 5,000-meter run.

DO

The Arthur Ashe Jr. Sports Scholar awards recognize minority men and women who have distinguished themselves academically and in athletics.

Bankston to lead science policy journal

Adriana Bankston, a principal legislative analyst for the University of California, became the new chief executive officer and managing publisher of the Journal of Science Policy & Governance in May.

"Adriana's vision, dedication and expertise in empowering the next generation of science policy leaders will be invaluable as JSPG enters its second decade of impact," Erin Heath, director of federal relations for the American Association for the Advancement of Science and chair of the JSPG governing board, said in an announcement.

BANKSTON

Bankston earned her Ph.D. from Emory University in 2013 and completed a postdoctoral fellowship at the University of Louisville in 2016. She has been a policy and advocacy fellow at the Society for Neuroscience and has worked with Future of Research, the National Postdoctoral Association and the STEM Advocacy Institute, among other advocacy and scholarly groups.

She began serving the JSPG in 2018, at which time she was named the journal's communications and outreach director. In that position, she orchestrated dozens of events, established partnerships and became the founding host of the journal's podcast. In January 2020, she was named its chief outreach officer.

"I cannot be more excited to welcome Adriana," said Shalin Jyotishi, the outgoing CEO. "She has excelled during her time with JSPG and has become a prolific and dedicated champion for engaging students, postdocs and early-career scientists and engineers in public policy."

In April, Bankston led a science policy session at the ASBMB's annual meeting. She is also a longtime contributor to ASBMB Today.

Robert James Pollet

Robert James Pollet, a professor emeritus of medicine and endocrinology at Emory University and a former hospital research administrator, died April 27. He was 79.

Born Jan. 24, 1942, in Brooklyn, Pollet was the son of New York City public school teachers and grew up with science in his home. He attended Columbia University as an undergraduate. During a summer internship in college, he worked at Cold Spring Harbor Laboratory, his first lab, and fell in love with research. He earned an M.D. and a Ph.D. in biochemistry at New York University's school of medicine, served his medical internship at the University of Chicago, completed his residency at the University of Michigan and did a fellowship in endocrinology at the National Institutes of Health.

Pollet was a professor of medicine first at the University of South Florida and later at Emory, where he also served as the senior assistant dean of the school of medicine. For more than 20 years, he was the associate chief of staff for research and development at the Atlanta Veterans Administration Hospital, where he launched major research initiatives and brought in funding to help build a world-class academic and medical research program. He was a founding board member of the Foundation for Atlanta Veterans Education and Research and served as its president from 1989 to 2016.

In an obituary, his family wrote: "He brought so much to our lives — the touch football games, the excellent advice after contemplating every possible available option, the quiet words of support throughout each of life's twists and turns, his love of poetry and classical music, the unassuming and easy physical affection, the confidence in each of us, and the enduring curiosity and desire for greater insight into all of life's mysteries."

Pollet is survived by his wife of more than 50 years, Donna, and also by his three children — Sarah; Adam and his wife, Natalie; and Joshua and his wife, Ashley — and five grandchildren.

Herbert Gutfreund

Herbert "Freddie" Gutfreund, an emeritus professor of biochemistry at the University of Bristol, died March 21 at age 99.

Born Oct. 21, 1921, in Vienna, Gutfreund moved to England after the 1938 Nazi invasion of Austria. As part of a British YMCA agricultural training program, he worked for three years as a dairyman, then took a position as a lab technician at the University of Liverpool, where he published his first scientific paper. He earned his Ph.D. in biophysics at Cambridge University and remained there for 13 years, working in several departments alongside such distinguished researchers as Fred Sanger, Peter Mitchell, James Watson and Francis Crick.

Gutfreund left Cambridge in 1956 to take a position as a research scientist at the National Institute for Dairying Research in Shinfield, Berkshire, where he continued work he had started at Cambridge on the kinetics and dynamics of protein reactions. In 1965, he was invited to join the newly established biochemistry department at the University of Bristol. There he established the molecular enzymology unit and remained until his retirement in 1986.

The application of rapid reaction techniques to biological systems was the cornerstone of Gutfreund's research career, along with his interest in biothermodynamics. With a collaborator, Tom Barman, he pioneered the application of the quenched-flow technique to identify short-lived intermediates in enzyme reactions that did not have an optical signal. He studied the mechanisms of proteolytic enzymes, including chymotrypsin and trypsin. He opposed the notion of metabolite channeling in glycolysis.

Gutfreund wrote several textbooks on enzyme catalysis. He was elected to the Royal Society in 1981.

Stephen Halford, a Bristol colleague, wrote in an obituary that one of Gutfreund's favorite aphorisms was "If you buy a machine, you can do the same experiment as everyone else, but if you build your own machine, you can do an experiment that no one else can."

Can probiotics change fish behavior?

By Laurel Oldach

CHELSEA FRANK

As salmon mature, they are transferred into saltwater pens like these. "If you have a more flexible fish, are they better able to cope with that transfer?" asked Chelsea Frank.

Fishery salmon lead charmed lives compared to their seafaring wild counterparts, but they still face some stresses. Juvenile fish are raised in freshwater tanks and later transferred to saltwater pens. That transition, already stressful, also adds new predators; at Yellow Island Aquaculture in British Columbia, harbor seals sometimes haunt the edges of pens, trying to take a bite out of an unsuspecting fish.

According to Chelsea Frank, a graduate student in ecology and evolutionary biology who studies farmed chinook salmon at Yellow Island, the fish are at an extra genetic disadvantage. Instead of two copies of the genome, they have three; hatcheries use special treatments to prevent eggs from getting rid of an extra haploid genome, the polar body, after being fertilized. Triploid fish tend to be larger and less aggressive than their diploid siblings, which is good for aquaculture. However, triploidy also has drawbacks: It compromises the fish's immune systems and seems to make them less adaptable to stress.

CHELSEA FRANK

Graduate student Chelsea Frank performs a fish dissection.

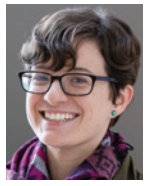
Frank and her colleagues in Christina Semeniuk's lab and co-mentor Daniel Heath's lab at the University of Windsor in Ontario are trying to determine whether an unlikely intervention — a probiotic supplement in fish food — might help triploid chinook salmon fare better. They're starting with how the fish behave.

"Behavioral flexibility and sensitivity … would be an immediate measure for physiological (and neural genomic) change, given the connections between the gut–brain–behavior axis," Semeniuk said.

Frank tested how probiotic supplements added to fish food affected the way hundreds of fingerling diploid and triploid fish respond to novel stimuli such as a glass bead tossed into the tank, a predator-shaped dummy passing overhead and an approaching human researcher. She presented her work as part of the genomics poster session during the 2021 American Society for Biochemistry and Molecular Biology Annual Meeting.

In the future, Frank plans to integrate transcriptomic analyses with her behavioral studies, an approach known as behavioral genomics. Little is known about how triploidy affects genes related to learning and memory, so even if probiotics have little effect, she stands to learn something interesting.

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



Could corals use sound to communicate?

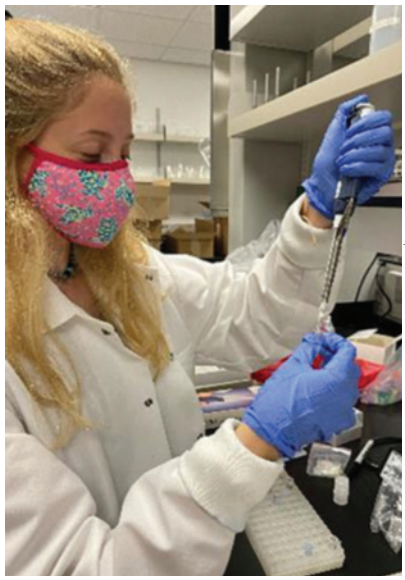
New evidence suggests corals may have genes involved in receiving or emitting sound

By Nancy D. Lamontagne

Corals are part of a highly complex ecosystem, but it remains a mystery if and how they might communicate within their biological community. In a new study, researchers found evidence of sound-related genes in corals, suggesting that the marine invertebrates could use sound to interact with their surroundings.

Coral reefs make up less than 1% of the ocean floor yet support more than 25% of all marine life. Around the world, coral reefs are being threatened by climate change, ocean acidification, diseases, overfishing and pollution. A better understanding of coral communication could help inform policies that aim to protect this critical ecosystem.

"A growing number of studies have shown that trees can communicate, and that this communication is important for ecosystems such as rain forests," said Camila Rimoldi Ibanez, a high school student in the dual enrollment program at South Florida State College. "Coral reefs are often referred to as the rainforests of the sea because of the habitat they provide for a wide variety of plants and animals. Thus, we wanted to find out how coral communicates."



CAMILA RIMOLDI IBANEZ AND JAMES HAWKER, SOUTH FLORIDA STATE COLLEGE

Camila Rimoldi Ibanez works with extracted coral DNA in the lab.

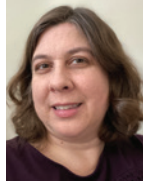
Ibanez presented the new findings at the 2021 American Society for Biochemistry and Molecular Biology Annual Meeting. Her mentor is James Hawker, dean of arts and sciences at South Florida State College.

Many organisms that live in coral reefs perceive sound and use it to find their way to the reefs. Based on this information, the researchers decided to look for the presence of genes related to the reception and/or emission of sound in the coral Cyphastrea. Using PCR amplification, the researchers found probable evidence that two of the four genes they examined may be present in coral DNA. The genes they found — TRPV and FOLH-1 — are used for sound emission or reception in sea anemones and freshwater polyps, respectively.

In addition to performing more testing, the researchers want to sequence the TRPV and FOLH-1 genes they found to add additional evidence that these genes, or genes related to them, are present in coral.

"As we learn more about the negative impacts of sound in different kinds of ecosystems, it is vital that we set policies to protect and manage human noises in natural environments," Ibanez said. "The more we know about how corals communicate, the better we can develop restoration and conservation projects to help corals as they face bleaching epidemics and other threats."

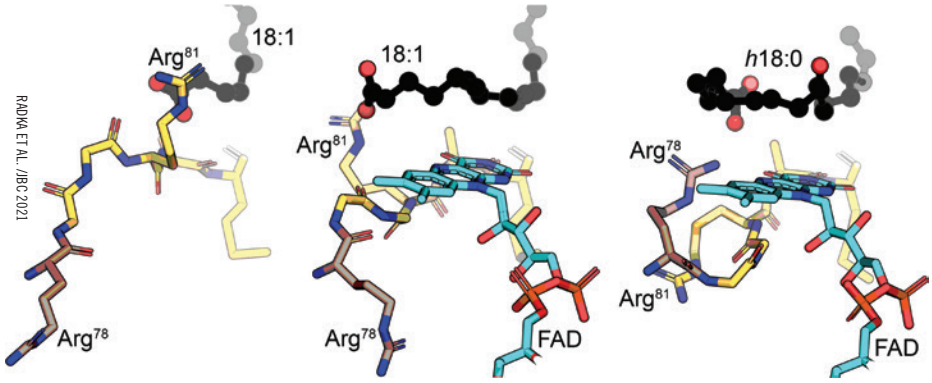
Nancy D. Lamontagne is a science writer and editor at Creative Science Writing based in Chapel Hill, North Carolina.



Arginine tango

How a bacterial enzyme enables immune evasion

By Nicole Lynn



RADKA ET AL. /JBC 2021

The 18:1 fatty acid substrate (black) first encounters Arg81 of OhyA, which blocks the entrance to the active site until FAD binds. Upon FAD (cyan) binding, Arg81 rotates, allowing the substrate into the active site. Arg81 continually rotates the substrate in the active site, allowing for inactivation of the antimicrobial fatty acid substrate to hydroxy fatty acid, or h18:0. After catalysis, Arg78 lunges to expel h18:0 from the active site.

The bacteria Staphylococcus aureus, found on human skin and in the nose, is the leading pathogen among dermal and soft-tissue infections. In immunocompromised people or those in hospital settings, S. aureus can cause serious infections.

As a means to evade the host immune response, S. aureus uses an enzyme called oleate hydratase, or OhyA, to inactivate antimicrobial unsaturated fatty acids in the membrane that otherwise would inhibit bacterial growth. Research scientists at St. Jude Children's Research Hospital have found the structure and catalytic mechanism of OhyA, and Christopher Radka of St. Jude's Department of Infectious Diseases presented this work at the 2021 American Society for Biochemistry and Molecular Biology Annual Meeting.

Radka and colleagues used X-ray crystallography to determine the structure of OhyA. Solving and evaluating multiple OhyA crystal structures highlighted a coordinated dance that occurs between key arginine residues and the unsaturated fatty acid substrate in the active site of the enzyme, a process facilitated by the nucleotide cofactor FAD.

In this dance, the substrate first is guided into the binding tunnel by the oleate carbonyl of OhyA and then encounters its first arginine dance partner, Arg81, at the entrance of the active site. FAD binding then triggers the rotation of Arg81 that guides the fatty acid as it curls into the active site. After catalysis, a second arginine, Arg78, rotates behind the fatty acid carboxyl to release the hydroxylated product from the active site.

"What's novel about the (active site) is how these conserved arginines guide the substrate through the donut-shaped active site," Radka said. "Here, the arginines dance like two partners in a tango."

This highly choreographed dance controls how the fatty acid substrate moves into and out of the active site. "In this coordinated tango at the active site, the FAD is the dramatic third character whose role is to come in and advance the dance so the chemistry can occur," Radka said.

In this reaction, FAD remains oxidized and unconsumed. This quality is advantageous for industrial biotechnology research looking to use OhyA; FAD-dependent reactions often consume FADH2 and require continued starting product, which can be costly.

Future goals for this research include determining the structural elements required for S. aureus OhyA to remove antimicrobial fatty acids from the membrane.

Nicole Lynn (nalynn@g.ucla.edu) is a graduate student at the University of California, Los Angeles in the chemistry and biochemistry department.

Using bacteria to clean the waterways

By Núria Negrão

In recent years, concerns have heightened about increasing amounts of drugs in the environment, particularly in water. While the impact of this environmental pollution is not well understood, some evidence indicates that these drugs may be entering the food chain. Researchers believe that most of the drugs that end up in fresh water first accumulate at wastewater treatment facilities. Therefore, there is a need to eliminate the drugs at these facilities.

Ashley Robinson, a senior biochemistry major at Hamline University who plans to start graduate school in the fall, started doing research in her sophomore year. She presented a poster at the 2021 American Society for Biochemistry and Molecular Biology Annual Meeting on this topic, the third research project she has worked on with Betsy Martínez–Vaz.

The researchers' goal was to find bacteria that break down metformin, a drug commonly used to treat diabetes in the U.S. and around the world. Little research has been done on the impact of pollution with metformin and its byproduct, guanylurea, which are not metabolized fully by humans and thus are excreted into wastewater systems. "We consider them to be emerging pollutants," Robinson said.

Studies have demonstrated the potential for metformin to disrupt some hormones, she explained. The drug is considered an endocrine disruption agent in some small fishes, and guanylurea has been shown to interfere with the nitrogen cycle in soil. Little is known about its bioaccumulation potential.

KATHRYN MALODY

Ashley Robinson works in the biological safety hood at the Martínez–Vaz lab.

"Can these molecules pass up the food chain?" Robinson said. "That is one concern that we have."

The research team collected samples at a local wastewater treatment facility from several stages of the treatment process. The bacteria in the samples then were grown in the lab under limiting conditions, meaning the bacteria were not given all the nutrients they needed. In this case, their only source of nitrogen was metformin, so most of the bacteria that survived were species that could use metformin as a nitrogen source. The team then used metagenomics to identify the enzymes involved in the breakdown of guanylurea and its transformation product guanidine. They identified three enzymes: guanylurea hydrolase, carboxyguanidine deiminase and allophanate hydrolase.

Robinson and her colleagues now are working to identify the enzyme that breaks down metformin in the initial step that forms guanylurea. They hope the enzymes they find could be used to break down metformin and guanylurea at wastewater treatment facilities, keeping these pollutants out of freshwater systems.

Núria Negrão (nurianegrao@gmail.com) is a medical writer and editor at Cactus Communications. Follow her on Twitter: @nurianegrao.

Gene changes might explain long-haul COVID-19 symptoms

By Nancy D. Lamontagne

COURTESY OF NICHOLAS EVANS

Nicholas Evans changes the growth media in the Transwell plate that is used to grow and differentiate airway cells.

Results from a new cell study suggest that the SARS-CoV-2 spike protein can bring about long-term gene expression changes. The findings could help explain why some COVID-19 patients — referred to as COVID long-haulers — experience symptoms such as shortness of breath and dizziness long after clearing the infection.

Severe acute respiratory syndrome coronavirus 2, or SARS-CoV-2, the virus that causes COVID-19, is covered in tiny spike proteins. During infection, the spike proteins bind with receptors on cells in our body, starting a process that allows the virus to release its genetic material into the inside of the healthy cell.

"We found that exposure to the SARS-CoV-2 spike protein alone was enough to change baseline gene expression in airway cells," said Nicholas Evans, a master's student in the laboratory of Sharilyn Almodovar at the Texas Tech University Health Sciences Center. "This suggests that symptoms seen in patients may initially result from the spike protein interacting with the cells directly."

Evans presented the research at the 2021 American Society for Biochemistry and Molecular Biology Annual Meeting.

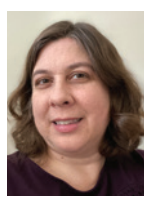
Culturing human airway cells requires specific conditions that allow cells to mature into the differentiated cells that would be found in the airway. The researchers optimized a previously developed culturing approach known as the air–liquid interface technique so that it would simulate more closely the physiological conditions found in the lung airway. This involved exposing cells to air and then giving them time to mature into airway cells.

The researchers found that cultured human airway cells exposed to both low and high concentrations of purified spike protein showed differences in gene expression that remained even after the cells recovered from the exposure. The top genes included ones related to inflammatory response.

"Our work helps to elucidate changes occurring in patients on the genetic level, which could eventually provide insight into which treatments would work best for specific patients," Evans said.

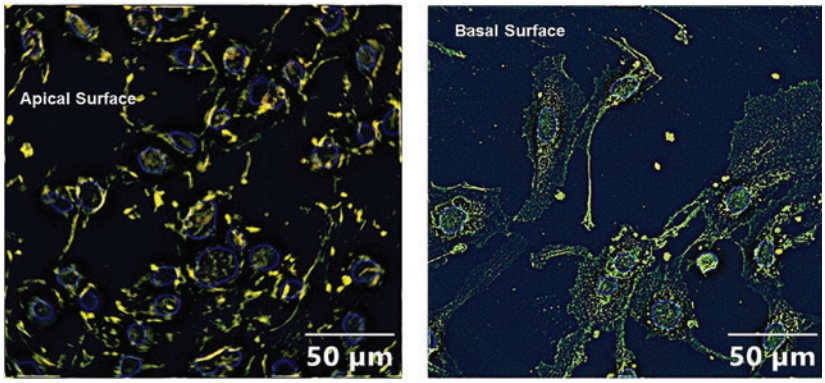
The researchers also compared their cultured human airway cells to cells from other studies that were collected from patients with COVID-19 infection. They were able to confirm that the optimized cell culture approach reflected what occurs in patients, making it useful for future translational studies. They plan to use the new approach to understand better how long the genetic changes last and the potential long-term consequences of these changes in relation to long-haul COVID-19 cases.

Nancy D. Lamontagne is a science writer and editor at Creative Science Writing based in Chapel Hill, North Carolina.



Pesticide exposure may increase COVID-19 susceptibility

By Nancy D. Lamontagne



SAURABH CHATTERJEE/UNIVERSITY OF SOUTH CAROLINA

ACE2 (yellow), the receptor for COVID-19, was more highly expressed in the apical surface (left) when lung epithelial cells were exposed to organophosphates and IL-6. The right image shows less ACE2 expression on the basal surface. Apical surface expression causes more virus to attach to the ACE2 receptor.

A study using human lung airway cells has shown a potential link between exposure to organophosphate pesticides and increased susceptibility to SARS-CoV-2 infection.

"We have identified a basic mechanism linked with inflammation that could increase susceptibility to COVID-19 infection among people exposed to organophosphates," said Saurabh Chatterjee , a researcher at the University of South Carolina and the Columbia VA Medical Center. "This mechanism could also increase risk for people with metabolic diseases and cancer because they tend to exhibit the same type of inflammation."

Exposure to these pesticides is thought to be a possible cause of Gulf War illness, a cluster of chronic symptoms estimated to affect more than 25% of Gulf War veterans. In previous work, the researchers found increased interleukin 6, or IL-6, levels in samples from veterans and a mouse model of Gulf War illness. The body produces these pro-inflammatory proteins to fight infections and respond injuries. However, continued production of IL-6 can lead to chronic inflammation and has been shown to decrease the immune system's viral response.

In the new study, the team wanted to find out whether exposure to the pesticide chlorpyriphos and increased levels of IL-6 could increase risk of SARS-CoV-2 infection. For six hours, they exposed human lung airway epithelial cells to IL-6, chlorpyriphos or both.

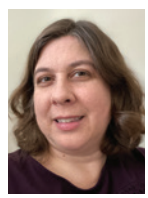
The researchers then treated the cells with spike proteins from SARS-CoV-2, the virus that causes COVID-19. Spike proteins bind with angiotensin converting enzyme 2, or ACE2, receptors in cells, starting a process that allows the virus to release its genetic material into the healthy cell. The researchers found that cells exposed to IL-6 and the pesticide exhibited increased apoptosis — or controlled cell death — when the spike protein was present.

The cells exposed to both the pesticide and IL-6 also had significantly more ACE2 expression on the apical cell surface compared with cells that were unexposed or exposed to the pesticide alone. The apical membrane of airway cells faces the interior of the airway, while the basolateral membrane touches the surrounding tissues. Increased ACE2 receptor expression on the apical surface means more virus will attach to the cells.

"To our knowledge, this is the first study demonstrating that the ACE2 receptor translates from the basolateral cell membrane to the apical cell upon co-exposure to organophosphate and IL-6," Chatterjee said. "Since people with obesity, Type 2 diabetes or cancer also have high circulatory IL-6 levels, we think people with these conditions will also have increased susceptibility to SARS-CoV-2 infection because of increased translocation of ACE2 receptor to the apical cell surface."

Ayan Mondal, a postdoctoral fellow in Chatterjee's lab, presented the research at the 2021 American Society for Biochemistry and Molecular Biology Annual Meeting in April.

Nancy D. Lamontagne is a science writer and editor at Creative Science Writing based in Chapel Hill, North Carolina.



Saving injera

Lessons from a teff grain's drought-tolerant cousin

By Laurel Oldach

If you've ever sampled Ethiopian cuisine, you've probably tasted teff. The cereal grain is the key ingredient of injera, Ethiopian flatbread, and a staple crop in the Horn of Africa. Researchers at Michigan State University are studying a closely related grass that is hardier, hoping to use its tricks to help teff survive severe drought.

Eragrostis nindensis is known as a resurrection plant: Even after a drought that would kill other grasses, and even if it has shriveled to a dead, brown husk, it can rebound and sprout new green shoots when water becomes available.

When a lab down the hall began a genomic comparison of teff and E. nindensis, which belong to the same genus, Kiran Shivaiah, a research associate at the MSU Plant Resilience Institute, struck up a collaboration to study the resurrection plant's physiology. He started by letting his study subject wither and keeping it that way for weeks.

"It was completely desiccated. Dead," Shivaiah said. "Nobody thought it would come back. But I started watering and within four weeks … it came back to life."

Like other researchers in Peter Lundquist's lab, Shivaiah is interested in how plastoglobules, lipid droplets found in the chloroplast, mediate stress responses. He found that as nindensis stems dry, their plastoglobules increase in size. Nindensis is known to destroy its chlorophyll while drying out to prevent photo-oxidation. Using lipidomics, Shivaiah observed that crash in chlorophyll level and an increase in smaller lipids and sugars, which he thinks are breakdown products. He suspects that some lipids are converted into sucrose to stabilize proteins as drier conditions introduce osmotic stress. The adaptation also seems to involve reductions in the level of many plastoglobule proteins.

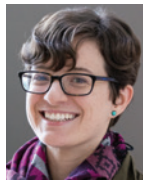
KIRAN SHIVAIAH

Despite drying out completely during a simulated drought, a laboratory specimen of E. nindensis was able to recover and thrive once water was available.

Shivaiah presented this research at the 2021 American Society for Biochemistry and Molecular Biology Annual Meeting. The findings are preliminary, he said. After replicating them to solidify his conclusions about how the plastoglobule changes, he hopes to investigate what differentiates teff plastoglobules from those of E. nindensis.

"Teff is dessication-sensitive. It can tolerate water scarcity for a while, but not as long as E. nindensis," he said. "Can we do genetic modification to the teff plant to make it as desiccation-tolerant as the nindensis plant?"

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



A sensor for fast, inexpensive on-site Ebola detection

By Nancy D. Lamontagne

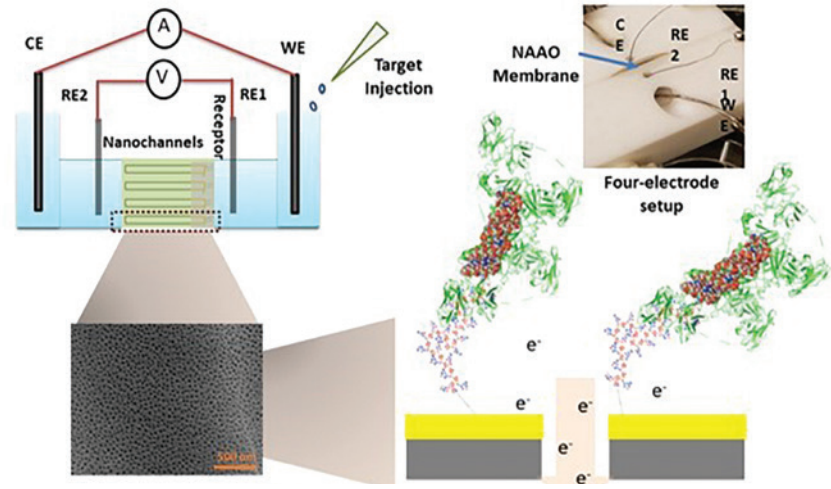
Researchers are developing a new sensor that can detect Ebola in a single drop of blood and provides results in just an hour. With further development, the technology also might enable fast and inexpensive detection of other viruses, including the virus that causes COVID-19.

Ebola is one of the deadliest of all known viruses, killing up to 90% of those infected. Stopping its spread requires quickly detecting and isolating infected people. However, outbreaks tend to occur in remote areas of Africa, requiring blood tests to be transported to distant laboratories for analysis. This leads to significant delays in identifying a new outbreak.

Soma Banerjee, a visiting scientist in Marit Nilsen–Hamilton's laboratory at Iowa State University, research associate in Ames National Laboratory and research scientist at Aptalogic Inc., presented the research at the 2021 American Society for Biochemistry and Molecular Biology Annual Meeting in April.

The new sensor is being developed by a multidisciplinary team led by Nilsen–Hamilton, who is also chief scientific officer of Aptalogic, and Pranav Shotriya from Iowa State University. The team has members with expertise in virology, bioinformatics, molecular biology and mechanical engineering from the University of Iowa, Iowa State University and the National Center for Biotechnology Information.

The Ebola sensor is based on DNA aptamers, which are short, single-stranded DNA molecules that selectively bind to a specific target. The researchers identified aptamers that bind to Ebola virus soluble glycoprotein, a protein that appears in the blood before symptoms appear.



MARIT NILSEN–HAMILTON AND PRANAV SHOTRIYA, IOWA STATE UNIVERSITY

Ebola biomarkers are exposed to an aptamer-coated aluminum oxide membrane. Binding of biomarkers to the aptamer-covered surface sets off a change in transmembrane impedance that is registered by sensors, shown here as four electrodes.

Current tests to detect Ebola are based on analysis techniques that require laboratories and trained individuals to perform the tests. Although alternative methods do exist, they tend to be difficult to read by personnel wearing protective gear or require special storage conditions.

"Our new sensor doesn't require any special storage conditions," Banerjee said. "This is an immense advantage because Ebola outbreaks occur frequently in remote areas where even electricity can be a luxury."

So far, the researchers have shown that the aptamers they selected work well on a portable nanoporous aluminum oxide sensor. They also found the sensor can detect the Ebola glycoprotein in infected macaque serum, providing results comparable to the standard ELISA-based assay performed using Ebola antibodies.

"Once our device is fully optimized for detecting Ebola, we plan to develop a multiplexed version that can perform multiple tests and detect other viruses and microbes, all from one drop of blood," Banerjee said. "We're also using what we've learned so far to identify aptamers that could be used to detect COVID-19 and other similar viruses."

Nancy D. Lamontagne is a science writer and editor at Creative Science Writing based in Chapel Hill, North Carolina.

How plants use lipids to protect themselves from freezing

By Núria Negrão

Freezing temperatures can kill certain plants, while others adapt to survive cold winters. And a sudden cold snap can damage or kill even winter-hardy plants.

Zachery Shomo, a graduate student at the University of Nebraska–Lincoln, studies how lipids protect plants from freezing and dying. He presented his recent research at the 2021 American Society for Biochemistry and Molecular Biology Annual Meeting.

"We would like to increase the ability of plants to withstand unseasonable climate events," Shomo said. "In fall, when we have frost that occurs too soon, the plants are experiencing that cold stress before they are acclimated to do so."

The opposite can happen in early spring, when warm weeks might make the plants lose their protective ability.

Shomo works on SFR2, short for Sensitive to Freezing 2, an enzyme that spurs lipid remodeling in response to cold or freezing stress, producing lipids that have multiple sugar residues as a head group. "These lipids are essential for most plants to survive a freezing response, but we don't know their functional role," Shomo said.

This is the most interesting part of this project, he said: Researchers know so much about this enzyme, but there is much still to learn about how these lipids function to protect plants from freezing.

COURTESY OF ZACHERY SHOMO

Zachery Shomo, a grad student in the Roston lab at the University of Nebraska–Lincoln, presented his research on oligogalactolipids at the 2021 ASBMB Annual Meeting.

Shomo and his colleagues in Rebecca Roston's lab have a few hypotheses about how SFR2 works to modify the lipid bilayer and protect the plant. The first is that the enzyme uses lipids that are not very good at forming bilayers as a substrate to produce oligogalactolipids, lipids containing two or more galactose molecules as a head group, to take their place. The resulting oligogalactolipids then form a more stable bilayer and protect cells. Another hypothesis is that as the temperature drops, plant cells start to accumulate different chemicals to prevent the liquids in them from freezing, and oligogalactolipids might interact with these as well. A third hypothesis is that these lipids act as spacers, preventing the membranes of different cells from fusing during freezing and keeping the cells' structure intact.

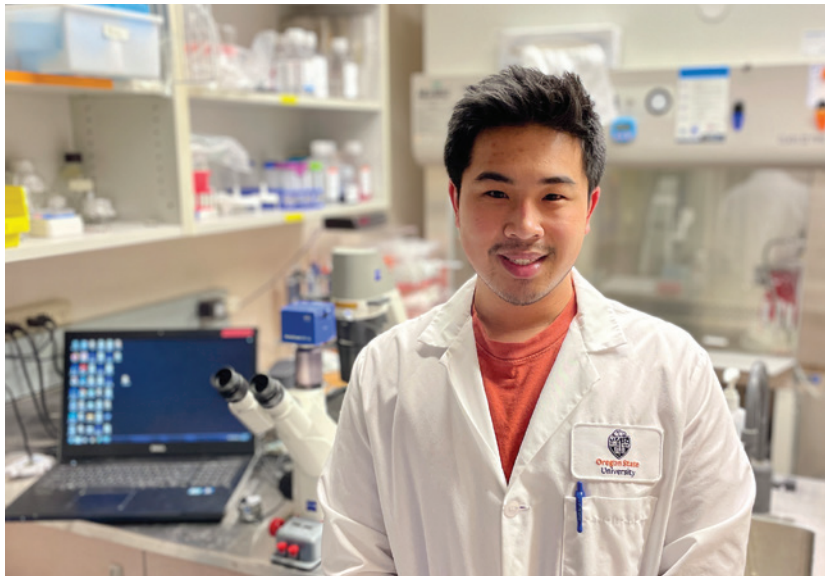
The researchers found out how SFR2 activity is regulated by temperature. They used mass spectrometry analysis of SFR2 from plants grown at several temperatures (including freezing), which showed that the protein had different phosphorylation profiles at varying temperatures. They then used a mixture of site-directed mutagenesis, in-silico modeling and synthesis of the mutated protein to show phosphorylation of surface amino acids is necessary for SFR2 to function. These experiments showed that SFR2 is activated by the phosphorylation of various amino acids. Their next goal is to identify which specific amino acids have to be phosphorylated for this to happen.

By understanding the metabolic signals that are activated to protect plants from freezing stress, the researchers hope to devise ways to increase cold tolerance in crops.

Núria Negrão (nurianegrao@gmail.com) is a medical writer and editor at Cactus Communications. Follow her on Twitter: @nurianegrao.

Targeting nitrated proteins could lead to new cancer drugs

By Núria Negrão

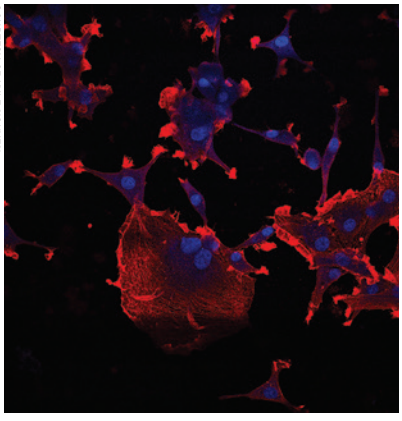


FRANCO LAB

Kyle Nguyen in one of the Franco lab's tissue culture rooms.

Glioblastoma multiforme is a type of cancer that develops in the brain. Aggressive and difficult to treat, glioblastomas respond to few drugs, and most patients are treated with methods developed about 20 years ago. Kyle Nguyen, a second-year Ph.D. student in Maria Franco's laboratory at Oregon State University, has been looking for a new way to target these tumors. He presented his work at the 2021 American Society for Biochemistry and Molecular Biology Annual Meeting.

In broad terms, the Franco lab is interested in the role of oxidative stress in diseases of the nervous system. Oxidative stress is a chemical imbalance inside cells that leads to an accumulation of oxidants that damage healthy cells. It has been linked to aging and various diseases, including cancer. The lab studies the role of oxidants in the development and growth of tumors of the nervous system.



COURTESY OF KYLE NGUYEN

A confocal microscope image of actin polymerization within glioblastoma cells. Actin is in red; cell nuclei are in blue.

Peroxynitrite is the most powerful oxidant produced in cancer cells and in cells associated with other diseases. When peroxynitrite reacts with proteins, it causes oxidative changes that can affect negatively the way the proteins work in the cells. "As far as we know, these are permanent chemical changes," Nguyen said.

The lab is interested in tyrosine nitration, one of the changes mediated by peroxynitrite. Tyrosine nitration is virtually undetectable in normal tissues, Nguyen explained, so drugs that target nitrated proteins would not affect healthy cells. His project looked at tyrosine nitration of a protein called heat shock protein 90, or Hsp90. Nitrated Hsp90 promotes the survival of tumor cells, and this role is mediated by nitration of tyrosine residues within this protein.

In his work, Nguyen shows that tyrosine nitration supports the survival and migration of glioblastoma cells and thus is important for tumor development and that nitrated Hsp90 may play more than one role in these tumors. Nontumor cells do not have nitrated Hsp90 and tumor cells do, so targeting nitrated Hsp90 or other proteins could kill tumor cells selectively with few side effects.

Núria Negrão (nurianegrao@gmail.com) is a medical writer and editor at Cactus Communications. Follow her on Twitter: @nurianegrao.

Talking glycoproteomics with Wells and Hart

By Anand Rao

Lance Wells and Gerald "Jerry" Hart are certified glycobiology geeks.

Hart got his start working with proteoglycans, proteins that are heavily decorated with glycans, and has spent the last 37 years studying O-GlcNAcylation, a nutrient- and stress-responsive post-translational modification. Since 2018, he's been a professor and Georgia Research Alliance eminent scholar at the University of Georgia.

Wells joined Hart's lab as a postdoc and became an expert in mass spectrometry. He is now a professor and Georgia Research Alliance distinguished investigator at the University of Georgia Complex Carbohydrate Research Center, or CCRC.

ASBMB Today talked to Wells and Hart about glycobiology and their glycoproteomics special issue in **Molecular & Cellular Proteomics**. The interview has been edited.

How did you get interested in glycobiology?

GH: Glycobiology is one of the last frontiers in biochemistry, partly due to the complexity and diversity of the molecules. Glycosylation is the most abundant post-translational modification by far. I founded the journal Glycobiology in 1989 and served as editor-in-chief for 12 years. So I've been involved with every aspect of the field for a long time. Mass spectrometry is probably the most important essential tool in analyzing post-translational modifications, particularly glycosylation. I've been involved with proteomics as well, or glycomics, as we call it.

LW: I went to Emory University School of Medicine for my Ph.D., for one reason — to work with Keith Wilkinson, who is an expert in ubiquitin biology. But first we had to do rotations. So I went to Judy Fridovich–Keil's lab, and I just fell in love with the power of genetics. In that lab, we studied galactosemia, the synthesis of sugar nucleotides and how defects can cause congenital disease.

JULIE NEWDOLL/BRUSHWITHSCIENCE.COM

This cover design highlights the MCP special issue on glycoproteomics' three main topic areas, from top to bottom. The first is capturing glycoproteins/glycopeptides (purple background) from the nonglycosylated species (green). The purple arrow represents introduction into a mass spectrometer for analyses by fragmentation (yellow). Finally, the area of post-acquisition data analyses (blue) takes the data generated (yellow arrow) and reassembles the pieces to map sites of modification and determine site-specific microheterogeneity (mosslike structures) on the protein backbone (stones at bottom).

I ended up staying in Judy's lab, and when it came time to do a postdoc, I wanted to take the next step by asking, "What are these sugar nucleotides actually used for?" It hadn't been that long since Jerry Hart's lab discovered the O-GlcNAc modification, which seemed like a really cool way for cells to take into account their nutrient status. Jerry took me into his lab, and I stayed for five years and developed a lot of mass spectrometry skills. Then I joined

the CCRC, where I've been studying O-GlcNAc and other types of glycosylation. I started collaborating with Kevin Campbell, who's a Howard Hughes investigator who studies O-mannosylation. (Note: Campbell is also this year's Herb Tabor Award winner.) Now half my lab does O-mannosylation and half does O-GlcNAc. That's how I got into it and just kind of fell in love.

How has mass spec evolved in glycoproteomics?

GH: Lance is probably one of the top glyco mass spec people on the planet. He learned his mass spectrometry skills on his own when he was in my lab, where we did liquid chromatography–mass spectrometry, which is very primitive compared to what they have now. Lance basically pioneered the use of mass spec in our lab.

JERRY HART

LW: We were on a Paul trap in Jerry's lab, which at the time was a workhorse, just an amazing instrument. But the amount of data I generated in all my years there could probably be generated in a week today. Certain key technologies have catalyzed progress. We used to do everything by collision-induced dissociation, or CID, which was our only option to dissociate molecules for tandem mass spectrometry. Now we have so many electron dissociation techniques, but what probably doesn't get enough attention from biologists is the backend software. In this special MCP issue, about a third of the articles are about how to turn the data that's generated into something we can use in biology.

GH: Probably the most astonishing thing about the development of mass spectrometry in the last decade is the increase in sensitivity and mass accuracy. The very first MALDI (matrix-assisted laser desorption/ionization) instrument I owned was about as accurate as gel filtration. They have gotten much better. The development of the orbitrap was a major breakthrough.

Why an MCP glycoproteomics special issue now?

LW: Eight years ago, we put together a special issue about glycomics — the characterization of glycans released from proteins. Since then, the field has moved forward fast. Hardware, sensitivity, separations and tools to analyze data have made tremendous progress. So, in this special issue, about one-third of the articles are about enriching for glycoproteins or glycopeptides, one-third are about analyzing them on a mass spectrometer, and one-third are, OK, you've generated all this data, how are you going put it back together?

It's also a good time because of COVID-19. The SARS-CoV-2 spike protein has 66 N-linked glycan sites and a few O-linked sites, and the ACE2 host human receptor, to which the spike protein attaches, is also a heavily N-linked glycosylated protein. And so the collection is very timely in that way.

What are some challenges in the field?

LW: All mass spectrometers, no matter how fancy they are, do the same thing: measure mass over charge. With proteins, 18 of the amino acids have unique molecular weights, with leucine and isoleucine being the exception, but they have a template. With glycans, however, a lot of things weigh the same: GlcNAc and GalNAc, all your hexoses — glucose, mannose, galactose. And that's what we measure in mass spec. That's what we call the isomer problem in glycobiology. Some of these gas phase separation techniques offer a lot of promise.

LANCE WELLS

GH: One big challenge of mass spectrometry, particularly with glycobiology, is that if you don't see something, it doesn't mean that it's not there. Also, a protein may have 50 modification sites, but binding for enrichment isn't always a 1-1 ratio, and it tends to be cell-type dependent. So the level of complexity goes up enormously, and all of that information is biologically important.

What's the next frontier in glycobiology?

GH: Any glycoprotein, particularly N-linked glycoproteins, may have, as I said, 50 structures at one site and 50 at another, and they're very cell-type dependent. Where does this heterogeneity come from? If you look at the single cell, is the same level of heterogeneity still

there? Or is it dependent on the fact that you have 50 cells and they all have a different Golgi apparatus, and that's where it's coming from? The technology is getting close to where we can answer that question.

LW: We're usually looking at around 5x105 cells, which is pretty good sensitivity — it's less than a million cells — but what about that heterogeneity? Every one of those cells may be doing something a little bit different.

What advice would you give scientists in training?

GH: Be fearless and follow your data. Never be technique oriented. Be a problem solver. If you have to learn mass spec to answer your question, then learn mass spec. Also, there's only one reason to be in science, and that's because you love it. If you don't love and eat and breathe science, go sell shoes.

LW: I'd say just be bold. The technologies are out there, and the glycobiology community is so open to new people joining, and it's so supportive. I can contact almost any person that's published in this special issue and say, "Hey, can you send me your method file?" or "Can you send me those plasmids so I can generate that protein?" And they're in the mail the next day.

Anand Rao (arao@asbmb.org) is an ASBMB science communicator. Follow him on Twitter: @AnandRaoPhD.

Upcoming ASBMB events and deadlines

JULY

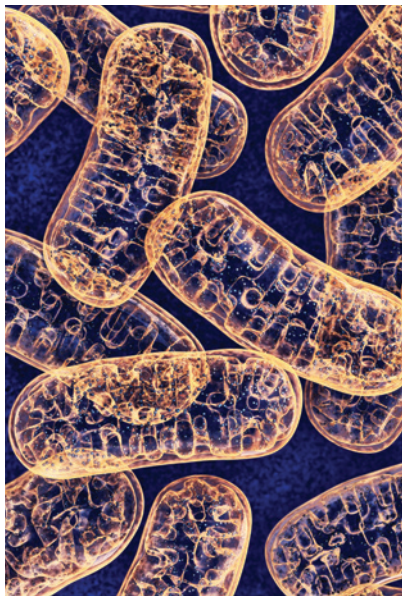
JULY	
18	**National Ice Cream Day**
21–23	***Extracellular vesicle studies: From benchtop to therapeutics***
23	Summer Olympics
AUGUST	
1	**RNA Day**
5	Abstract and early registration deadline for ***Emerging roles of the nucleolus***
9	National Breastfeeding Month
SEPTEMBER	
1	**Cholesterol Education Month**
1	Abstract deadline for ***Serine proteases in pericellular proteolysis and signaling***
8	**Blood Cancer Awareness Month**
15	**Hispanic Heritage Month**
29	**World Heart Day**
30	Early registration deadline for ***Serine proteases in pericellular proteolysis and signaling***

A balancing game with impact on neurodegenerative disease

By Leia Dwyer

Mitochondria in healthy cells have a stable balance of fission and fusion, the processes by which these cellular organelles divide and merge. Mitochondrial DNA is essential for their proper function, and mitochondrial fusion can help overcome genetic malfunctions and recycle proteins of nonfunctioning mitochondria in the cell. While researchers still have many questions about mitochondrial fission and fusion, we know these processes are particularly important in the brain and nerves, and recent studies suggest that mitochondrial fission and fusion are altered in several neurodegenerative diseases including Alzheimer's.

Ken Nakamura, a professor at the Gladstone Institute of Neurological Disease at the University of California, San Francisco, focuses his research on mitochondrial function and association with neurological disease. In a recent paper in the **Journal of Biological Chemistry**, Lauren Shields, then a grad student, and a team from the Nakamura lab describe research into how mitochondrial fission is related to the toxicity of a key Alzheimer's disease protein, amyloid-beta precursor protein, or APP. Shields, who was always interested in the neurosciences field, pushed the lab beyond its previous focus on Parkinson's disease and recalls that she was the "first graduate student to venture into Alzheimer's."



The research focused on understanding the role of dynamin-related protein 1, or Drp1, an essential mitochondrial fission protein that is increased in the brain tissue of Alzheimer's disease patients and may be associated indirectly with metabolism of the calcium ions, or Ca^{2+}, in the cell.

"Mitochondria are unusual organelles," Shields said. "This all goes back to the theory of evolution that mitochondria were bacteria-like and were encompassed by cells … they've maintained this fission and fusion function."

The researchers studied mice that were genetically altered to express mutant human APP, known as hAPP mice, with a targeted deletion of Drp1 that prevented fission in mitochondria. They found that the Drp1 knockout intensified the spatial learning and memory impairments observed in the hAPP mice.

Shields and the team also found that the loss of Drp1 combined with mutant hAPP to produce mitochondrial Ca^{2+} overload, possibly due to excessive influx of Ca^{2+} from the cytosol into mitochondria. They concluded that mitochondrial fission may be a protective mechanism against mitochondrial Ca^{2+} overload, which may be an initiating factor in the cascade of toxic insults that combine to cause neuronal dysfunction and degeneration in Alzheimer's disease.

This work clearly shows the need for the delicate balance of mitochondrial fusion and fission in healthy cells. Because Drp1 is known to be increased in post-mortem Alzheimer's disease patient tissue, the team originally had hypothesized that Drp1 could be a good therapeutic target. However, they concluded that Drp1 actually would be a risky target, given the need for careful calibration of the fission–fusion balance and Drp1's protective role in Ca^{2+} homeostasis.

"A lot of what my time in the neurodegenerative field really underscored for me is how complex humans are, how complex the brain is and how complex neurodegenerative cascades are," Shields said. "This is one more small piece of that big story."

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Cholesterol lessons from bears

By Arti Dumbrepatil

In humans, high cholesterol leads to clogging of arteries and is an underlying cause of heart attacks and cardiovascular disease, which causes one out of three adult deaths worldwide. On the other hand, hibernating bears have elevated cholesterol and triglyceride levels, but their arteries do not become clogged. Why?

To answer this question, researchers recently investigated lipoprotein composition and functions in free-ranging Swedish brown bears during winter hibernation, when the bears are fasting and sleeping, and in summer, when they are eating and physically active.

The team, led by Matteo Pedrelli of the Karolinska Institutet and Eva Hurt–Camejo of AstraZeneca and the Karolinska Institutet, collaborated with Ole Frobert of the Scandinavian Brown Bear Research Project to unravel the furry secrets that might help prevent heart disease in humans. Their study was published in the **Journal of Lipid Research**.

"Hibernating bears, despite high levels of plasma triglycerides and cholesterol, do not show any sign of atherosclerosis," Hurt–Camejo said, "whereas in humans, elevated plasma cholesterol is the main factor associated with atherosclerosis and cardiovascular disease. This bear physiology provided us with a unique opportunity to investigate this apparent paradox, as it enabled us to study an individual bear for the impact of extreme seasonal environmental changes on plasma lipid levels and lipoprotein composition."

While conducting experiments in brown bears, the team overcame the lack of bear-specific antibodies by applying basic biochemistry techniques to measure lipoprotein size, charge and lipid–protein composition. Thus, using conventional biochemistry approaches in an innovative way, they were able to obtain data for comparing human and bear lipoproteins.

The researchers found that lipoproteins in the two species have structural and functional differences. Atherosclerosis is not caused only by high levels of plasma total lipids but also by the specific biochemical structure of the lipoproteins carrying plasma total lipids, which in turn affects their functions. The brown bears' plasma cholesterol levels during winter are twice as high as human levels, but their low-density lipoproteins are larger in size and have less ability to bind to arterial extracellular proteoglycans; this binding capacity is what causes cholesterol to accumulate on artery walls in humans and other mammals.

Comparing their findings to human studies, the team found that the major factor controlling the deposition of cholesterol in arteries, the initial step in atherogenesis, appears to be the presence of a specific apoprotein B-100 amino acid sequence that binds to proteoglycans in the arterial wall. This sequence contains more positively charged lysine and arginine residues in humans than in bears, allowing more binding to those negatively charged proteoglycans.

"Histological analysis of the arteries of bears who died due to natural reasons like aging showed no atherosclerosis or even fatty streak," Pedrelli, the study's first author, said. "Our investigation of the bear plasma samples established that independent of the lipoprotein lipid composition change, which was elevated during winter and decreased in the summer, the apoB-containing lipoproteins showed significantly lower affinity toward arterial extracellular matrix proteoglycans compared to healthy humans."

To further evaluate their results, the research team plans to study the structure and composition of the arterial wall, comparing the extracellular matrix proteoglycan composition of bears and humans.

And Pedrelli and Hurt–Camejo have one piece of advice for readers: "Keep your cholesterol and triglycerides low — we are not brown bears."

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From the journals

By Brian O'Flynn, Anand Rao & Shravanti Suresh

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

Increased HDL levels might reduce COVID-19 risk

Preexisting conditions that increase the risk of contracting SARS-CoV-2, the virus that causes COVID-19, have been a focal point in understanding the virus. Why these conditions increase risk is not well understood. In a recent paper in the **Journal of Lipid Research**, James R. Hilser, Yi Han and a team from the University of Southern California, the Cleveland Clinic and UCLA explore the connection between SARS-CoV-2 infection and biomarkers linked to preexisting metabolic conditions, such as obesity or coronary artery disease. The team compared high-density lipoprotein, or HDL, cholesterol and apolipoprotein A1, or ApoA1, levels in individuals who contracted the virus with data collected from the general population prior to the pandemic.

The findings indicate a connection between increased HDL cholesterol or ApoA1 levels and reduced infection rates. In people with high levels of these biomolecules, the reduced rate was as high as 20%. Hilser, Han and their team reasoned that this is potentially tied to immune-mediating properties of HDL cholesterol, writing, "HDL-cholesterol can protect against infections by a variety of pathogens, including bacteria and parasites, and can directly bind and

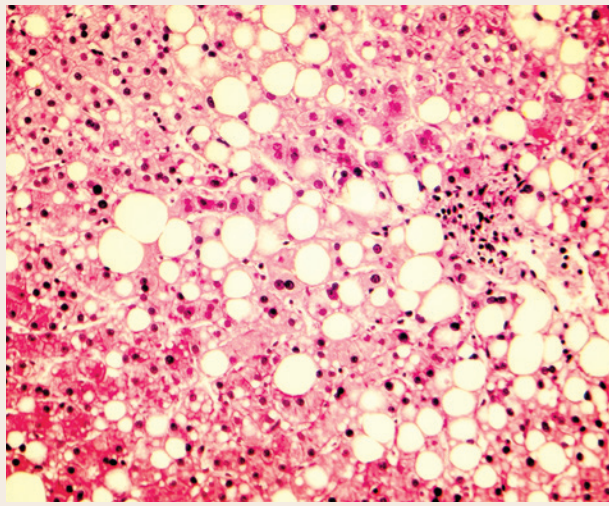
Reversing alcoholism's effects on lipid droplets

Alcohol-related liver disease, or ARLD, caused by chronic alcoholism is a major public health concern. An early sign of ARLD is fatty degeneration, or steatosis, which is caused by dysregulation of lipid metabolism and accumulation of lipids within the liver.

In a recent paper in the **Journal of Lipid Research**, Carol A. Casey and a team from the University of Nebraska and the Mayo Clinic explore the impact of chronic alcoholism on the function and composition of lipid droplets, or LDs, organelles in the liver that play a vital role in lipid metabolism and excess lipid storage. LDs consist of a phospholipid monolayer enclosing neutral lipids. This monolayer is also home to numerous proteins that regulate lipid metabolism — the LD proteome.

The researchers examined how feeding an alcohol heavy diet to rats affected the composition of the LD proteome and whether subsequent replacement with a control diet over seven days (refeeding) or 48-hour fasting reversed the effects.

They observed that an ethanol-heavy diet led to a greater number and volume of LDs in liver sections as well as higher levels of triglycerides and nonesterified fatty acids, or NEFAs. Refeeding reversed these effects for both triglycerides and NEFAs. Fasting did so partially, albeit with NEFA levels similar to those resulting from the ethanol-fed diet.



This photomicrograph shows large lipid droplets accumulated inside liver cells. Liver steatosis occurs in alcohol overuse as well as under the action of toxins and in diabetes.

Additionally, the levels of 388 LD proteins were altered with chronic alcohol intake, demonstrating a trend of reduced lipid utilization. For example, CIDEB, a protein known to induce LD fusion, was upregulated. This effect was reduced by both refeeding and ethanol fasting through recovering lipid utilization and mitochondrial function and reducing the levels of those proteins found to promote lipid accumulation. As Casey and the team wrote, "our data clearly support the notion that alcohol withdrawal, along with adequate nutritional support, is necessary for managing alcohol-induced liver injury."

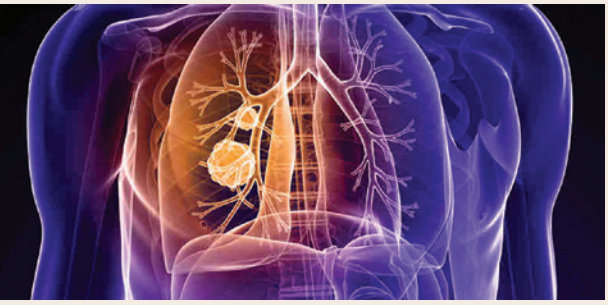
DOI: 10.1016/j.jlr.2021.100049

— Brian O'Flynn

A dual-acting antibody to treat lung cancer

Lung cancer remains the leading cause of cancer deaths worldwide, and non–small cell lung cancer, or NSCLC, is the most common type, accounting for 84% of all lung cancer diagnoses according to the American Cancer Society.

In 2004, researchers found that activating mutations of the epidermal growth factor receptor, or EGFR, and mesenchymal–epithelial transition factor, or MET, cell signaling pathways drive tumor proliferation and growth in NSCLC patients. This discovery led to the development of tyrosine kinase inhibitors, or TKIs, targeting EGFR, which are now the standard of care for NSCLC patients with EGFR mutations; however, many patients go on to develop resistance to TKIs, making future treatments ineffective. A similar resistance is developed against MET pathways, and strategies combining TKIs that target MET and EGFR cannot overcome the wide range of mechanisms responsible for the development of resistance. For these reasons, researchers now seek new treatment strategies that can circumvent resistance and achieve therapeutic benefit.



LISA MARIE CANON/NIH FLICKR

This illustration shows a tumor in a person's right lung.

Enter bispecific antibodies, or bsAbs — a family of molecules that can recognize two different epitopes or antigens. This makes them attractive candidates for targeting and acting on two separate biological targets. In a recent study published in the **Journal of Biological Chemistry**, Joost Neijssen of Genmab and an international team of collaborators including researchers at Janssen Pharmaceuticals developed a bsAb that can target EGFR and MET.

Using sequential screening methods, the team sorted through a panel of bsAbs derived from EGFR and MET antibodies. The researchers used tumor cell lines to assess the ability of the bsAbs to bind EGFR and MET as well as alter signaling pathways. After a lead bsAb candidate emerged, the researchers used antibody engineering to boost therapeutic potency and named the resulting product amivantamab. Using X-ray crystallography, the researchers revealed the atomic details of amivantamab when bound to its target molecules, and they showed that the bsAb effectively halts tumor-promoting cell signaling both in cultured cells and in a cancer animal model.

Based on its unique mode of action, amivantamab could be a powerful treatment for NSCLC, particularly in patients whose disease has developed resistance. Since the publication of this paper, Janssen has sought Food and Drug Administration approval of amivantamab for treating patients with NSCLCs that contain mutations in the EGFR gene.

DOI: 10.1016/j.jbc.2021.100641

— Anand Rao

neutralize various DNA and RNA viruses through ApoA1-mediated inhibition of viral fusion and entry into host cells."

The sample size in this study was, however, too small to demonstrate a genetic link between HDL cholesterol levels and COVID-19 risk.

DOI: 10.1016/j.jlr.2021.100061

What triggers toxic tau?

Alzheimer's disease, which affects more than 6 million Americans age 65 or older, is typified by the presence of abnormal proteins in brain cells, called amyloid plaques and tau tangles. Treatment for the disease — which remains incurable, with only symptomatic relief available — has focused on the elimination of amyloid plaques and has failed largely in clinical trials. Researchers are now looking at tau, a protein that interacts with cellular support elements called microtubules, as a therapeutic target.

In a paper published in the **Journal of Biological Chemistry**, Alberto Carpentino Soares and colleagues at Janssen Pharmaceuticals studied how endosomal pathways, pathways that sort and deliver cargoes within cells, may take in misfolded tau proteins from the extracellular environment and spread them in a cell, where these proteopathic tau proteins can seed new misfolded tau aggregates. Using drug studies, microscopy and biochemical techniques, the researchers identified the proteins dynamin-1, actin and Rac1 as key players in the spread of toxic tau seeds in cultured cells. The authors also discovered that disruption of the activity of PIKfyve, a protein downstream of Rac1, reduced both the trafficking of toxic tau seeds and the buildup of misfolded tau.

This work shows that tau aggre-

gates can be internalized by a process involving endosomes and that the consequences of their internalization can be altered using pharmacological compounds, which may represent a promising therapy for the treatment of Alzheimer's disease and other tauopathies.
DOI: 10.1016/j.jbc.2021.100636

How kinase responses affect plant development

Protein phosphorylation is an important mechanism that responds to environmental stimuli, especially in eukaryotes. Nearly 4% of the proteins encoded in Arabidopsi plants are protein kinases, suggesting a strong link to protein regulation. In plants, a serine/threonine protein kinase known as the Mut9-like kinase, or MLK, is linked to light, circadian and abiotic stress signaling. Previous studies have shown that MLKs provide a link between light and circadian signaling, which in turn affects plant growth and development. Researchers aim to identify roles of such kinases that use environmental inputs such as light and abiotic stress to generate altered developmental outputs.

In a recent paper in the journal **Molecular & Cellular Proteomics**, Margaret Wilson and colleagues at the Donald Danforth Plant Science Center describe using quantitative phosphoproteomics and global proteomic analysis to investigate the role of MLKs in daily protein dynamics. This study shows that in the absence of MLK, many proteins involved in light, circadian and hormone signaling as well as chromatin-modifying enzymes and DNA damage response factors have altered phosphorylation levels. Using several analytic methods, the authors showed that MLKs may help alleviate DNA damage through the regulation of multiple response pathways. They also observed higher levels of glucosinolate accumulation in MLK mutant plants, which could be related to the sensitivity to DNA-damaging agents. This is pivotal in understanding the role of MLK in multiple metabolic pathways that are regulated by this kinase in common.
DOI: 10.1016/j.mcpro.2021.100063

Archaic enzyme creates new phospholipids

Cardiolipins, or CLs, are a class of lipids that assist with the organization of membranes, enzyme functioning and regulation of water in cells. Researchers have studied the biosynthesis of CLs extensively in eukaryotes and bacteria but not in archaea, which have membranes made up of phospholipids that differ structurally from eukaryotes. As a result, cardiolipin biosynthesis processes may differ in archaea.

In recent work published in the **Journal of Biological Chemistry**, Marten Exterkate of the University of Groningen and colleagues identified the cardiolipin synthase from the archaea Methanospirillum hungatei. Using liquid chromatography–mass spectrometry, the authors characterized this enzyme's activity and discovered that it uses the substrates archaetidylglycerol and phosphatidylglycerol indiscriminately to generate its products: glycerol-di-archaetidyl-cardiolipin, or Gro-DACL, and glycerol-di-phosphatidyl-cardiolipin, or Gro-DPCL, respectively. This promiscuity enables the enzyme to process both substrates when they're presented simultaneously, resulting in an archaeal–bacterial hybrid cardiolipin that is not found in nature. The ability of this enzyme to create unnatural phospholipid species may be of interest for biocatalytic purposes.
DOI: 10.1016/j.jbc.2021.100691

Shining light on the cholesterol–GPCR relationship

Cholesterol maintains structural integrity within cell membranes. Many G protein–coupled receptors, or GPCRs, require cholesterol. Researchers believe cholesterol allosterically binds GPCRs with high affinity and induces a conformational change favorable for endogenous ligand binding. This mechanism has not been explored fully, however.

In a new study in the **Journal of Lipid Research**, Laura Lemel, Katarzyna Nieścierowicz, M. Dolores García–Fernández and an international team developed an assay based on ion channel–coupled receptor technology to study the interaction between cholesterol and GPCRs. They examined the relationship in the context of the oxytocin receptor, OXTR, which mediates uterine contractions and lactation during and after pregnancy as well as playing a role in some social behaviors.

The team discovered that cholesterol and the GPCR ligand have a reciprocal relationship; ligand-bound OXTRs formed stable interactions with cholesterol even after cholesterol depletion. As the authors state, "New prospects arise for clearly identifying the binding site(s) of functional cholesterol molecules and for understanding the molecular mechanism of the dependence of OXTR on cholesterol, thanks to the possibility of selectively stabilizing the interaction of these molecules with the receptor."
DOI: 10.1016/j.jlr.2021.100059

Identifying protein interactions in prostate cancer

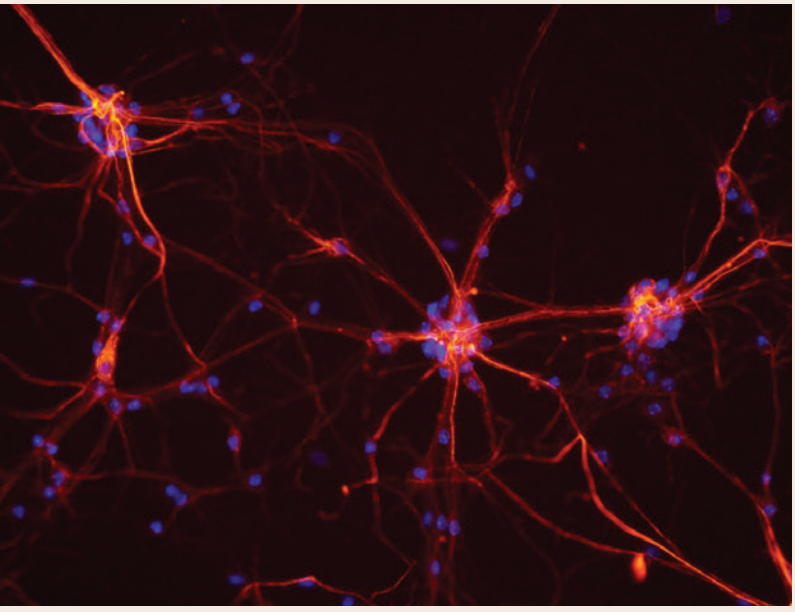
One in nine men are diagnosed with prostate cancer at some point in their lives. The growth and initiation of prostate cancer is caused by the androgen receptor, or AR, NR3C4, a steroid receptor. The AR acts as a transcriptional factor, regulating target genes involved in cell proliferation, survival and growth. While ARs are known to be regulated by several proteins affecting transcriptional location and ligand binding, researchers don't know the extent of this regulation and aim to identify the AR protein interaction networks to understand better how prostate cancer starts and spreads.

In a recent paper in the journal **Molecular & Cellular Proteomics**, Lauriane Vélot and colleagues at the Centre de recherche sur le cancer de l'Université Laval, Quebec, write that they used BioID proximity

Linking phosphorylation and synaptic vesicles recycling

In the nervous system, signals are transmitted through cellular junctions known as synapses from presynaptic neurons to postsynaptic neurons. When an action potential arrives at the nerve terminal, the presynaptic neuron depolarizes and releases an influx of calcium ions through channels in the active zone. This connects the presynaptic neuron to the postsynaptic membrane. These fused synaptic vesicles, or SVs, need to be retrieved and recycled to sustain continuous neurotransmitter release and to maintain the structure and composition of the plasma membrane. Defects in these processes can cause neurological disorders.

In mice with a mutation that causes the progressive neurodegenerative disease amyotrophic lateral sclerosis, a hyperactive enzyme called Cdk5 normally kills spinal cord neurons such as those pictured here.



S. JEONG/EUNICE KENNEDY SHRIVER NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT, NIH

Scientists have many hypotheses about the exact mechanism of this endocytosis and vesicle recycling. An increasing body of data points toward phosphorylation and dephosphorylation of proteins involved in the SV recycling as actions regulating this process. While some studies show an indirect relation between the two, changes in protein conformation that accompany assembly and disassembly of protein complexes during SV recycling may affect access to phosphorylation sites. Therefore, we cannot determine the effect of phosphorylation on SV recycling directly.

In a recent study published in the journal **Molecular & Cellular Proteomics**, Ivan Silbern and colleagues at the Max Planck Institute for Biological Chemistry, Germany, used botulinum neurotoxins, or BoNT, to differentiate between calcium-induced changes and phosphorylation events that are linked to SV recycling. By conducting a quantitative phosphoproteomic analysis using synaptosomes as a functional model for a synapse, they identified 1,500 sites that are affected by BoNT treatment, implying a direct connection to SV recycling. They also identified SV-cycling–dependent phosphorylation sites on syntaxin 1a, synaptobrevin and cannabinoid receptor 1.

This study demonstrates that the phosphorylation of these sites on the synaptosome can have a pronounced effect on exocytosis and endocytosis in cultured hippocampal neurons, establishing a firmer link between phosphorylation/dephosphorylation and SV recycling.

DOI: 10.1016/j.mcpro.2021.100061

—Shravanti Suresh

labeling proteomics, which fuse a mutant biotin ligase with a protein of interest to deduce AR interactions. By applying this in androgen-dependent LAPC4 cells expressing wild-type AR, they were able to indicate precisely a network of 267 proteins, 213 of which had not been reported previously. The authors also identify Kruppel-like factor 4, or KLF4, as a new AR-associated protein that represses KLK3, commonly known as the prostate-specific antigen, without regulating AR expression. The authors speculate that by establishing high confidence interaction networks, they could learn about prostrate cancer's complexity.

DOI: 10.1016/j.mcpro.2021.100064

Linking carbs and liver fat

An increasing number of people around the world are developing disorders characterized by metabolic dysfunction. Among these is nonalcoholic fatty liver disease, or NAFLD, which is characterized by excessive liver fat accumulation in individuals without a history of alcohol abuse. The overconsumption of dietary sugars is associated with the disease; however, researchers do not yet understand the processes responsible for the generation of fat, or lipogenesis, in liver cells.

Using recombinant adenovirus experiments, immunoprecipitation, nuclear localization studies and gene expression analysis, P. Vineeth Daniel and colleagues at the Indian Institute of Technology Mandi established a link between increased lipogenesis and nuclear factor kappa-light-chain-enhancer of activated B cells, or NF-κB. The authors showed that a high-carbohydrate diet caused the shuttling of liver p65, a component of NF-κB, and repressed transcript levels of sorcin, a cytosolic interacting partner of the lipogenic transcription factor carbohydrate response element-binding protein, or ChREBP. The researchers went on to show that the resulting reduced sorcin levels prompted ChREBP nuclear translocation, leading to enhanced new lipogenesis and fat accumulation in the cultured liver cells and in the livers of mice fed a high-carb diet.

These findings, published in the **Journal of Biological Chemistry**, describe a previously unknown role of NF-κB in regulating the biological response to high-carb diet and may be useful in developing treatments for NAFLD.

DOI: 10.1016/j.jbc.2021.100714

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The Reimagining Issue

Alternatives to animals

Could organoids and computational techniques replace mouse models?

By Lisa Nicole Learman

When Thomas Hartung was a medical student in Germany in the early 1990s, he interviewed a 35-year-old mother of three who was waiting for a liver transplant. Without the transplant, she would die, and Hartung recalls thinking, "I would do any experiment on mice if I could save this woman."

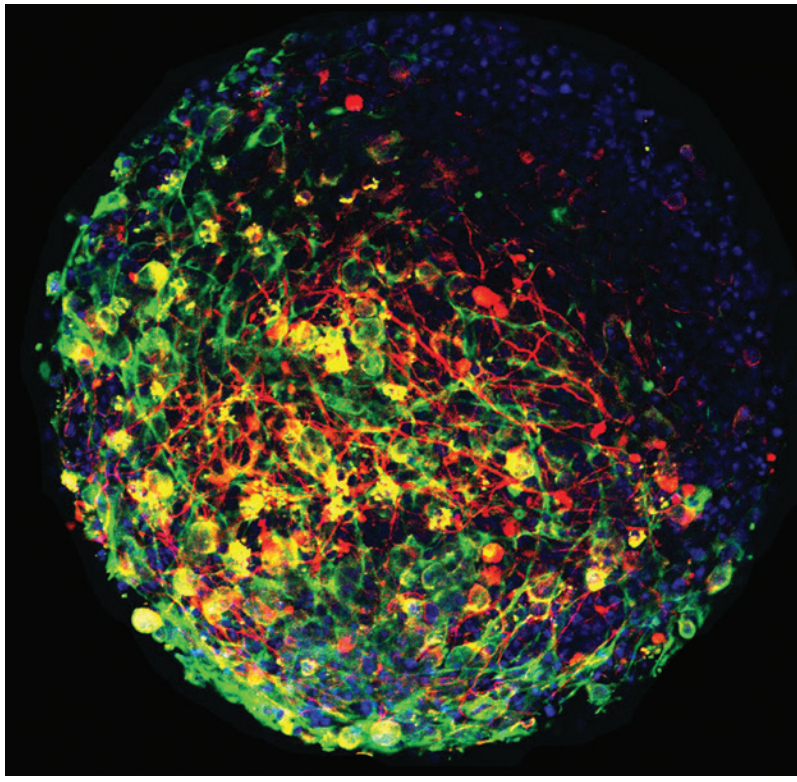
Animal experiments have been the foundation of most medical advances in the past century, including vaccination technologies, cancer treatments and new treatments for neurological diseases. According to a 2007 report, "Medical Advances and Animal Research," most Nobel laureates in physiology or medicine used animals in their research, considering it unfortunate but necessary.

The ethical obligation of researchers to reflect on their use of animal models is outlined in a set of principles known as the three R's, which most nations use as a guideline for laws governing animal experiments. Zoologists William Russell and Rex Burch introduced the three R's — replacement, reduction and refinement — in "The principles of humane experimental technique" in 1959. The three R's stipulate that researchers first determine whether their animal experiment can be replaced with a nonanimal experiment. If this is not possible, experimenters should strive to reduce the number of animals they use. Finally, the experiment should be refined to minimize animal suffering.

Hartung, who successfully replaced animal experiments with cell cultures in his graduate research, is now director of the Center for Alternatives to Animal Testing, or CAAT, at the Johns Hopkins Bloomberg School of Public Health. He believes the biggest step researchers can take toward reducing animal experimentation is a change in mindset; animal models have been useful for so long, it's hard to believe that there are better models out there, even if the data exist.

Hartung suggests that scientists start with a commitment to reexamine the three R's each time they design an experiment: "Ask yourself: Are there new technologies? Can I use fewer animals? If you strive for this, it is a good compromise. Be open to truth and willing to change your mind."

COURTESY OF THOMAS HARTUNG



This minibrain organoid system is made of human neurons and other brain cells.

Promising techniques

A growing number of techniques that can replace animal experiments have been developed in recent decades. In addition to being more humane than research on animals, these alternatives often produce results that predict human health outcomes equally well. Human cell lines, organoid systems and computational methods are the three most promising new technologies.

In the mid-20th century, the only cells scientists could grow successfully in a dish were derived from cancers. Cancer cells could be cultured easily because they grow and survive better than noncancer cells, but they were not appropriate for studying the physiology of a healthy cell. Eventually, scientists determined that stem cells — cells that are not fully developed — could be grown in a dish because they have an inherent ability to self-renew.

Initially, researchers could get stem cells only from

embryos, an ethically complex and heavily scrutinized practice. Now, cells scraped from inside the cheek or from the skin of adults can be transformed back into their early developmental state. These induced pluripotent stem cells can be developed into any type of cell researchers want to study, making them a powerful research tool. These healthy human cells reflect the unique genetic background of the human from whom they were taken, allowing researchers to study the unique disease mechanisms of an individual.

COURTESY OF THOMAS HARTUNG

Thomas Hartung is director of the Johns Hopkins Bloomberg School of Public Health Center for Alternatives to Animal Testing.

Hartung said that when he was a student researcher working with cell cultures, he performed animal experiments just to prove to his colleagues that his cell system could predict human physiology as well as mouse models.

Although progress has been made in the development of better cell culture systems, a major justification for animal research is that cells in a dish cannot reflect completely what is happening in the human body. Cell cultures typically consist of one type of cell arranged in a flat layer in a Petri dish. In the body, not only are different types of cells interacting in any given organ, but these cells are organized into a complex 3D architecture. Organoid systems attempt to recreate this complex cell diversity and architecture outside the body.

COURTESY OF EVA RATH

Eva Rath, a postdoctoral researcher at the Technical University of Munich, studies the intestine using miniguts.

Eva Rath, a postdoctoral researcher at the Technical University of Munich, studies the intestine using an organoid system called a "minigut" made from a small piece of intestine removed from a patient during a biopsy or bariatric surgery. Each minigut reflects the unique physiology of the patient. This is useful, as gastrointestinal disorders are complex. The same symptoms can have different causes from person to person because each individual has a unique immune system and collection of bacteria in their gut.

"It's an individual disease," Rath said.

Using miniguts, Rath and colleagues have discovered how inflammation can disrupt cellular metabolism and contribute to Crohn's disease. Organoid systems have been developed to model human lungs, blood vessels, pancreas and even brains.

In addition to human cell culture systems and organoids, advancements in computational methods have made it possible to learn from computer models of disease. Before the advent of artificial intelligence, a computer was only as smart as the person who made it, and programs were only as smart as the person who coded them. According to Hartung, computational methods have made significant strides in the last decade.

"Now, computational methods can find patterns in data that humans never saw," he said.

This is especially true in the area of computational toxicology, where algorithms that use similarities in chemical structure to predict toxicity outperform the reproducibility of animal tests, according to a 2018 report in the journal Toxicological Sciences. These new technologies make it possible to extrapolate existing data to gain new, useful insights without using animals.

Small but meaningful differences

In addition to saving animals, these new technologies often predict human health outcomes better than animal models because they use human cells or data. Although humans and the animals used as scientific models share a large percentage of their DNA, small genomic differences can have considerable effects.

Research on COVID-19 exemplifies this. Nicole Kleinstreuer, director of the National Toxicology Program's Interagency Center for the Evaluation of Alternative Toxicological Methods, or NICEATM, noted that mice don't get severe COVID-19 the way humans do. "They catch it, but they don't get sick," Kleinstreuer said. "They don't need to go on ventilators. They don't die from it."

Moreover, researchers have found that drugs tested in mice, the most common model organism, often fail clinical trials in humans and that preclinical studies using mice are often not reproducible. This could be because such studies are often statistically underpowered. Although it may seem counterintuitive, sometimes an individual experiment must use more animals to avoid wasting animal lives. If an experimenter uses only a few animals per condition and that is not enough to see the difference

COURTESY OF NICOLE KLEINSTREUER

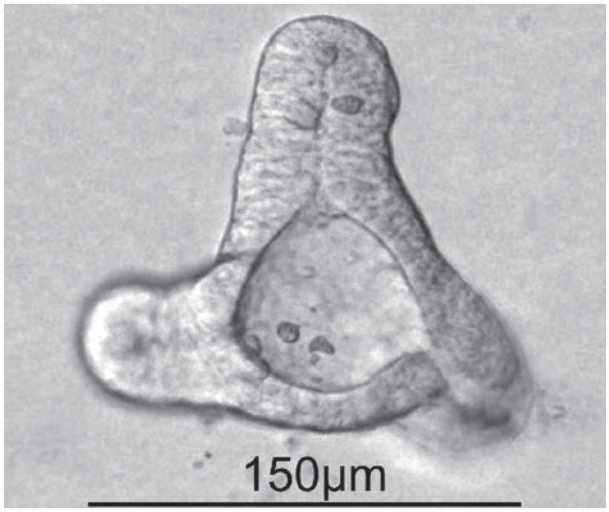
Nicole Kleinstreuer is acting director of the National Toxicology Program Interagency Center for the Evaluation of Alternative Methods.

that they expect to see, they might get a false negative result. In such a case, the animals used in the experiment were wasted. They died, no biological insight was gained and the experimenter will perform underpowered animal experiments repeatedly. Ultimately, making sure that necessary animal experiments are appropriately powered is a way minimize animal use overall. Another reason mouse studies may fail clinical trials is that in many cases, even though humans and mice have similar genes, these genes serve different biological functions in animals and humans.

The current culture around alternatives to animal experimentation may prevent the timely implementation of new technologies. According to a 2019 report by David Lewis of Leeds University, there is low adherence among researchers to the three R's guideline of replacing animal experiments when possible. "Despite the effort and resources being devoted globally to the development of alternatives, there is considerable reluctance amongst the research community to adopt them," Lewis wrote.

In 1995, Hartung and a colleague found a way to test for the presence of fever-causing toxins in pharmaceuticals without using animals, forever changing the pharmaceutical testing industry. Typically, pharmaceuticals have been injected into rabbits to test for toxins. The researchers developed a method to test for toxins in donated human blood that could better predict adverse outcomes for humans. In their test, blood is mixed with the pharmacological compound. If toxins are present in the compound, the blood cells start to produce the immune protein interleukin-1-beta. By measuring the amount of this protein in the blood, scientists can determine whether a given compound contains toxins.

COURTESY OF EVA RATH



This minigut organoid system is made from a piece of human intestine.

Hartung's passion for alternatives to animal testing stems from his belief that overreliance on animal models hurts people. "If I say, 'These poor rabbits,' they say, 'Why should I worry about them? It is so much more important to know what is toxic to humans,'" he said. "I say 'No, it is so much more important to know what is toxic to humans, and this is why I don't want to use rabbits.'"

Validation and policy

For scientists to reduce reliance on animal experiments, alternative methods must be available and validated. The availability of such alternatives varies widely among research areas. For example, it is much easier to get tissue for organoids from the intestine than to get it from the brain. A neuroscience researcher interested in studying a behavior needs an animal to model that behavior. Hartung understands that, for some scientists, animal experiments are the only appropriate tool to answer their research questions.

"If you have nothing better, I'm happy to endorse the animal experiment," he said.

Even when an animal model is the best option, scientists often overestimate what that model is delivering. According to Hartung, this may be due to pressures from funding agencies and publishers. While researchers should be aware of the limitations of any animal model, this mindset doesn't work in the quest for publication and grants — especially when reviewers are convinced that animals are the only way to ensure results are translatable.

"If you want to publish your findings in a cell culture model, most likely your reviewer will say 'Where's the animal experiment to validate this?'" Hartung said. "They don't understand that human cell line systems can give results that are as good as or even better than the animal experiment. They say that without a mouse model, research done in human cells has no value."

How can researchers be convinced to trust and use advancements in medical technology that do not use animals? Sonja von Aulock, editor-in-chief of the journal

COURTESY OF SONJA VON AULOCK

Sonja von Aulock is editor-in-chief of the journal ALTEX, Alternatives to Animal Experimentation.

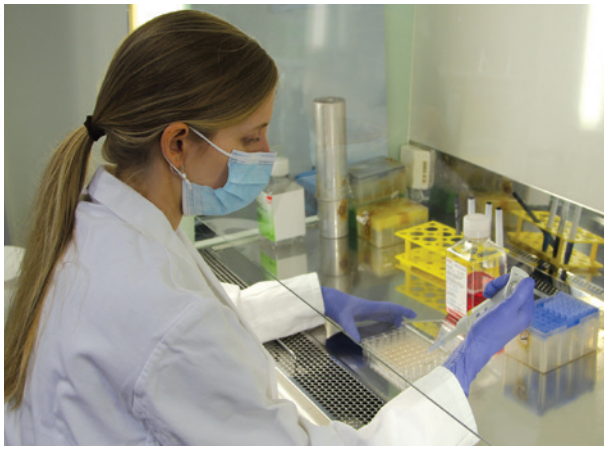
ALTEX, Alternatives to Animal Experimentation, believes that public policy could be key to getting researchers to consider nonanimal models.

"In Europe, animal testing for cosmetics was banned in 2013," von Aulock said. "At that time, they didn't have the alternative methods that they would need to test cosmetics without animals, but they innovated. Sometimes, you really need those higher-level decisions that say, 'Come on, people. You've got to make this happen.'"

Minigut researcher Eva Rath agrees that policy plays a significant role in promoting alternatives and thinks science publishers should lead the charge. "Scientific journals should enforce their own criteria for accepting publications," she said. "You should need to show that you use as few animals as possible."

In her role at the NICEATM, part of the U.S. Department of Health and Human Services, Kleinstreuer connects the science of animal testing alternatives to policy development. Her office "conducts data analyses, workshops, independent validation studies, and other activities to assess new, revised, and alternative test methods and strategies," according to its webpage.

Results from these NICEATM studies provide support for the Interagency Coordinating Committee on the Validation of Alternative Methods — a committee representing 17 federal regulatory and research agencies including the departments of Agriculture and Defense, the Environmental Protection Agency, the Food and Drug Administration, and the National Institutes of Health. Through the NICEATM, representatives from these agencies ask scientists to design research to inform their policy decisions, and scientists communicate their needs to policymakers. For example, in 2018, analyses from the NICEATM informed the EPA's decision to adopt a new policy to accept defined combinations of in vitro and computational methods instead of mouse tests when examining pesticide ingredients for skin sensitization.



COURTESY OF EVA RATH

Elisabeth Urbauer, Ph.D. student mentee of Eva Rath, replaces the liquid in which her miniguts are growing to remove the waste and add new nutrients.

Funding and revolution

Beyond creating programs to promote alternative research methods, policymakers also must allocate funding to those programs, Hartung said, adding, "Where there is funding, the science morphs and changes."

Funding also is needed for the infrastructure required to support nonanimal models. "Labs have been working with animals forever," von Aulock said. "Changing to other technology can be a big and expensive step."

Kleinsteuer said the NIH is trying to expand the funding opportunities around human biology–based models.

It is a tall order to shift the collective mindset of scientists. Hartung draws on an idea from science philosopher Thomas Kuhn, saying, "Science doesn't change continuously, but in waves. It takes a lot to believe that the current paradigm is not fitting anymore, accept something new, and suddenly change to a new paradigm. This is called a scientific revolution.

"Right now, we are entering a phase of revolution. Science is not giving justice to new methods because the old farts are reigning. These are the ones thinking that their methodologies are right and should continue to be used."

Von Aulock agrees that the revolution starts with young scientists. "Question the status quo," she said. "Think about whether you agree with how it has been done for the last 30 years. You are the generation that can make change. If you continue to plow on without being open to new developments, then things are not going to change."

Lisa Nicole Learman (llearman@jhmi.edu) is a Ph.D. candidate studying molecular neuroscience at Johns Hopkins University School of Medicine. She is passionate about dystopian fiction, increasing public understanding of science and the music of Charles Mingus. Follow her on Twitter: @LearmanLisa.

Putting body weight in context

By Robert Rosencrans

When we step into a doctor's office, the first step we take is onto a scale. That's before talking with a clinician, before a blood pressure or temperature check, and certainly before we tell our story, the symptoms bringing us to the doctor's threshold. Sometimes it seems there's a scale between us and our care. The architecture of the clinic declares that our health is determined first and foremost by our weight, and often, basic science recapitulates and reinforces this framework.

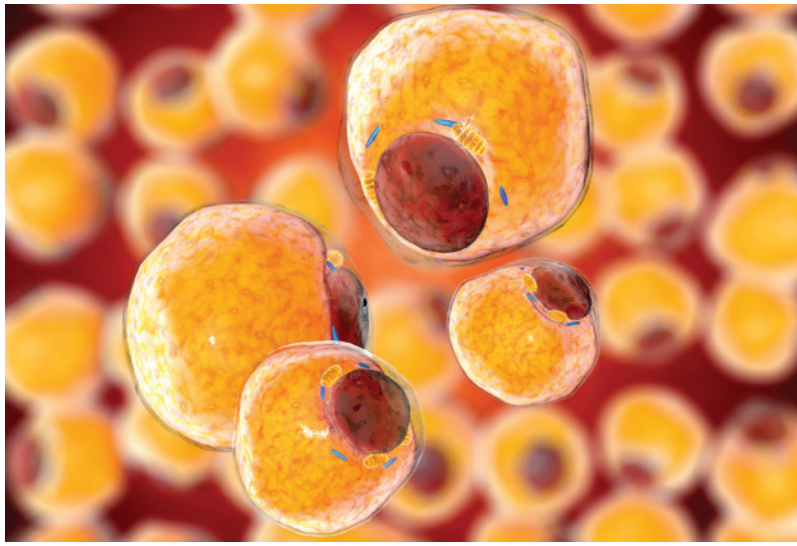
I write about scientific and medical fatphobia as a student, a young scientist and an intermittently fat person. I didn't expect to start seeing the intersections of fatphobia with environmental racism or police violence. I didn't expect to see them in my medical school classes. Or in my own care. I didn't think about this issue at all until recently. But once you start seeing the redundant harms larger people are exposed to, it's hard to stop.

Let's start with biology

This is the easy part, the pre-political part. I admire adipose tissue. It stores free fatty acids as triglycerides, safeguarding this fuel source for moments of need. Free fatty acids are also powerful signaling molecules, the basis of both anti- and pro-inflammatory cascades. Adipose tissue shields the body from unregulated contact with these molecules; it participates with the nervous system in their careful and regulated release, the process of lipolysis I study every day.

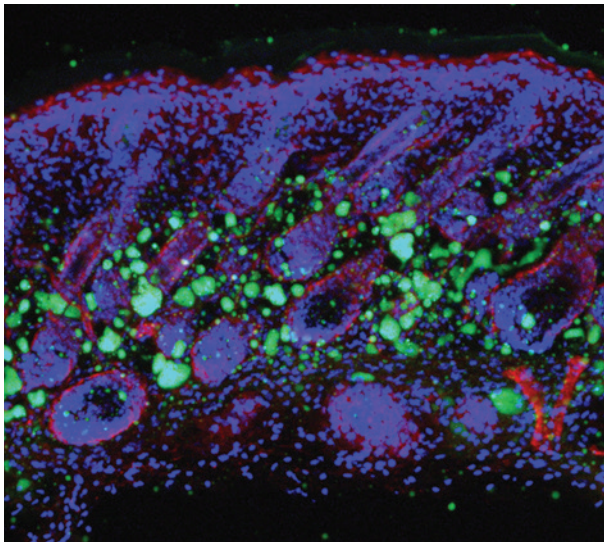
On a macroscopic scale, fat acts as a biomechanical cushion. From the backs of our eyes to the joints of our knees, it prevents acute trauma. Fat is also part of our immune system: The greater omentum, one of the visceral fat pads thought to play a role in cardiovascular disease, hunts down infections and cancers in the peritoneal cavity, walling them off until they are resolved. Adipocytes, the functional units of fat tissue, line our blood vessels, helping to maintain normal blood pressure. Fat tissue communicates with the brain through hormones called adipokines and through sensory nerves, apprising us of our nutrient status.

Adipose tissue is essential for life. Mice engineered to lack adipose are lean but die young, destined for fatty liver disease and diabetes. Conversely, in humans, all-cause mortality is as high in underweight people (as defined by body mass index) as it is in patients with higher BMIs. In conversations about this topic, one question comes up above all others: "Aren't very thin people typically experiencing another disease process, only indirectly related to their weight?" This kind of skeptical inquiry is critical; indeed, low body mass is associated with many pathologic processes, including cancer cachexia and other terminal conditions. For a thin person, the average scientist and physician believes that cancer, not thinness, is killing that patient. They can locate the source of mortality in something other than body weight or adipose stores. What scientific reason prevents them from extending the same courtesy to larger people?



Fat defines fat people

Fat comes first. First in the doctor's office, first in the scientific literature. Fat is never incidental in a fat person's body. Every other pathology must somehow be linked to it, and all disease processes in a fat person can be improved by weight loss. This is the dominant paradigm. After all, we think we know what fat does when it hurts us: hypertension, diabetes, cancers, immunosuppression, even a tendency to lie, according to a recent article in Scientific



RICHARD GALLO, UC SAN DIEGO HEALTH AND LING-JUAN ZHANG, XIAMEN UNIVERSITY

This microscopic image of the skin shows skin cells stained blue and fat cells stained green. The fat cell layer forms the final barrier against bacteria entering deep into the body. The number of fat cells in the skin decreases with age, making the skin more susceptible to infection.

Reports. Notably, this article has been retracted. Can we say the same of the scientific milieu that made its peer review and publication possible?

When body weight is on the scale, we seem incapable of remembering the first rule of statistics: Correlation is not causation. Our language often reflects this failure: "Diet-induced obesity causes x, y or z outcome in mice," "Weight-loss trials demonstrate improved insulin sensitivity in patients." My research-methods professor taught me that to claim causation, something should be manipulated. Because I want to understand adipose, I started paying attention to all the studies that claim it plays a key role in one or another pathophysiologic process. I slowly began to realize they all were manipulating something else: diet, exercise, drug exposure. These manipulations also, often, produce changes in adiposity: sometimes weight loss, sometimes weight gain. No matter what, however, the downstream benefits and harms were attributed to weight changes, not to the manipulation. Fat doesn't get to be a correlate; it's all causation, all the time.

Liposuction studies are the rare exception. Liposuction removes adipose tissue acutely and specifically. And there is no clear metabolic benefit. Because most liposuction is cosmetic, it involves the removal of subcutaneous fat. Metabolism-savvy readers know, however, that the accumulation of visceral fat is more strongly associated with disease on an epidemiological level. As such, perhaps we should expect that the removal of visceral fat, not subcutaneous fat, will improve health. Strikingly, a recent meta-analysis showed that the removal of omental fat, a large visceral fat pad, on its own or in conjunction with bariatric surgery, does not have clear metabolic benefits.

Fat can be dysfunctional

Like any tissue, fat can play a role in disease. I read this literature carefully; as such, I was interested in a recent report showing that removal of mesenteric fat (which lines the intestines) can improve insulin resistance in primates. But we don't call hypertension "kidney-associated high blood pressure." We recognize that hypertension mechanistically occurs due to a constellation of complex factors connecting kidneys, vasculature, the nervous system and, yes, adipose tissue.

As a researcher, I'd like to extend that same curiosity to diseases such as diabetes and conditions such as insulin resistance, those phenomena most intimately correlated with adiposity on a population level. But when we write papers on metabolic disease, we call high-fat diet "diet-induced obesity," and whatever else happens in those models often is considered downstream of the weight gain. Thousands of research projects use this most common model of metabolic disease, the rough equivalent of eating two sticks of butter a day. This model drives brain inflammation, alters the microbiome and induces hypertension, along with myriad other pathologies. Rarely are these other effects presumed to be the dominant, upstream factor. The model is called "diet-induced obesity," and that choice reflects our belief that adiposity is the fundamental cause of the rest of the constellation.

Fear of fat

My father has Type 2 diabetes, as did his grandmother. Weight was a central fact of their lives. My father remembers conversations about body weight from as early as his fifth year of life. By his 50th, when he was diagnosed with diabetes, metformin already was approved for use in the United States. Initially, he didn't take it, opting instead to increase his exercise and change his eating patterns. He felt he had earned his metabolic disease; it was his obligation to pay that bill.

That doesn't tell the whole story, however. When I asked my father years later why he waited so long to accept a frontline medication, he explained to me that it caused weight gain. That belief was not accurate, but

his fear of fatness had its own causal power. My father was afraid of the medicine that would have ameliorated the insulin resistance underlying his disease. He attributed that disease to his adiposity, and, in a bizarre twist, he feared that medicine for diabetes would somehow worsen diabetes by worsening his adiposity.

In reading the landmark work of Sabrina Strings, a sociologist at the University of California, Irvine, studying the intersection of racism and fatphobia, I came to realize that avoiding medicines for fear of weight gain was not a rare behavior but potentially a common one. Strings first observed this pattern in people with HIV/AIDS who chose not to take lifesaving anti-retroviral medication due to fear of weight gain.

My father and I had our conversation walking in Audubon Park in New Orleans shortly after he was discharged from the hospital for a geriatric onset of a severe autoimmune disease. He was cachectic but recovering, in a wholly unexpected medical miracle. He told me it was nice not to worry about "those kinds of things anymore." When I asked him what he meant, he explained calmly: He was finally thin.

I've been both fat and thin in my life. I've been hospitalized for a gastroenterological problem and have seen "obesity" in my chart. It didn't feel good — nor did the curt, and incorrect, admonishment from a fellow medical student that I shouldn't be looking in my own chart. We never did learn what caused my illness, neither during the first nor the second hospitalization. I offered my own theory: serious psychosocial stress brought on by the strain from illness in the family, medical school and the recent loss of a dear friend. That didn't garner much interest. I don't think I received substandard care, but I know "obesity" was in my chart. And I know the profound emotional pain I was experiencing wasn't. Whether in an article title or a medical chart, what we record reflects what we value and what we imagine to be reasonable causes of disease.

Chronic disrespect

Medical provider bias against larger people is endemic. In a survey of 4,732 first-year medical students, approximately two-thirds endorsed explicit biases against fat people. Where do they learn those attitudes? I know that some studies show mortality in larger people with high cardiovascular fitness is no different than in lean people who do not exercise, but I didn't learn that in class. In medical school, I was taught a different, seemingly fundamental truth: "Let's be honest and straightforward here. Most people are obese because they eat too much. Period, moving on, next sentence."

I play that audio back for myself sometimes; its blaming bigotry is so plain, so jarring and so unthinking. We should worry deeply about the effects of that kind of bias, offered with neither shame nor awareness, on our understanding of human illness. I heard those words in Alabama, a state marked by extreme inequity and extreme health disparities. That context was missing. Period. Moving on. Next sentence.

Missing pieces

I care about preventing and treating diabetes. Most of our preclinical research on diabetes focuses on dietary causes. I use these research models too; they have great utility at times. High-profile journals publish

Two views of the perimeter of a Superfund site in Birmingham, Alabama. These coke foundry plants are at the intersection of 35th Avenue North and F.L. Shuttlesworth Drive, a road named for a leader of the civil rights movement. Resident organizations such as People Against Neighborhood Industrial Contamination continue to fight for health and safety from this pollution.

ROBERT ROSENCRANS

LANCE CHEUNG/U.S. DEPARTMENT OF AGRICULTURE

Researchers at Navajo Technical University, including Robinson Tom, pictured, won a grant in 2018 to develop biosensors for glucose and bisphenol compounds, endocrine disruptors found in receipts from thermal printers and certain plastic bottles and containers.

hundreds of articles a year on high-fat diet. These models are good at making mice gain weight, but I fear they are missing essential pieces of the puzzle.

Most major journals never have published an article on an endocrine disruptor, though these molecules are endemic, though we can readily expose mice to them, though they induce metabolic diseases readily and though they are inequitably distributed — from bisphenol A–lined receipts that selectively poison the blood of grocery store clerks to the smokestacks of the 35th Avenue Superfund site in my own city, Birmingham, Alabama. Inequitable exposure is not the exception; it's the rule.

Comparably, drinking water at prisons in the southwest United States contains unusually high levels of arsenic. Arsenic is a classic beta islet cell toxin, and beta islet cell dysfunction is a necessary event in the transition from insulin resistance to frank diabetes. Where is the research on the epidemic of public poisoning that plays a likely role in exacerbating metabolic disease? Will our research agenda serve these most marginalized members of our society?

Taking responsibility

The models and frameworks used in biomedical research teach us that disease happens to individuals, not communities. We largely understand body weight to reflect an individual dietary choice, and our country builds public policy on that premise. This framework obscures the health impacts of structural violence, whether pollution, chronic stress, neighborhood segregation and disinvestment, or any other mechanism of nonconsensual harm.

I began seriously considering this problem during the intersection of the COVID-19 pandemic and the uprisings for racial justice in the summer of 2020. At that time, I was struck by a publication showing that police violence predicted the incidence of various components of metabolic syndrome, including adiposity.

In marked contrast, Bill Cassidy, a United States senator and medical doctor, attributed racial disparities in COVID-19 rates to preexisting conditions, claiming that systemic racism was only rhetoric and concluding, "As a physician, I'm looking at science." He did not consider the possibility that inequity is a fundamental cause of those preexisting conditions. That wasn't what he saw in the science, or what he was willing to recognize as science.

The readers of ASBMB Today are scientists. I advocate that we, as scientists, think critically about how our understandings of health and disease are used. The research we do, and the research we don't, informs or delays policy actions to address health inequities. Grappling with that truth should fall under the responsible conduct of research. That's all I'm in pursuit of: taking responsibility for the work I do, doing that work responsibly, being responsive to the communities affected by the illnesses I study and how I study them.

It's time to reimagine body weight, a reimagining best achieved by listening to people harmed by the status quo. Their voices share so much context: lifetimes of fear and disrespect. Voices calling for a more equitable society, free from public poisonings, free from police violence. They are calling for context. Perhaps it's time our research agendas put body weight in it.

Robert Rosencrans (robert.rosencrans@gmail.com) is an M.D.–Ph.D. student in the Medical Scientist Training Program at the University of Alabama at Birmingham. Follow him on Twitter: @rfrosencrans.

Challenging science stereotypes with a video game

By Ken Hallenbeck

What was your first lab experience? I clearly recall a 10th grade biology class where we swabbed various surfaces in the lab and cultured the resulting bacteria. Gross! This early exposure to the laboratory helped inform my decision to become a scientist. Others might not see a biochemical reaction in real time until they're taking college courses, if ever.

Research suggests that gendered stereotypes about who can succeed as a scientist or engineer directly impact student career exploration. It makes sense, then, that when girls engaged in learning experiences with a female science, technology, engineering or math role model, a 2020 study by Spanish researchers found that the girls' interest in STEM studies and careers increased.

The demographics of current STEM professionals do not provide underrepresented students with the role models they need to consider STEM careers seriously. It does not take much looking around the lab to realize why. White men are still overrepresented in research, particularly at the management level. Students who explore research careers are unlikely to encounter a role model from an underrepresented demographic. This perpetuates and reinforces preconceived notions about what scientists and engineers look like and places an unfair burden on already overburdened minority researchers to inspire the next generation of scientists.

To break this cycle, TerraPrime is developing a digital game in a laboratory setting that creates a lab experience accessible to all and populated by all. In a virtual world, scientists can look and act now as we hope the broader scientific world will in the future. Students can see themselves in their player characters and simultaneously explore a laboratory setting that might be out of their real-world reach.

Our game, titled Research Rush, is played as a 3D top-down view of a biochemistry lab. Players create their own scientist and then run around a lab, interacting with instruments to generate resources and gain experience. Gain enough of both, and players can expand the lab and build new instruments.

In Research Rush, we have reimagined lab protocols as video game quests. Players either can create their own lab adventure in free play mode or follow a task list that walks them through a research experience such as purifying a protein or cloning a gene of interest. Eventually, each lab scenario will have unique win conditions. Players can challenge themselves to complete their goals in record time and to progress through their scientific career as they level up and unlock new skills, new instruments and new lab space.

You can watch a concept trailer showcasing the gameplay or even play a tiny bit of the prototype version of the game in your browser right now by visiting our website,

This screenshot shows the prototype of Research Rush, a video game that simulates lab research.

KEN HALLENBECK

terraprime.org/research-rush-game, and subscribing to updates.

I dreamed up Research Rush when coronavirus stay-at-home orders went into effect. One day I was doing full-time lab work, and the next I was sitting at home passing the time with my main hobby: video games. I was struck by how similar the progression at the core of video games was to my now-on-pause lab experiments. Soon I was downloading game development software and digging into coding tutorials. The result is a virtual lab and a vision to change the cultural landscape of scientific research, one player at a time.

Now is the perfect time to develop digital learning tools. The past year has introduced significant involuntary changes in education, primarily through remote and internet-based schooling. Implementing new teaching techniques is always challenging, but teachers everywhere are more comfortable now with virtual learning concepts and techniques than ever before. I see this change as an opportunity to introduce students to lab research in a whole new way.

Educational games have been used to enhance learning in a wide variety of situations. However, games are underrepresented in science and engineering compared to computer science and information technology. While makers of commercial video games have partnered with government agencies to expand public engagement, the impact of these collaborations remains limited. At the same time, video and online gaming has surpassed cinema and television as the most consumed media in the U.S. and around the world. Now is the time for research scientists to use video games to engage students and the public more broadly.

TerraPrime is partnering with high school science teachers to design Research Rush. We aim to make the final product a tool that teachers can use effectively in the classroom. To achieve this, we are talking with high school scientific educators and learning what they want from Research Rush. I hope that, in addition to enjoying the game, students soon will be able to see virtual scientists who look and act as they do.

Ken Hallenbeck earned a Ph.D. in pharmaceutical sciences from the University of California, San Francisco, and now is an early drug-discovery researcher. He serves on the board of directors of Relmagine Science, a nonprofit that empowers and connects scientist advocates, and is the life sciences lead at TerraPrime, a consulting firm that works with startups that aim to disrupt scientific publication and education systems. Follow him on Twitter: @kenkhallenbeck.

Rewarding curiosity

What if we started grading students on their ability to ask well-constructed questions?

By Daniel Dries

"The scientist is not a person who gives the right answers, (they're) one who asks the right questions."

— CLAUDE LÉVI–STRAUSS

"What is the white stuff? Where did it come from?" I was in the lab, working on a demonstration I would use as part of an upcoming award lecture. As he watched, my 7-year-old son peppered me with questions: "Maybe they're bubbles. Oh, look — the white stuff is falling down! What happens if you shake it up?"

In the two-and-a-half years since, this once-curious kid has been asking fewer and fewer questions. Instead, he's more concerned with telling me everything he knows. I'm a proud father, of course, but I miss his questions (or, rather, looking up answers to his questions). So what happened?

When I look back on my own time in grade school, I don't ever remember being rewarded for asking a question — not in a letter grade and certainly not socially. My job was to absorb facts and practice skills. Questions advertised my shortcomings, the things I did not know and could not do. Questions interrupted the flow of class, irritating my classmates and teachers alike. Questions implicitly criticized the authority and competence of my teachers. Questions got me into trouble; answers got me praise. But shouldn't my teachers and parents and friends also be celebrating my questions, my vulnerability, my willingness to learn?

While being taught chemistry and biology, I also was being taught to be ashamed of my ignorance and curiosity. Did Levi–Strauss have it wrong? If science is all about asking questions, where do the questions come from? If not from me, then whose questions will I answer? What if I'm not interested in those questions? Do I get a say in what questions I get to answer?

JASON JONES/JUNIATA COLLEGE

Dan Dries works with students in a chemistry class at Juniata College.

"The (person) who asks a question is a fool for a minute, the (person) who does not is a fool for life."

— SOURCE UNKNOWN (FREQUENTLY MISATTRIBUTED TO CONFUCIUS OR MARK TWAIN)

As instructors, we routinely solicit answers — on exams and quizzes, in discussion and in activities. Using answers as tools to identify concepts students still do not understand is problematic, as the answers are tightly constrained by the context of the question. Other techniques, like the muddiest point technique (in which students write down something from the lecture they still find confusing), are a start, but they tend to serve the instructor, soliciting hasty and superficial feedback from students rather than encouraging thoughtful development and refinement of a deep and meaningful line of inquiry.

So if asking questions is a fundamental and, indeed,

indispensable element of scientific inquiry, why don't we teach it? Why don't we explicitly develop capacity for it in our students? Why don't we incentivize it in our grading schemes?

A quick search through the literature returns several articles devoted to student-generated quiz questions or opportunities for student feedback but few devoted to contextualized, authentic inquiry. The dearth of such articles reflects my lived experience as both a student and a faculty member: Questioning skills ranks far behind instructional design, classroom and laboratory activities, assessment of learning outcomes, and building an inclusive learning environment, to name just a few of the teaching establishment's priorities. Moreover, this list of priorities is replete with top-down approaches for which the student is the object.

Imagine for a moment that students had more agency: What if students used questions to drive their own learning, to construct their own understanding of a topic?

"Each time one prematurely teaches a child something (they) could have discovered (them)self, that child is kept from inventing it and consequently from understanding it completely."

— JEAN PIAGET

Cognitive psychologist Jean Piaget recognized that we derive our knowledge from our experiences, the basis of constructivist pedagogies. Knowledge cannot be poured into a capped vessel. Our potential for growth is limited by our curiosity.

"But I have to teach my students the content," I hear colleagues say, as if the only way their students could possibly learn would be from their instructors' lips and/or writing.

Consider a class where you've just talked about the basics of enzymes. You've covered K_M and v_{max} and showed velocity vs. substrate concentration plots. Sure, you could next lecture and set up activities covering Lineweaver–Burk plots and enzyme inhibition. But what if you instead showed your students a Lineweaver–Burk plot with and without inhibitor, told them it was a double-reciprocal plot, and asked them to interpret it?

After a minute or two of befuddlement (and possibly cursing your name), they might look at the axes and ask how the plot is related to the Michaelis–Menten equation. They might even infer the nature and utility of a double-reciprocal plot along the way. They might look for equations that describe a line. They might ask why the slopes of the lines or x- or y-intercepts differ. As they look into inhibitors, they might stumble across Lineweaver–Burk plots as tools for determining modes of inhibition. They might even then learn about the modes of inhibition themselves, leading them to allostery. All the while, they would be constructing their own knowledge by consulting textbooks, websites and one another. And as you listen to (or read) their conversations, you, the instructor, could learn about their misconceptions, graph literacy and problem-solving process, giving you insights into future lessons.

I have applied this inquiry-based approach to my own biochemistry courses. In doing so, I have borrowed from my mentor and former instructor Hal White at the University of Delaware. (And from another scholar: Socrates.) As early as the second undergraduate year, students explore primary articles in teams, using their own questions to drive discovery.

I no longer see blank faces during a lesson or unengaged students during activities — even in 8 a.m. classes. Small-group discussion dominates, and I hop from team to team to hear the questions students are asking (and to ask a few of my own). It's refreshing, it's liberating and it's downright scary at times. Are they getting the content? Are they going to ask me something I don't know? Am I even needed? These questions arise from my own self-doubt, never my students' abilities, and the students and I are all better learners for it.

Over the six years since I adopted it, this method has worked beautifully: As I share in an upcoming manuscript, students perform equally well and show much more critical thinking on exams, with the added benefit of large gains in both science identity and collaborative learning.

"There are no right answers to wrong questions."

— URSULA K. LE GUIN

"We thought that we had the answers, it was the questions we had wrong."

— BONO

If we want students to be curious, we must teach them to ask deep, meaningful questions. To colloquially paraphrase Le Guin and Bono: Garbage in, garbage out. Those few studies in the literature that explicitly ask students to develop authentic questions also note the need for — and the struggles to achieve — high quality. Indeed, similar to Hal White's experiences and those of his peer facilitators, I've witnessed lively conversations grind to a halt when students see no need to move past a superficial understanding of a technique or figure.

For this reason, my students and I spend a significant amount of time writing, critiquing and refining questions — for which the students are graded. More than 10% of their final grade is based on their ability to develop high-quality, contextualized, answerable questions. In addition, students are asked frequently on an exam to develop questions based on a scientific passage. After all, if I'm not asking students to ask good questions, I'm setting them up for failure beyond the classroom, where life rarely hands them clearly articulated questions.

I've found that some of the best questions come from my more middling students; I've also found that some of those who struggle most with questions are the traditionally high achievers. After all, it's the middling students who frequently need to ask more questions and the highest-achieving students who do not. By rewarding inquisitiveness, I'm acknowledging the willingness of students to reveal gaps in their knowledge. This has the added benefit of beginning to level a playing field skewed by students' differences in access to opportunity and resources. Moreover, acknowledging the inherent value of another's question validates that person's right to be in my classroom and the unique perspectives they offer.

"The principal goal of education is to create (people) who are capable of doing new things, not simply of repeating what other generations have done — (people) who are creative, inventive, and discoverers. The second goal of education is to form minds which can be critical, can verify, and not accept everything they are offered."

— JEAN PIAGET

"The important thing is to not stop questioning. Curiosity has its own reason for existence. One cannot help but be in awe when (one) contemplates the mysteries of eternity, of life, of the marvelous structure of reality. It is enough if one tries merely to comprehend a little of this mystery each day."

— ALBERT EINSTEIN

The effort I put into having students develop good questions — and the grading incentives I offer — sends a message to my students: To be a lifelong learner, you must ask questions of the material you consume. Anything less is deferential to power (and ego). Frequently, this power is rooted in whiteness and maleness, and the reluctance of an instructor to be questioned is a fear of being exposed. (Author's note: I know that my own whiteness, maleness and other aspects of my identity give me the personal and professional privilege to make such a statement, whereas others feel they cannot. Therefore, I hope we can all acknowledge the power dynamics and privileges that present a barrier to classroom reform and keep these in mind as we support and empower our colleagues who engage in pedagogical risk-taking.)

And isn't asking questions something that good scientists — and good citizens — do? Listen, research, formulate an understanding and question existing knowledge? Anything less is pedagogical despotism.

So start asking your students to generate questions. Look at what your students come up with, and ask how you might build your students' capacity to ask better questions. (In their 2014 paper, "Student-generated reading questions: Diagnosing student thinking with diverse formative assessments," Erika Offerdahl and Lisa Montplaisir provide several lenses through which to do so.)

Reawaken your students' childhood curiosity and empower them to question what they are told. But most importantly, listen to their questions: You might just learn something.

Daniel Dries (dries@juniata.edu) is an associate professor of chemistry and biochemistry at Juniata College in central Pennsylvania.

Building a scientific community one meme at a time

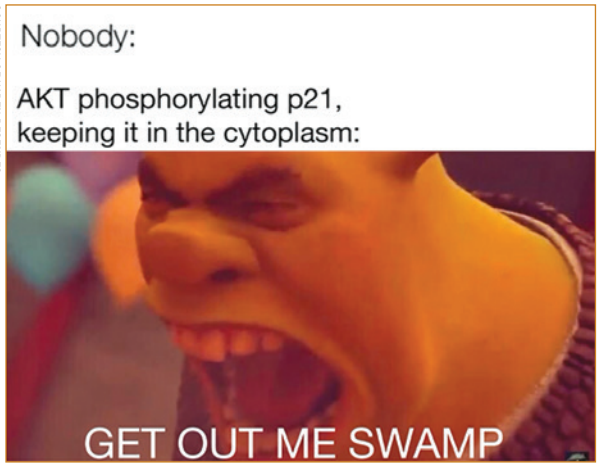
By Karen K. Resendes

Memes snuck into my classroom in a very unassuming way just three weeks into my spring 2020 cancer biology course. At the end of a class period, in response to an informational email from me, student Tyler Snodgrass replied all, not with a question about lab but instead with a Shrek meme, poking fun at the topic of a tumor suppressor we had just discussed.

At the time, I mostly heard a lot of giggling as the students filed out of lecture, but later I learned I could use memes to get students to explain concepts. For example, student Annika Erdely later described the Shrek meme: "AKT is the molecule that phosphorylates p21, which sequesters it in the cytoplasm. Typically, p21 enters the nucleus, but AKT phosphorylates it to 'keep it out of the swamp' (i.e., the nucleus)."

This wasn't a one-off event. By the end of the week, seven more emails, each with a new meme, had been added to the thread. With that, a semester-defining phenomenon had begun.

The abrupt transition to online learning in spring 2020 and the awkward blend of in-person and virtual learners in the subsequent semesters forced me to reconsider how I encourage community among my undergraduates. Student engagement with peers and faculty mentors in the classroom can build the baseline for their interactions with both scientists and nonscientists after graduation. I emphasize the idea of the classroom as a scientific community in the guidelines for scientific communication projects in my undergraduate cell and molecular biology courses, noting, "This assignment involves presenting to other scientists: your fellow classmates and myself."

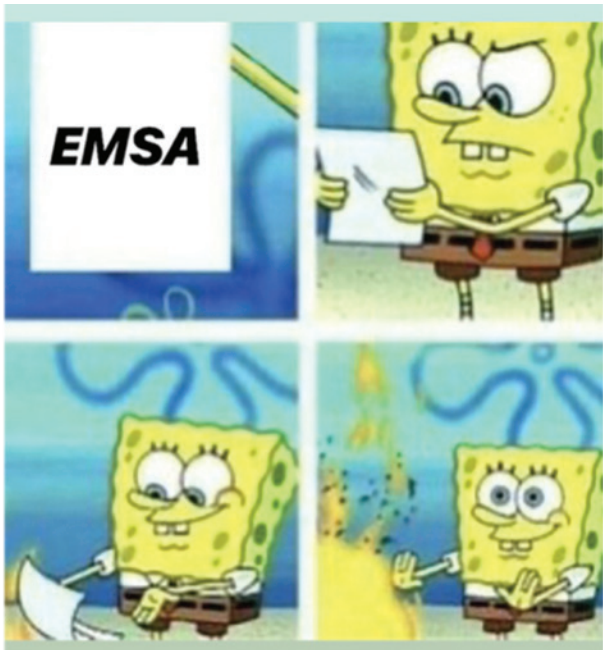


COURTESY OF KAREN RESENDES

As the pandemic changed how the classroom looked and how we all interact, I had to adapt my way of engaging students in learning and communicating with their first scientific community. I'd like to say I had an epiphany for overcoming the hurdle of not being physically together, but in reality, my students handed me the best idea. Their solution was one I never would have contemplated and likely might even have dismissed — using memes. As you probably know, a meme is an amusing or interesting image (such as a captioned picture or video) that is spread widely online. That first Shrek meme led to an email thread where I encouraged (but did not require) students to share class-related images with the group.

These memes not only provided a creative outlet for students to explain scientific concepts to one another but also helped to build a much-needed community. In addition to memes related directly to content, students began creating memes about the online course experience and other difficulties, taking solace in their shared disruptions and struggles. These ranged from the stress of being a senior to the stress of the pandemic, using the "red button" meme, to joking about course topics and methods that the students had difficulty mastering. For example, when Annika Erdley created and shared a SpongeBob SquarePants electromobility shift assay meme, senior Taylor Gatesman commented that it was "an accurate description of how the students view EMSA — no-one knows how to read one correctly." In an end-of-semester survey, all the students strongly agreed that meme use helped them maintain a feeling of class community when we were physically separated from one another.

Beyond developing community and communication,



COURTESY OF KAREN RESENDES

this student-generated activity turned out to be a novel method for learning and reviewing content. Students felt that developing memes helped them internalize biological concepts. Using memes helped them connect to the material and make the course content more interesting and accessible. Even those less interested in creating memes themselves said that reviewing the work of others helped them study and was comparable to making diagrams or reviewing notes.

One class favorite was Natalie Horstman's depiction of the DNA repair enzyme MGMT, which she creatively described, "If an alkylating agent tries to alkylate DNA, MGMT is able to combat the alkylation (hence the punching)." Her classmate Rachael Woessner responded: "I still laugh about it to this day, and I'm pretty sure I will always remember MGMT and DNA."

COURTESY OF KAREN RESENDES

After the spring 2020 semester, I began to consider how I could build on the momentum memes brought to my pedagogy. In my fall cell and molecular biology course I introduced bonus meme activities and contests, which helped to build rapport between the mix of in-person and virtual learners. The students from the spring course, including those who had graduated, were invited to participate as well, connecting students and recent college alumni to a broader community. The new students became comfortable in their peer group and networked with older peers.

These exercises built confidence and helped ease my undergraduates into the required communication assignments in the course, including data-focused Zoom discussions and presentations. Again students told me that creating and exploring memes provided a unique avenue to study detailed pathways or concepts. As such, I hope to keep exploring and developing the use of memes across my courses.

In a broader context, how does my example of stumbling upon a new pedagogical tool lead us to reimaging scientific education, community and communication? My meme experience suggests we should consider following the lead of undergraduates, the newest members of our scientific community.

Memes can help us begin to broaden our image of scientific communication and concepts, forcing us to think about the multitude of goals behind building our ability to explore science and share it with one another. Beyond that, it's as important to consider outreach to the general public as it is to share within the scientific community.

Finally, I think using memes can push us as faculty, as well as our students, to consider approaching science as we would other social aspects of our lives. Memes help us think creatively about how to build and share our knowledge with each other and with nonscientists to help make science a topic that is relatable and not feared.

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The STEM Academy: A necessary remedy to med school tunnel vision

By Brian O'Flynn

The term "premed" fascinates me. Over my six or so years in the U.S., I have come to understand it as a choice — a personal contract signed by thousands of incoming undergraduates that says, "In four years, I WILL be going to medical school." This hypermotivated tunnel vision is comparable to that seen in many musicians, artists and athletes: "I must dedicate myself entirely to my craft. There can't be a Plan B. There can only be a Plan A."

This mentality is due to what we are exposed to growing up. Pop culture makes arts and sports seem like appealing and lucrative paths. Prestige in these professions requires complete dedication and commitment. But who are the rock stars of the science world? Naturally, we turn to the caregivers and lifesavers who have a personal impact on our lives to fill this role. Even in the fictional worlds of TV shows and movies, we rarely see health care workers depicted as anything short of heroic. The past year has emphasized this as nurses, doctors and surgeons with bruised faces and weary eyes but determined smiles became the human manifestation of our fight against COVID-19.

And where does that leave researchers — those who strive to improve the world through discovery and innovation? They seem to be somewhere in the supporting cast or, if social media conspiracy theorists are to be believed, even not to be trusted.

How many 10-year-olds want to be researchers? Never mind that, how many incoming undergraduates? Students are rarely exposed to scientific research in their early college years, and that produces a net loss to the pool of potential researchers and thus to scientific advancement. Personally, I was introduced to this path by an attentive professor who could see I thrived in the lab. (The offer to move across the Atlantic to Florida for graduate school just happened to sweeten the deal.)

COURTESY OF RICHARD POLLENZ, UNIVERSITY OF SOUTH FLORIDA

The 2018 STEM Academy cohort poses together at the University of South Florida. The innovative program for first-year students was introduced at the university in 2015 by biology professor Richard Pollenz and supported by the Howard Hughes Medical Institute.

More emphasis must be placed on steering undergraduate science majors toward understanding that being a medical doctor is not their only option.

This was the central dogma of the STEM Academy, a program introduced at the University of South Florida in 2015 by biology professor Richard Pollenz and supported by the Howard Hughes Medical Institute. At its core, the STEM Academy was a one-week camp held before the fall semester. Incoming science, technology, engineering and mathematics undergraduates from all backgrounds were placed in groups of 24, each group under the guidance of a graduate mentor and four undergraduate mentors. Special emphasis was placed on diversity and inclusion, as those who benefit the most from such programs are those most often overlooked. Throughout this week,

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Academy scholars Camilo Plata, Serena Patel, Morgan Matalaga and Kristin Luongo testing their reflex times under visual and physical stimuli during an Academy physiology lab.

the students participated in exercises, lab experiments, workshops and seminars. The goals were to instill a sense of belonging to the STEM community, to expose students to the wide range of career options and paths available, and to introduce the concept of research.

I was a graduate mentor in the second iteration of the academy in 2016. Some 250 students worked with 10 grad student mentors and a slew of undergraduate mentors. The week was long — starting at 8 a.m. most mornings and usually not finishing until about 8 p.m. — and included three main components: technical development, professional development and personal growth.

Many students had their first exposure to experimental science during the technical development portion, which also covered data analysis. The experiments were lighthearted, such as extracting DNA from strawberries or distilling limonene from oranges using dry ice.

Professional development included CV workshops, research lab tours, discussions on getting involved in undergraduate research, meetings with professionals and learning about career opportunities outside the medical field — all in a fun and engaging manner. For example, students met with a different professional every 10 minutes in "Career Speed Dating."

These first-year college students underwent significant changes in one short week. From a professional standpoint, they now understood that their choice was not medical school or bust. We also saw emotional growth in almost all the students. They made close, potentially lifelong friends, and being in a structured environment with likeminded people pushed even the most introverted to come out of their shells. To encourage this further, the evenings were reserved primarily for reflecting on how they felt about the day's activities and about the students' individual experiences. We usually ended with games to

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STEM Academy coordinator Richard Pollenz and graduate mentor Haley Hanson peer through foldscopes — cardboard microscopes assembled by students in the academy.

UNIVERSITY OF SOUTH FLORIDA RESEARCH & INNOVATION

Academy scholars Marlana Grant and Brianna Nicholas filter the pulp from strawberries — the first step in extracting the fruit's DNA.

decompress after a long day.

The program was structured to prioritize inclusion and camaraderie. I was consistently delighted to find that those who barely looked me in the eye on Sunday would recognize by week's end that the academy was an opportunity to share experiences and create friendships. One evening we asked the students to explain what motivated them to enter the STEM world. One took all 300 of us on her emotional journey of coming to terms with being transgender and how that pushed her toward a medical career. Another told us how math and science became his new passion after a torn knee ligament ended his promising baseball career.

On the first and last days of the academy, we asked each student to write down five words describing how they envisioned their upcoming time as an undergraduate. I like to think there is some correlation among the words mostly chosen by the students before and after the academy. Anxieties become opportunities. Medicine becomes graduate school. People become friends.

I was a mentor for four iterations of the STEM Academy, from 2016 until my final defense in 2019. Every year I met students who reminded me that the kids really are all right, and I consider the STEM Academy the most fulfilling part of a very pleasant stint in graduate school. An added bonus came when students who started as premed realized they had a passion for research. Several even became undergraduate researchers in my lab, earning authorship on publications. Students who chose to continue on their premed path were now better equipped both to be more competitive, thanks to early experience in undergraduate research, and to view future experiences as alternative career opportunities.

The HHMI funding was for five years, so 2019 was the final year for the STEM Academy. Many of us hoped the university would see the obvious merits to continued funding of Dr. Pollenz's program; retention rates for STEM Academy students were significantly higher than a matched comparison group, with 98% first-year retention and 92% STEM major retention. Additionally, data from the 2015 cohort showed that 68% of underrepresented minority students (Hispanic and Black) in the academy were retained in STEM compared with 49% for the matched group.

No funding came. The STEM Academy was a short-lived but wonderful program whose legacy lives on through the 1,000-plus students and mentors who experienced it and have the lab coat and memories to prove it.

While metrics such as retention can be quantified, the true effect of such a program is felt in the quality of researcher that it produces. By focusing on how students perceive research and introducing them early to basic concepts, the societal perception of science as a whole can be reimagined, and we can begin to view not just those with stethoscopes as biomedical rockstars, but also those with pipettes.

UNIVERSITY OF SOUTH FLORIDA RESEARCH & INNOVATION

STEM Academy scholars use their newly assembled foldscopes to explore and photograph the University of South Florida campus at a microscopic level.

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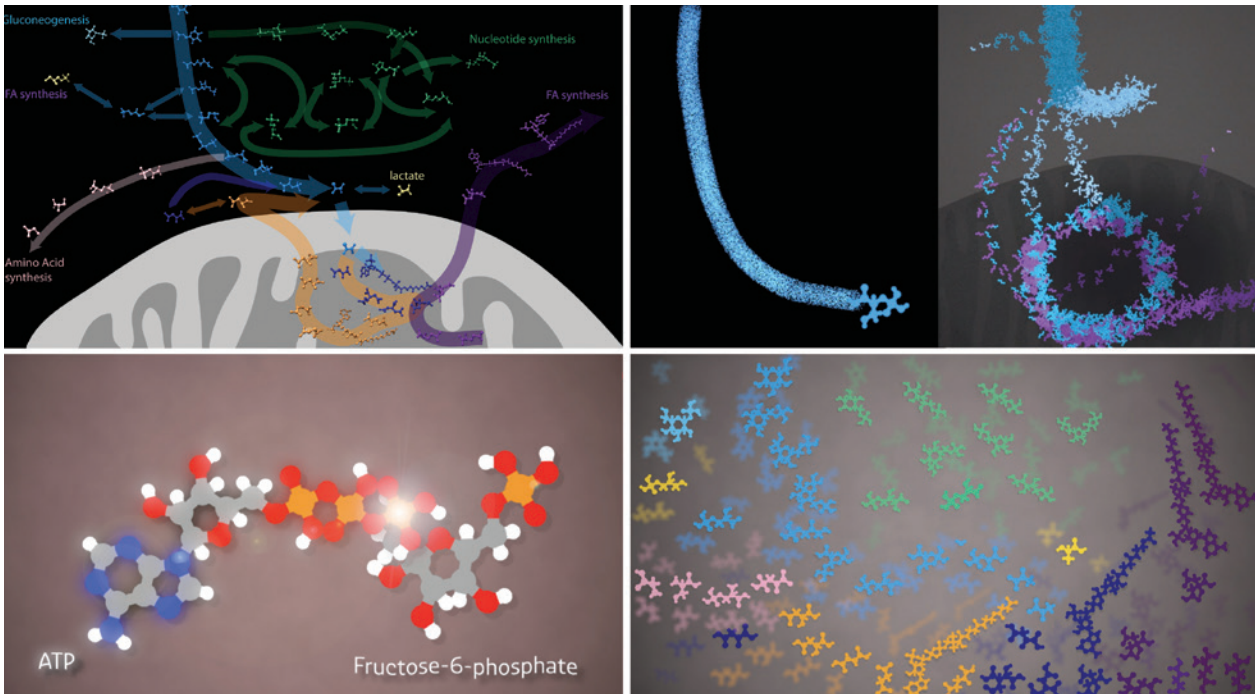
In a constant state of flux

By Shraddha Nayak

COURTESY OF SHRADDHA NAYAK



The author made these snapshots while she planned and explored. Note a few depictions of flow in terms of the path metabolites follow. She experimented with 3D and 2D structures of metabolites and colors to represent them. She tried out a few ordered and disordered arrangements of pathways as well.

As soon as I joined the Animation Lab at the University of Utah Department of Biochemistry in early 2019, Janet Iwasa, the head of the lab, challenged me to visualize the flow of metabolites. Although metabolic flux was unfamiliar territory, the biochemist in me leaped at the opportunity.

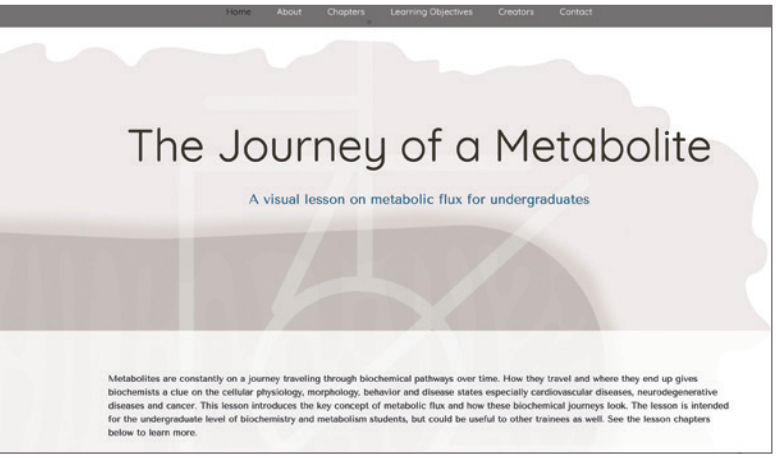
A subset of biochemists studies metabolic flux, tracing metabolites through biochemical pathways in our bodies; how they travel through these pathways can change as conditions change, especially during disease. Although mathematical tools exist to compute flux and visualize it in the context of complex pathways, there is no simple way to visualize metabolites' dynamic journeys intuitively. Greg Ducker, one of our scientist collaborators who studies flux, emphasized this. Ducker and Jared Rutter at the University of Utah School of Medicine were interested in visualizing how flux changes during cancer. Thus began my own journey to imagine a way to do that.

For a couple of months, some questions floated around in my mind: How do I represent metabolites? How do I depict cellular compartments? How do I show flow — would trails be formed by the metabolites? Should I make the pathways random, as they are in reality, or should I follow current conventions? For example, should I use a circle to represent the tricarboxylic acid cycle, something biochemists are already familiar with? I wanted to keep the audience in mind and consider what would be most intuitive or useful to them. That was a challenge.

Change in flux

And then we were enveloped by the pandemic. I began to see COVID-19–related data visualizations in public media. The New York Times came up with a remarkable visualization showing the flow of infected people from Wuhan, China, to neighboring countries and other parts of the world.

Naturally, I envisioned carbon from glucose moving from outside the cell to different compartments or through various pathways. I was inspired to revisualize



COURTESY OF SHRADDHA NAYAK

The screenshot shows a portion of the website home page that hosts the metabolic flux lesson.

and use roads as a pathway guide to the viewer. This was not a new concept; metabolism educators often use Google maps and traffic to convey the concept of flow of metabolites through networks.

I developed a pilot animation of carbon flux through the central carbon metabolic pathways using flux data from published research. I excitedly presented it to our scientist collaborators. However, we soon realized this might not be useful to them if they are unable to customize flux input and pathways for their own research study. But could it be used to teach the concept of metabolic flux to trainees and students?

Thus was born the idea of a short lesson around this animation: "The Journey of a Metabolite."

Flux can go both ways

We harnessed the power of social media — Janet Iwasa's Twitter community — to find potential educator collaborators who would provide input on the lesson. We received an overwhelming response and realized that science instructors need reimagined visualization in metabolism. A group of talented and driven educators of undergraduates exposed me to the world of teaching and suggested that we include instructions to educators, add illustrations of a few individual pathways before showing an integrated view with all pathways, connect the material to examples used in classrooms and make sure not to overwhelm students with complexity. I realized that we were only scratching the surface.

Metabolic flux is part of undergraduate biochemistry instruction only in a few cases, perhaps dependent on the instructor. It may be more accessible in institutions that have active flux research infrastructure. I was not exposed to these concepts as a student, and I now believe this fundamental topic could enhance any student's systems-level understanding of metabolism and biochemistry.

In its initial release, the lesson provides an introduction to metabolic flux via several animations. Through five modules, a student can learn:

1. The concept of flux.
2. How carbon flows through common metabolic pathways such as glycolysis, fermentation, the TCA cycle, the malate-aspartate shuttle, citrate to fatty acid synthesis and the pentose phosphate pathway.
3. How these pathways in central carbon metabolism are interconnected.
4. The alteration of carbon flux under conditions such as hypoxia and cancer.
5. How one can measure flux in a lab.

Each module includes instructions for teachers on how to weave these visuals into their biochemistry and metabolism classes, questions for further discussion, and resources to dig deeper in case of piqued curiosity. We hope this free visual lesson can be a valuable supplement to any biochemistry teacher's instruction materials worldwide. We plan to conduct a modest evaluation of our lesson this fall. Explore the lesson at biochem.web.utah.edu/iwasa/metabolism/.

To be in a state of flux

Although reimagining education has been a trending topic for a couple of years, the COVID-19 pandemic may have accelerated this process. Researchers and educators have been forced to think how they can use rapidly evolving technologies for learning and student engagement when students are not in the classroom or lab.

Visual lessons such as the one we have developed can be incorporated easily into hybrid learning models (a mix of flipped, blended, remote, distance and online learning). We as scientists, educators, and teachers need to be flexible and adaptable. We need to re-think meaningful ways to deliver important and difficult science topics to trainees so they continue to comprehend and be inspired and engaged.

Shraddha Nayak (shraddha.m.nayak@gmail.com) is a postdoctoral fellow in the Animation Lab at the University of Utah. She earned her Ph.D. in pharmacology and toxicology from the Medical College of Wisconsin in late 2015. Before joining the Animation Lab in early 2019, she freelanced as a scientific illustrator in the United States and India. Follow her on Twitter: @Na_y_ak.

We need to make scientific papers understandable for nonscientists

By Elisabeth Adkins Marnik

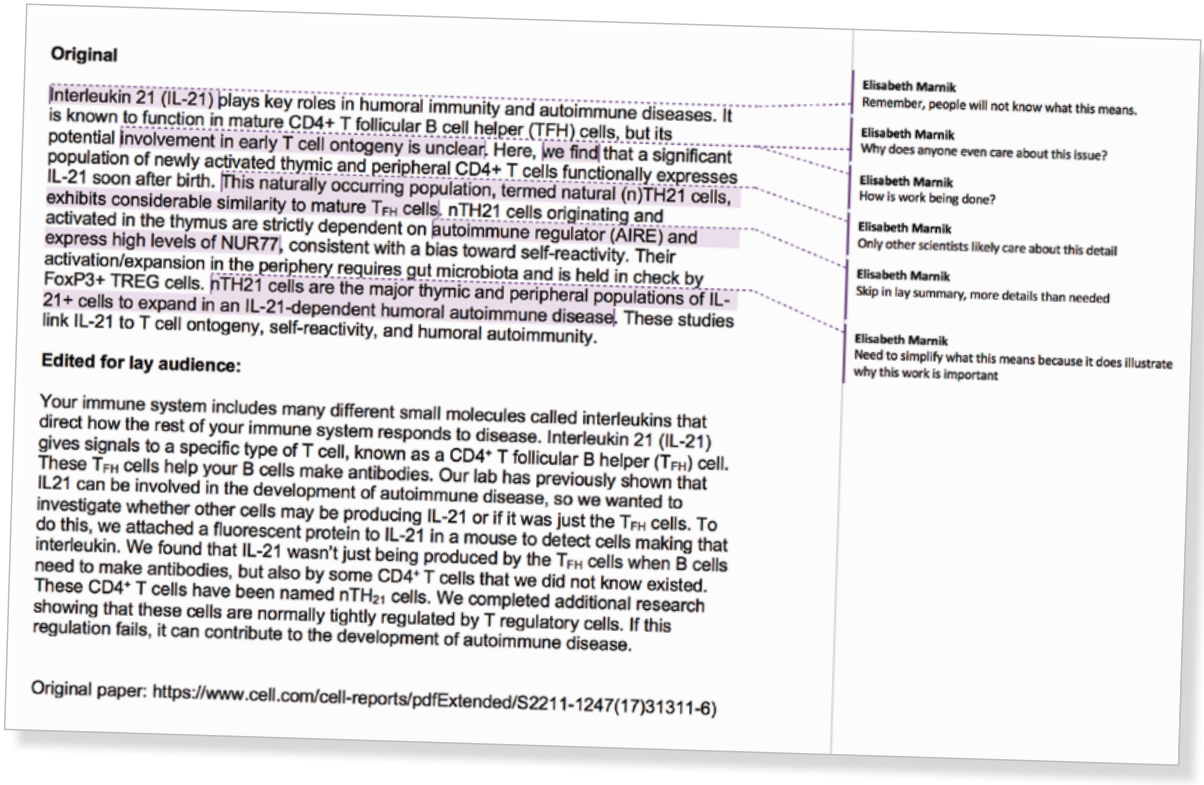
The COVID-19 pandemic has put science in the spotlight. Many people have been waiting on science to save the day. On the other hand, this pandemic also has laid bare the skepticism many people have about the scientific community. This has been illustrated by debates over the effectiveness of masks, arguments over hydroxychloroquine and distrust of vaccines. I believe this skepticism has many causes, but one is undoubtedly our failure to communicate.

As scientists, we are usually behind our lab benches and computers. We are not always good at getting understandable science out there for public consumption. Instead, people rely on the media and alternative sources for their scientific information. Sometimes this works out fine because their sources are reliable. Other times, it ends in disaster and erodes trust in science. No wonder the public doesn't understand or trust scientists. People spouting misinformation are much more accessible and understandable. So what can we do about this?

For starters, the public is not well equipped to understand the information we publish, because it is technical and full of jargon. This makes going to the source — our publications — virtually impossible for the general public.

Thus, they turn to the other sources mentioned above. We need to use the pandemic as the catalyst to change this.

Scientific journals should implement a requirement that scientists submit a short layperson summary to be made available online with the publication. This summary would provide the general takeaways from the data and its significance in ways that are widely understandable. This would make it more difficult to twist or blatantly lie about scientific information. People could



Original

Interleukin 21 (IL-21) plays key roles in humoral immunity and autoimmune diseases. It is known to function in mature CD4+ T follicular B cell helper (TFH) cells, but its potential involvement in early T cell ontogeny is unclear. Here, we find that a significant population of newly activated thymic and peripheral CD4+ T cells functionally expresses IL-21 soon after birth. This naturally occurring population, termed natural (n)TH21 cells, exhibits considerable similarity to mature T_{FH} cells. nTH21 cells originating and activated in the thymus are strictly dependent on autoimmune regulator (AIRE) and express high levels of NUR77, consistent with a bias toward self-reactivity. Their activation/expansion in the periphery requires gut microbiota and is held in check by FoxP3+ TREG cells. nTH21 cells are the major thymic and peripheral populations of IL-21+ cells to expand in an IL-21-dependent humoral autoimmune disease. These studies link IL-21 to T cell ontogeny, self-reactivity, and humoral autoimmunity.

Edited for lay audience:

Your immune system includes many different small molecules called interleukins that direct how the rest of your immune system responds to disease. Interleukin 21 (IL-21) gives signals to a specific type of T cell, known as a $CD4^+$ T follicular B helper (T_{FH}) cell. These T_{FH} cells help your B cells make antibodies. Our lab has previously shown that IL21 can be involved in the development of autoimmune disease, so we wanted to investigate whether other cells may be producing IL-21 or if it was just the T_{FH} cells. To do this, we attached a fluorescent protein to IL-21 in a mouse to detect cells making that interleukin. We found that IL-21 wasn't just being produced by the T_{FH} cells when B cells need to make antibodies, but also by some $CD4^+$ T cells that we did not know existed. These $CD4^+$ T cells have been named nTH_{21} cells. We completed additional research showing that these cells are normally tightly regulated by T regulatory cells. If this regulation fails, it can contribute to the development of autoimmune disease.

Original paper: https://www.cell.com/cell-reports/pdfExtended/S2211-1247(17)31311-6)

Elisabeth Marnik
Remember, people will not know what this means.

Elisabeth Marnik
Why does anyone even care about this issue?

Elisabeth Marnik
How is work being done?

Elisabeth Marnik
Only other scientists likely care about this detail

Elisabeth Marnik
Skip in lay summary, more details than needed

Elisabeth Marnik
Need to simplify what this means because it does illustrate why this work is important

go directly to the source without having to rely on the interpretation of the media or other individuals.

Writing a lay summary is a lot of work, and some scientists might not be happy with this requirement. However, this pandemic has taught us that the status quo is not acceptable. If we continue to make science hard for the general population to understand, distrust of science will only increase. We need to take an active role in changing this. Giving the public access to the data in a way they can understand is an important starting place.

You may be wondering if people actually would care and read the research. This is a slightly different example, but a few months ago I shared a post on my science Instagram that summarized the current data we have from papers and preprints on how much COVID-19 vaccines may reduce asymptomatic COVID-19 cases. I did it just focusing on the findings in the papers related to that information. After only three days, the post had reached 12,100 people. Of all my posts, this one had the most views and shares. Why? I believe it is because people want to understand the data; it's just hard for them to do. Weeding through complicated papers to find the important parts is not something most people can do without formal training.

So what could this look like in practice? Many of us need to write short layperson summaries when we submit grant applications to the National Institutes of Health. This would be an extension of that. I envision a one- to two-page summary max. The goal would be to make the key findings, data and significance understandable to those without formal scientific training. This could be done via bullet points, full paragraphs, illustrations or perhaps a combination of all three. Scientists would need to avoid jargon or to carefully define the jargon that is necessary. Researchers even could link to background information that could be helpful if the reader wants more resources on the topic.

Is this a perfect solution? No. Will it require more work from us? Yes. But making science understandable to the general public is necessary and could help us avoid, or at least mitigate, the next public health crisis.

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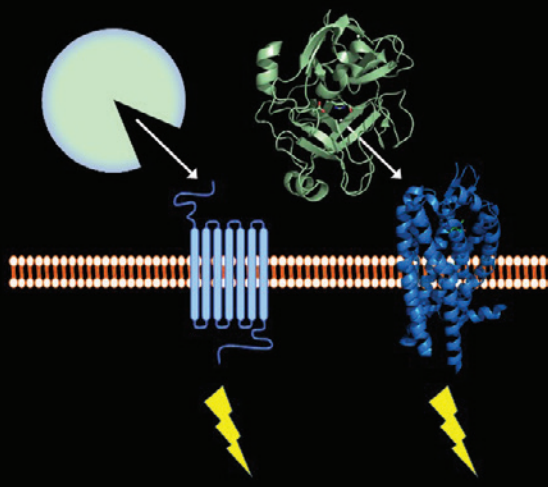

Rethinking the NIH review system

Some modest (and some not so modest) proposals

By David A. Gewirtz

Winston Churchill famously noted, "It has been said that democracy is the worst form of government except all the others that have been tried." I would not say the same about the system of reviewing and funding grants at the National Institutes of Health. In fact, I am fully confident that the NIH has made every effort over the years to be as fair and equitable as possible. However, as with all enterprises that involve fallible human beings, it is not perfect; if asked, both applicants who have succeeded in generating research support and those who have failed in this regard (likely especially those who been unsuccessful in successive rounds of submission) would have much to say about what they perceive as the system's deficiencies and would have suggestions for its improvement.

As a long-time reviewer as well as an applicant who has failed more often than succeeded, I have undertaken the perhaps Sisyphean task of making suggestions that in my mind might be worthy of consideration. I have divided this article into three sections: (1) changes that I believe could be considered and instituted now; (2) serious suggestions for future consideration; and (3) a few more provocative ideas.

Immediate changes

A tiered system of funding: My first suggestion relates to leveling the playing field. It has always struck me as quite unfair that nascent assistant professors, attempting to obtain their first competitive extramural grant, often are competing with full professors who have years of experience and publications behind them and are likely supported by large and productive laboratories.

Many years ago, some agency (in this case not an NIH review panel) decided to award additional funds to currently funded researchers in a particular cancer-related area. By far the best grant was submitted by a very well-known and high-profile investigator whose laboratory at that time was supported by approximately $4 million in grant funding. Of course, an unbiased review resulted in this being the highest scoring grant, and I do not disagree with the evaluation of the quality of the science proposed. But I could not help thinking how the money awarded to this investigator could have been more useful as a number of smaller grants for young researchers just setting up their first laboratories or early-stage investigators with novel, even if unproven, ideas. It further occurred to me that this individual did not actually need these additional funds and that they could have performed the proposed work using their available resources if they felt that the problem was worthy of investigation.

My solution is a tiered approach. Individuals at different career stages should be able to compete with others at approximately the same career level. That is, assistant professors would compete with other assistant professors, associate professors with other associate professors, and full professors with other full professors. Of course, some tinkering would be needed to reliably define where individuals stood in their career paths, but this could be accomplished quite easily.

The tiering would not be limited to the applicants' career stage. The maximal funding for each level also would have tiered steps, such as three-year grants with maximal direct costs of $150,000 a year for the assistant professor level, four-year grants at the associate professor level at a maximum of $200,000 per year and five-year grants at the full professor level at $250,000 per year. Again, these tiers could be modified after consideration of the different possibilities.

Furthermore, this approach would not prevent an assistant professor from submitting a five-year grant if they felt that they could be competitive with more established investigators. But it would not work the other way around, with full professors dipping into the assistant professor pool of funds. For many years, I have served as the PI at my home institution for the American Cancer Society Institutional Research Grants mechanism that supports junior investigators. It would be a travesty if senior investigators could compete for this same pool of funds.

A tiered approach might have the additional benefit of stretching out the available NIH funds, since, in general,

only well-established investigators would apply for five-year grants.

The R21 mechanisms might be thought to have the same utility; however, the R21 allows for a maximum length of six pages for grant applications; in my experience (and I think others would agree), this is not sufficient to incorporate a comprehensive background, preliminary data and detailed experimental approaches. Although preliminary data is not officially required for an R21, I would postulate that rarely has an R21 been funded without it. I would eliminate this mechanism entirely and substitute the tiered system envisioned above.

The scoring system: The system of scoring from 1 to 9 without intermediate values allows far less discrimination and subtlety than the prior system running between 1 and 5 with the option of scoring by decimal increments.. I strongly advocate moving back to the previous system. Those of us who served on panels in the "old days" could distinguish between a grant that scored at 1.6 and one at 1.4 or better. Any score below 1.5 indicated that the grant fell into the outstanding range and should be considered for funding. The scientific review officers always were required to say that the study section does not actually make funding decisions; however, there was clearly an elephant parked in the center of the room where the grants were being evaluated, since that is precisely what every reviewer was thinking about during scoring phase.

The current scoring situation is one that I personally find quite frustrating. A score of 1 is rare as a hen's tooth. A score of 2 means "Yes, clearly support the grant for funding." A score of 3 means "Good try, you came close, but you aren't going to get the money; still, it's likely worth trying again." A score of 4 means "Unless you come up with some new ideas that will blow our socks off, a resubmission is probably not worth the bother." And anything above a score of 5 largely adds insult to injury.

But what happens when the scores for what might be termed competitive grants fall between 2 and 3, as is likely often the case? The panel members who scored at 3 may have considered the proposal to be relatively strong but not ready for prime time. Perhaps a panel member made an offhand remark that diminished its worthiness in the minds of the group. Panel members scoring at 2 may have felt some of the same reservations as those who scored at 3, but being unable to score at 2.3, 2.4 or 2.5, these reviewers gave the applicant the benefit of the doubt. Similarly, the panel members who scored at 3 also might have wanted to place the project between 2 and 3 but were unable to do so.

The innovation criterion: I expect serious disagreement with this suggestion but would argue that this criterion should be eliminated. The innovation criterion largely provides an effortless mechanism for reducing the enthusiasm for a grant, with little relevance to the potential value of the proposed research. A grant can be highly innovative yet have little chance of succeeding due to other deficiencies. More importantly, to my mind, a grant need not be innovative to have significant and groundbreaking impact. I suggest that this criterion be replaced by one such as potential impact, and see the sections below relating to the significance criterion.

The environment criterion: The criterion of environment should not be scored. A reviewer might simply indicate whether the environment is adequate for the proposed research. In the rare cases where the environment is deemed to be inadequate, the grant could be eliminated from consideration.

Page length: Twelve pages is far too short for effective presentation of preliminary data, background and approaches with alternative strategies. I am not suggesting we revert back to the 25-page limit. However, 15 pages would be more realistic for an RO1. The Department of Defense recently increased its limit to 14 pages. Perhaps 8 pages for an R21.

Furthermore, one page is insufficient to respond to criticisms of the previous submission. Two pages should be allowed, which is still less than the previous system's three-page response.

Suggestions for future consideration

The significance criterion: I don't have a problem with this criterion other than its vagueness. Why not substitute something more straightforward, such as "scientific rationale," with wording such as "To what degree do the preliminary data support the proposed approaches?" or "Does the literature provide a sufficient foundation for the proposed studies?"

A related issue — the premise: For a while, the NIH imposed its own definition on this terminology but

could not sway reviewers from the standard meaning and finally gave up on trying to convince the reviewers that "premise" did not actually mean the underlying foundation for the grant. According to my dictionary (I guess in actuality Google), a premise is what forms the basis of a theory or a plot. In logic, the premise is the basic statement upon whose truth an argument is based.

Makeup of the panels: Recently, the NIH decided to temporarily sideline reviewers who had reviewed a set maximum number of grants during the previous 12 years. I believe this was a consequence of complaints from applicants who observed that certain names frequently appeared on the roster of study sections where their grants had been reviewed and not funded. This led to the impression that perhaps their grants were not receiving a fair review, since the same panel members might have been involved repeatedly.

I don't recall ever reviewing the same grant twice, although I cannot speak for other panel members. But I don't believe this is a productive strategy. Experienced reviewers provide the foundation for the most solid and sound review process and should be recruited with enthusiasm. (Yes, of course I can't wait to be invited back.)

A few more provocative ideas

Unscientific critiques: What can be done about absurd or inflammatory critiques? All of us have received review comments that clearly came from left field and had no relevance to the topic at hand. Inappropriate or irrelevant criticisms of this type should be parsed further by NIH personnel and expunged, if at all possible, although I fully recognize the challenge of doing this and further realize how this would delay the delivery of summary statements to the applicants.

Internal review: Does the NIH analyze which types of funded grants have had the greatest scientific impact? I believe this would be a highly productive exercise, and perhaps this has been occurring at intervals throughout the history of the NIH. There long has been a concern in the larger scientific community that the NIH is fundamentally conservative and largely hesitant to fund novel ideas.

Specifically, should there be fundamental change to what types of proposals are funded? Should there be far less focus on mechanistic aspects of research projects and more attention to the larger potential scientific impact? Should there be greater emphasis on supporting higher risk/higher gain projects? Should the NIH identify specific areas of need and solicit grant applica-

tions for these areas rather than allowing for the currently broad nature of the grant solicitation process? Should there be a secondary level of review, as is the case with the Integration Panels at the Department of Defense research programs, where grants scored in the outstanding range by the review panels have frequently not been funded?

I am not advocating for any of these approaches but only suggesting that these could be considered. Furthermore, in the case of a second level of review/oversight, there could be a real danger that the funding process could be politicized.

Continuous submission: For a number of years, continuous submission, which allowed applicants an additional time period (I believe about six or eight weeks after the standard due dates) for grant applications to be submitted, was one of the few perks provided to scientists who had given generously of their time and expertise to review a certain number of grants or serve on a certain number of panels during the course of a year. It recently has been eliminated, unfortunately entirely without explanation. Living in Richmond, Virginia, it was always fairly easy for me to attend study section meetings in the Washington, D.C., and Maryland area. But I very much admired those reviewers who lived on the West Coast and their commitment to carrying out this service. This perk should be reinstated.

Conclusion

I believe that our system of study section reviews and funding approaches is, like democracy, fundamentally strong. It has weathered both good and bad times, has withstood potential external interference and is overseen by scientists with the goal of supporting research that will improve the lives of our citizens. One can only marvel at the speed with which the COVID-19 vaccines were developed. We have to be grateful to industry but must at the same time acknowledge that these breakthroughs never would have been achieved in the absence of decades of basic research supported by the NIH in many disciplines. But this does not mean that we should become complacent and fail to consider how the system might be further improved.

Jack Yalowich at the Ohio State University read drafts of this manuscript and made insightful comments and suggestions.

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Can an engaging online workshop replace the in-person experience?

By Audrey Shor & Josh Beckham

BioMolViz is a community of educators who promote instruction in visual literacy. We host community-building workshops where faculty share tools for teaching biomolecular visualization and learn to write effective visualization-based assessments in teams. The assessments are designed to probe students' visual literacy, and the work in teams builds diverse connections and collaborations within the biomolecular visualization community.

When the SARS-CoV-2 pandemic hit, we had to figure out how we could engage participants in applied, hands-on workshops that didn't feel like just another Zoom meeting. To succeed, we needed to provide support for BMV educators and maintain a community of practice for the explicit instruction of visualization. Thus, we aimed to continue to foster the sense of community in the online space that we had worked so hard to build in our in-person workshops.

How could we reimagine the hands-on workshop experience in a virtual space? How do we take advantage of the benefits of online meetings to create valuable experiences? These adaptations have the potential to deliver professional development opportunities in a more inclusive manner. Educators who find travel challenging now have a world of training available from their homes.

Before March 2020, our core group operated as a dispersed team with members located across the country, so we knew how to work remotely. We had an online workflow that enabled us to collaborate, publish papers and secure funding. We modeled our remote workshop on these team experiences.

First, taking a lesson from our group's weekly remote meetings, we used the workshop agenda document as the launching place for all links, handouts and collaborative documents. This way, participants had one centralized file for all activities, from joining the Zoom meeting to developing their own assessment in groups.

To keep participants engaged, we decided that presentations needed to be brief, with a good balance of interactive activities. We provided a short introduction to each topic, immediately followed by an immersive experience intended to allow participants to put the idea into practice. For example, we integrated short breakout sessions of about 10-15 minutes where three to five participants shared an assessment question they've used in their teaching and matched it to our BioMolViz Framework, which details 12 overarching themes in visual literacy, 27 learning goals and 119 learning objectives.

We approached community building in several ways. We asked participants to introduce themselves using three photos, and we allotted significant time for introductions. At small working sessions shuffled between the main sessions, participants could interact and collaborate with new faces. We built in an optional morning coffee talk to start the day and an evening happy hour where participants could informally share their personal projects and visit in a low-key atmosphere.

BIOMOLVIZ

Participants at the last pre-pandemic in-person BioMolViz workshop included, in front, Shanen Sherrer; second row, James Endres Howell, Kristen Procko, Dina Newman, Judy Levine and Pumtiwitt McCarthy; third row, Josh Beckham, Jacqueline Fajardo, Kathleen Cornely and Rebecca Roberts; and in back, Brian Chiswell, Kelly Keenan, Wally Novak, Margaret Franzen, Paul Craig, Julia Koeppe, Dan Dries and Jamaine Davis.

BIOMOLVIZ

A more recent workshop included some of the same faces but in a virtual setting: top row, Rebecca Roberts, Kristen Procko, Shelly Engelman, Dan Dries and Pamela Mertz; second row, Aeisha Thomas, Karin van Dijk, Venkatesh Nemmara, James Nolan and Wally Novak; third row, Alberto Roca, Nik Tsotakos, Charmita Burch, Audrey Shor and Swati Agrawal; and bottom row, Josh Beckham, Ellis Bell, Margaret Franzen and Eva Rose Balog.

We ended the workshops by sharing the assessments that were created during the working sessions. We invited participants to remain engaged beyond the workshop by continuing to develop, enhance and/or vet assessments that will be included in the repository. Several of our workshop participants have continued remote work with us weekly, allowing us to make progress on our repository beyond the workshops.

In preliminary feedback from the two virtual workshops hosted this past winter, participants indicated that they enjoyed the workshops overall and that we met our goals. By the end of their online experience, attendees were able to build the requisite content knowledge, engage with the workshop material, review assessments written at prior workshops and create their own. Participants from both workshops lauded the workshop's organization and commented on our hands-on hosting. However, they had mixed feelings about belonging to the community, and some did not feel the connection to BioMolViz at the end of the workshop that we had hoped for.

Based on this feedback, we believe hands-on interactive workshops can be reimagined successfully in the online format. While a sense of community is not built easily during an online meeting even while engaging small groups and offering social events, it is not impossible.

Going forward, we hope to incorporate more strategies for building community. For example, we are creating multiple touch points beyond the initial workshops so participants can stay involved. The group now hosts semi-monthly Visualization Conversations on Zoom where presenters share their ongoing visualization-based work through informal discussions. And we have extended participant involvement by partnering returning contributors with a BMV steering committee member to work together through the assessment revision process.

We hope these regular interactions will engage participants and establish the sense of community we strive to build for successfully reimagining the workshop experience.

Kristen Procko of the University of Texas at Austin, Rebecca Roberts of Ursinus College and Shelly Engelman of Custom EduEval contributed to this article.

Audrey Shor (Audrey.Shor@saintleo.edu) is an associate professor of biology at Saint Leo University.

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Reimagining academic leadership

By Beronda L. Montgomery & Joseph A. Whittaker

Academic leadership may be in urgent need of a leadership revolution. At a minimum, we maintain that significant reimagining of academic leadership is long overdue. The disruptions associated with the global pandemic have revealed a need for more agile and equitable systems of leadership. COVID-19 upended many standard practices in higher education. The myriad consequences of the pandemic highlighted the need for rapid leadership pivots and innovations to minimize damage, maintain core functions, and adapt to new delivery modes and styles of learning and working — all while maintaining physical distance and transitioning to new frameworks of engagement.

This moment has brought to the fore the ongoing and significant impact of leadership regarding institutional (in)stability, stewardship of resources or (in)ability to navigate disruptions. Individual institutions routinely deal with the impact of leaders on the transition periods that follow change or disruption as well as on the deployment and implementation of plans to sustain stability. Yet a global disruption such as COVID-19, compounded with national disruptions such as addressing long-term systemic racism, has resulted in systemwide challenges to transition and sustainability in higher education.

While heightened in the current moment, the need for innovations in leadership is long-standing and predated this global crisis. A major need for reimagined leadership emerged due to factors such as rapidly advancing technology, persistent reductions in state and federal appropriations, and escalating enrollment challenges in higher education. The path to new conceptualizations of leadership will require a deviation from norms and thinking differently about persistent issues and pain points in institutional leadership and administration. Significant reimagining will require elevating and altering several aspects of academic leadership culture including selection and preparation, expectations and rewards, and advocating for equitable leadership practices.

In June 2020, a crowd in Eugene, Oregon, marched to the University of Oregon campus where local members of Black Lives Matter led a teach-in from the steps of what was then known as Deady Hall, an historic campus building named for a racist 19th-century judge. Days after this march, the building was temporarily renamed University Hall until a new name can be chosen.

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Selection and preparation

Individuals who have successfully navigated traditional faculty pathways frequently are selected for advancement into formal academic leadership roles. As Beronda Montgomery, co-author of this essay, discussed in her 2020 paper "Academic leadership: Gatekeeping or groundskeeping," leadership selection often relies on perceived loyalty to in-groups or traditional measures of success as an individual scholar rather than preparation for leadership through formal training. Leaders are selected based on their demonstrated success as disciplinary scholars and according to traditional metrics of perceived impact. Depending on whether the range of roles of a leadership position is informal or formal, departmental, or college or university wide, leaders may be selected based on perceptions of their relationships with colleagues or governing board members. In most cases, scholarly success and perceived relationship-building ability drive selection rather than formal leadership training, demonstrated ability, prior experience in leading through crisis or innovative, visionary stewardship.

In their 2016 book "Faculty Development in the Age of Evidence: Current Practices, Future Imperatives," Andrea Beach and colleagues described how formal leadership training is not universally required in higher education. Furthermore, where it occurs, such training frequently emphasizes tactical skills and transactional engagement. Yet the standard one-size-fits-all leadership training protocols no longer apply — if they ever did. New paradigms for leadership preparation and enactment must include cultivating abilities to detect, as well as to assess and steward, micro- and macro-level changes or needed disruptions within an ecosystem. Leadership selection, development and assessment rarely are driven by cultivation or demonstration of leadership vision and philosophy, according to authors Kendra Cheruvelil and Beronda Montgomery in "Women Leading Change in Academia: Breaking the Glass Ceiling, Cliff, and Slipper." Additionally, in "Connecting values to leader and leadership development," Joanne Smikle highlights that a focus on values and values-driven action rarely is incorporated into leadership development.

Recognized limits to innovation and agility in leadership may stem in large part from the traditional ways in which we select and prepare (or fail to intentionally prepare) leaders in academia. Attracting individuals who have the vision, passion and purpose needed for leadership of an entire academic system inclusive of people, infrastructure and resources — or ecosystems-based leadership — may require higher education to revisit the rigid structure of academic leadership positions as well as determinations of who can and should be selected as leaders. Current structures reflect patriarchal constructs and traditions, including noted gender differences in leadership attainment described by Anne Wong and colleagues in the article "What's the fuss? Gender and academic leadership." Also prevalent are individual success models that center on traditional hierarchies; for instance, those on a tenure-track faculty path are disproportionately valued for leadership consideration. These systems also value currencies of loyalty, external affirmations and self-preservation in access to and success in leadership roles. Additionally, many academic leadership roles necessitate major time commitments and sacrifices of individual scholarly pursuits and career–life balance or integration.

Reimagined leadership frameworks may expand the pool of potential leaders by elevating flexibility in structure — including collective or shared leadership positions, entrepreneurial approaches to leading, broadened paths of access to leadership positions, and more part-time executive positions that do not require a full pivot from engagement in research or scholarly pursuits. This pool could include nontenured individuals with demonstrated commitment and innovative skills. New selection paradigms could prioritize vision- and values-driven, as well as entrepreneurial, leadership rather than traditional tactical and transactional modes.

Expectations and rewards

In addition to traditional selection paradigms, we often require and reward academic leadership efforts that esteem quantitative metrics aligned with maintaining

prestige and standing in select national and international ranking systems. This often has led to selecting leaders who largely maintain a culture of status quo systems and practices. They enact traditional modes of leadership focused on incremental changes to a system to maintain and elevate status, especially national and international ranking, rather than encourage strategic and sustainable creativity, innovation and ecosystem transformation.

Changing expectations and rewards for leadership structures and effectively promoting a shift to leadership based on ecosystems rather than individual success and self-preservation will require revisiting metrics of leadership success. We need to review how we see leadership in terms of a pursuit of personal benefit (including individual career advancement) versus stewardship of and benefit to a larger higher education ecosystem including personal, professional, institutional and society-at-large benefits — not forgetting a view of institutions as economic drivers. Some prior leadership models, such as transformational leadership, are associated with innovation and improved satisfaction of those being led, as discussed by Athena Xenikou in the 2017 paper "Transformational leadership, transactional contingent reward, and organizational identification: The mediating effect of perceived innovation and goal culture orientations." Transformational leadership, as well as the leadership described as groundskeeping by Montgomery in 2020, are forms of leadership based on stewardship of academic ecosystems.

Common measures of transformational leadership largely focus on traditional quantitative metrics including numbers of new courses, new policies instituted or new or reallocated sources of dollars to support new measures, according to Peter Eckel in "Assessing change and transformation in higher education: An essential task for leaders." Eckel recognized that transformational leadership can include cultural factors that are more difficult to measure, and these factors often are not used as markers of leaders' impact or success by governing boards or accreditation bodies.

We argue that measuring the effectiveness of new approaches to leading would require adequately assessing what leaders do, the relationships they cultivate, and the cultural adjustments promoted by leaders. An ability to measure these aspects of leadership would increase the likelihood of assessing both quantitative metrics and qualitative measures such as cultural factors that together contribute to leaders' success and sustainable change in an ecosystem. Indeed, to accomplish such a complete reimagining of academic leadership will require embracing change at all levels and institutional flexibility about the definitions of excellence and success as a leader as well as an institution.

We need to redirect our understanding of leadership from traditional gatekeeping frameworks tied to narrow definitions of excellence that prize exclusionary, highly selective metrics and single-minded pursuit of rankings and prestige. Instead, we should consider successful academic leadership as the stewardship of complex and diverse ecosystems. We need individuals to drive ecosystem change rather than tending the status quo.

Equitable leadership frameworks

Current challenges have called on academic leaders to go beyond expressing commitments to promote diversity and equity — often in the form of diversity, equity and inclusion statements — to demonstrating lived commitments to equity in their local academic ecosystems. Despite long-term articulated commitments to such issues by leaders and institutions, real progress has been painfully slow. As Emma Whitford describes in the 2020 article "There are so few that have made their way," Black faculty are disproportionately underrepresented in advanced faculty ranks and administrative roles despite a long-standing focus on promoting diversity among faculty and administrators in higher education. Limits to rapid progress in pursuing equity are evidence of leadership shortfalls. Leaders set strategic direction and cultivate buy-in to support progress in alignment with their interests and lived commitments.

Many leaders also rely on institutional governing boards to drive decisions, which can limit independence of thought and implementation in making decisions. Powerful recent examples have emerged of governing boards reversing or failing to support faculty and leadership decisions related to hiring and review, as reported by Char Adams for a highly visible recent case in the article "UNC withholds tenure for '1619 Project' journalist after conservative backlash." The leadership interface with boards of directors/trustees can be affected by board members' sometimes limited understanding of the immediate needs and challenges of a local institutional culture, or by other factors, such as political leanings.

Leaders (and governing boards) must intentionally prioritize increasing the pace of change in diversity, equity and justice, deeming it essential to promote collective focus, structures of accountability and reward, and investments of key resources and capital — including human, financial, social and other critical capital.

Conclusion

The global pandemic presented seismic challenges in higher education, which completely disrupted business as usual. These challenges occurred during a heightened recognition of systemic racism and anti-Black policing in the United States. These synergistic challenges increased an already critical need for agility and cultural competence among academic leaders — traits that rarely are selected for during recruitment or critically assessed during review and reward.

Leaders have had to imagine new modes of operation, deploy them and assess their effectiveness simultaneously in the midst of these dual crises, as previously discussed by Montgomery in 2020. The leadership demands required by these current challenges opened a new opportunity to reflect on how we select and prepare leaders, what prevailing expectations and associated rewards are, and how leaders enact equitable frameworks. Reflections on the impacts of and responses to the global pandemic and recent increased awareness of systemic racism led us to examine and elevate the need to reimagine leadership in higher education more generally.

Next-generation leaders should not only identify and analyze challenges but also acknowledge the value of truth-telling and catalyzing paradigm-shifting institutional change by surmounting the cultural inertia characteristic of academic environments. A more expansive view on the future of effective academic leadership needs to focus broadly on key considerations, including the following questions: What specific models of leadership are needed to reimagine higher education and to bring this reimagination effectively and sustainably to fruition? What must institutions do to transform the process for selecting leaders to guide universities toward an equitable and sustainable future?

We believe this reimagining starts with new paths for preparing, selecting and rewarding individual leaders who are committed to promoting equitable ecosystems and long-term communal success.

Beronda L. Montgomery (montg133@msu.edu) is a professor and administrator at Michigan State University as well as a writer and science communicator. She is the author of "Lessons from Plants," published by Harvard University Press in 2021. The Montgomery lab pursues a common research theme of understanding how individuals perceive, respond to and are affected by the environments in which they exist, including responses of photosynthetic organisms to external light cues. Montgomery also pursues this theme in the context of effective mentoring and leading in academic environments. Follow her on Twitter: @BerondaM.

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Merging biochemical and analytical training

By Clément Vinauger

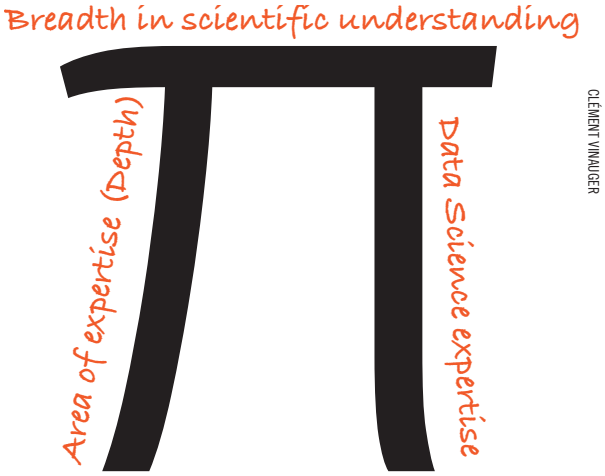
Recent advances in molecular and biochemical methods such as mass spectrometry and high-throughput sequencing have accelerated the rate of scientific discovery and exponentially increased the volume of data that a single study can generate. The COVID-19 pandemic has stimulated researchers to integrate genome sequencing, automatized large-scale testing, rapid and efficient sharing of information, modeling, and computational studies to generate evidence-based solutions to global problems.

We also have been challenged to be more creative and flexible in our approach to the way we work and teach. For some scientists, this has meant increasing our reliance on computer networks and computational methods to compensate for limited access to the laboratory bench. In other words, the pandemic revealed that while it is critical for us to specialize and have depth of knowledge in some domains, it is also essential that we cultivate some breadth in our skill set.

A need for programming literacy

Question-driven research often requires the analysis of large volumes of heterogeneous data to generate accurate and comprehensive answers. Often, these data must be integrated into predictive models. For example, in my laboratory we integrate headspace volatiles analysis, transcriptomics and electrophysiological recordings to understand the chemical basis of mosquito–host interactions.

Integrated multidisciplinary research is not new and not limited to the fields of biochemistry and molecular biology. In both academia and industry, scientists at all levels need to be able to work at the bench and operate advanced scientific equipment as well as process, wrangle, integrate and analyze heterogeneous data. Our colleagues in neuroscience combine behavioral data with neural activity recordings, functional imaging studies, gene expression profiles, computational approaches and mathematical modeling. Ecologists integrate temporal population census data with climatic and geographic information to discern how organisms interact with their environment. As these multidisciplinary approaches spread, we need to train what data scientists refer to as "pi-shaped" researchers: investigators possessing a broad understanding of the sciences supported by a deep knowledge of their specific area of expertise and a foundation in data science. The presence of these π-shaped experts on problem-solving teams facilitates the process of data collection, visualization and interpretation by freeing these teams from communication gaps between topic expertise and data scientists.



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Steve Brunton, an associate professor of mechanical engineering at the University of Washington, provides a great definition of the π-shaped expert concept (illustrated here) in his online lecture "Introduction to Data Science" on YouTube.

Training π-shaped researchers

Data science requires both computer literacy and familiarity with a programming language. While some students are curious about programming and learn how to code in Python or R on their own, others don't have this exposure to data wrangling unless they are part

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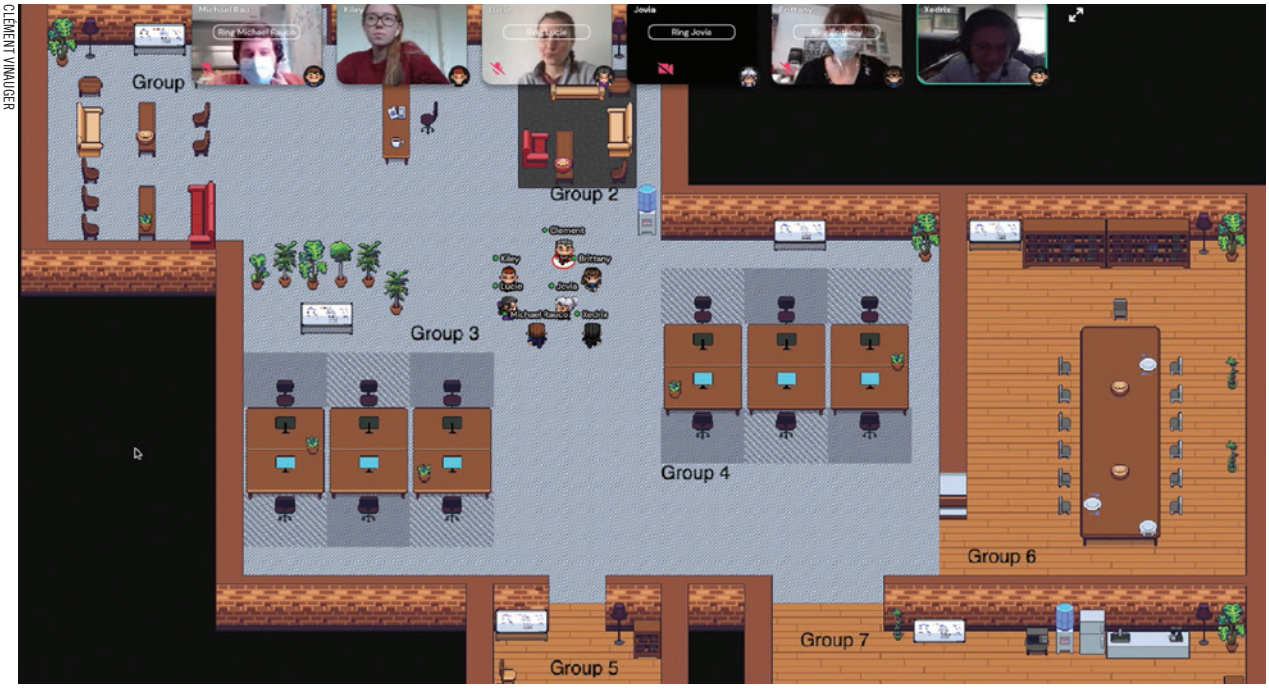

Students work in a virtual classroom on the video call platform Gather, where every student has an avatar and group areas can be defined, allowing them to interact privately, share a screen or use virtual whiteboards. A video demo was made by student volunteers Kiley Stackpole, Michael Rauco, Xedrix Barbeyto, Lucie Lefbom and Jovia Ho and teaching assistant Brittany Hart. See the video at asbmb.org/asbmb-today.

of the roughly 54% of undergraduates (averaged across science, technology and engineering and mathematics disciplines) who participate in extracurricular research. At most colleges and universities, an extensive set of prerequisites is required for students to take advanced specialty classes in computer science and statistics — a challenge for biochemistry students who already have full schedules. In most bench and field science majors, computational training is optional and not part of a student's core training. As a result, students have difficulty identifying how knowledge acquired in a statistics or computer science course can be applied to, for example, biochemistry.

In the biochemistry program at Virginia Tech, we developed a new course that exposes biochemistry majors to coding as they analyze large data sets relevant to the concepts and topics developed in class — for example, chemical communication. Students analyze large data sets collected in the instructor's laboratory, ranging from electrophysiological recordings of olfactory neurons to gas chromatography–mass spectrometry analyses of the chemical composition of plant and human scent samples. In addition to programming in the open source language R, they work in teams to clean, wrangle, visualize and interpret data. They manipulate inferential statistics and use multivariate analysis and machine learning while answering biochemical and biological questions.

Copy, paste and tweak

If you were to type, "La mer, la vaste mer, console nos labeurs!" (from Charles Baudelaire's poem "Moesta et Errabunda") on your computer, would you have written one line of French poetry? Yes. Does this mean that you now are a poet or know how to communicate in French? Not exactly, right? The same applies to learning a programming language. Providing students with functional scripts does guarantee that they will produce an anticipated output. However, such assistance reduces the likelihood that they will be able to then tackle a slightly different problem. On the other hand, expecting non–data science students to become programming experts in a single semester is unrealistic.

Through a compromise approach, our students can acquire a working understanding of the programming relevant to their area of study. By working with data that students can relate to and that is directly relevant to the topic of the course, we offer them an opportunity to leverage lecture content and reading materials to identify the biochemical problem they are trying to solve. The central pedagogical objective is to foster students' familiarity with key coding concepts and terms and to develop their ability to identify code syntax and structures that they can adapt to fit their needs and solve the biochemical problem.

Optimizing online

How does this look in the classroom? Before the pandemic, students worked side-by-side in small groups to brainstorm, code and debug while the instructor and teaching assistant moved between groups to provide individualized teaching. Physical distancing requirements have disrupted these activities, but online solutions exist that emulate these interactions.

During the spring semester of 2021, our class met in a virtual classroom on Gather.com, a video call platform. It is similar to Zoom or Teams, but each participant has an avatar that can move around the virtual classroom. Students worked collaboratively on their codes using platforms such as Google Drive and GitHub. With these tools, they were able to share their work with the instructors and get feedback and personalized help, and instructors were able more readily to comment, edit students' code in real time and explain core coding concepts. We recorded lectures and group activities so students with added responsibilities (such as parenting), disabilities or scheduling conflicts can come back to the material later.

Career benefits

Looking forward to the fall semester, now is a good time to reimagine a post-pandemic version of this new course in which analytical training can be even better integrated with core biochemistry education. Returning to in-person teaching should increase student engagement and mitigate some of the inequalities arising from their work-from-home environments. They still will be able to share and exchange data and work collaboratively online.

We have a unique opportunity to prepare undergraduates for professional scientific collaborations that are often long-distance, if not international. As we observed during the pandemic, online resources for collaborative work offer a remarkable medium to provide individualized feedback to students, bringing coursework one step closer to the one-on-one training students would get in a laboratory. By recording and sharing lectures and discussions via online platforms, we are able to reach students with varied learning styles and needs.

A foundation in data science tailored for biochemists and life scientists will give students an edge when applying to graduate or medical school or entering the job market. By exposing students to the use of online resources for collaborative work, we help them to hit the ground running when they move on to the next step of their training or the first step of their professional life.

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The University of California Davis School of Medicine

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https://careers.asbmb.org/job/chair-of-biochemistry-and-molecular-medicine/56889965/

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Postdoctoral positions are available in the Enns/Zhang Labs in the Department of Cell, Developmental, and Cancer Biology at Oregon Health & Science University, Portland, OR.

Our labs focus on identifying the molecular mechanisms by which the body senses iron and the pathways involved in maintaining iron homeostasis. Diseases that disrupt these homeostatic mechanisms include, but are not limited to, hereditary hemochromatosis, infectious diseases, heart failure, cancer and hematopoietic disorders. We combine state-of-the-art approaches involving mouse models, gene therapy, mass spectrometry, advanced light microscopy and bioinformatics in a collaborative environment.

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https://careers.asbmb.org/job/postdoctoral-fellow/56472894/

Teaching Assistant Professor

West Virginia University

The Davis College of Agriculture, Natural Resources and Design at West Virginia University invites applications for a Teaching Assistant Professor of Biochemistry beginning August 2021. Biochemistry is an intercollegiate program offered at WVU. This interdisciplinary program offers courses in biology, chemistry, mathematics, physics and molecular biology, providing a solid launching point for professional and graduate school. This is a 9-month, full-time, non-tenure track position with benefits and the opportunity for promotion, though promotion is not required for continued career stability. Teaching Assistant Professor appointments have renewable terms of up to three years, with no limit on the number of terms. Teaching faculty are expected to demonstrate excellence in teaching, and ongoing engagement in assessment-based advancement of curriculum and instruction. This is a non-research position.

https://careers.asbmb.org/job/teaching-assistant-professor/56969282/

Senior Scientist

Bio-Rad Laboratories

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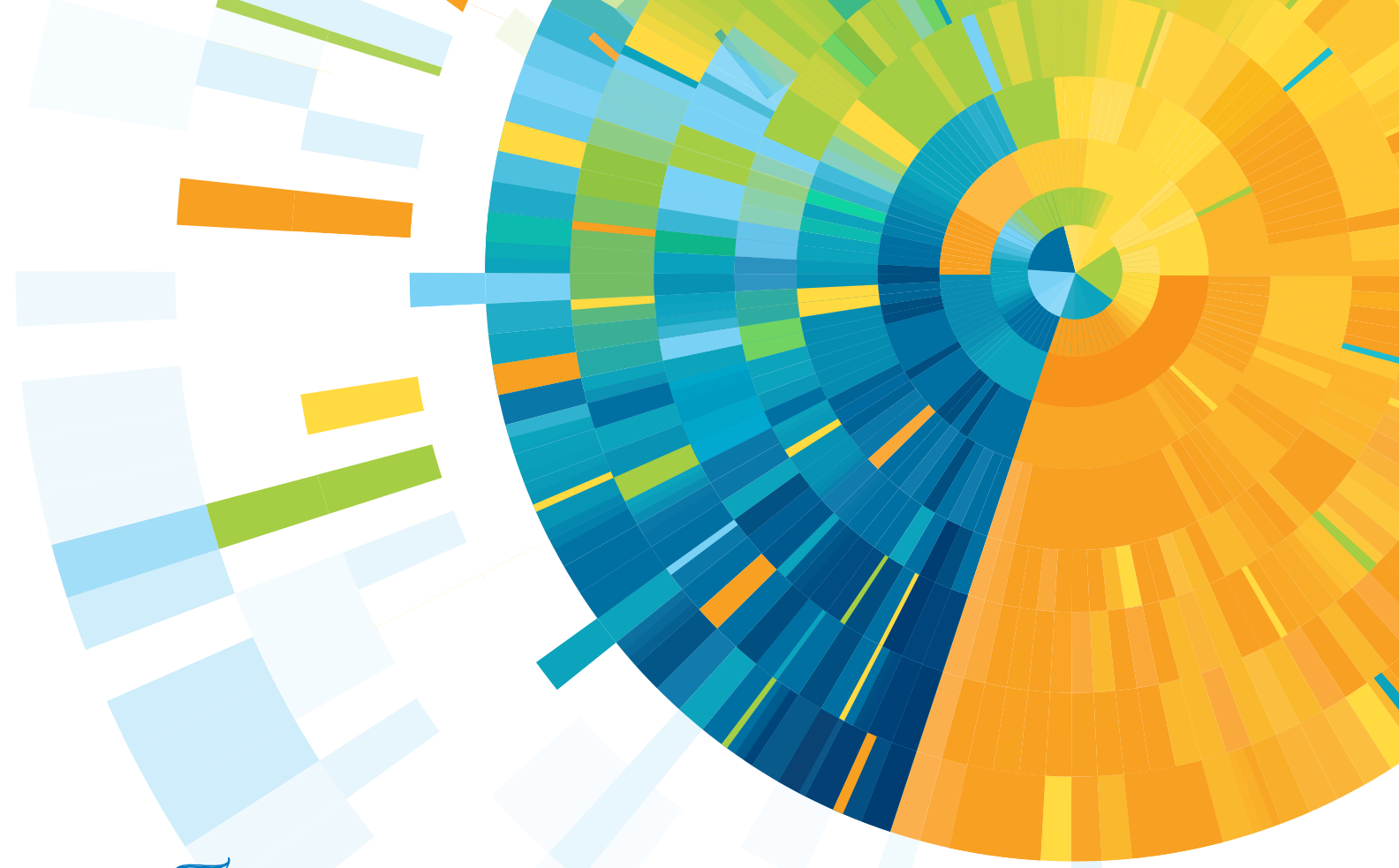

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