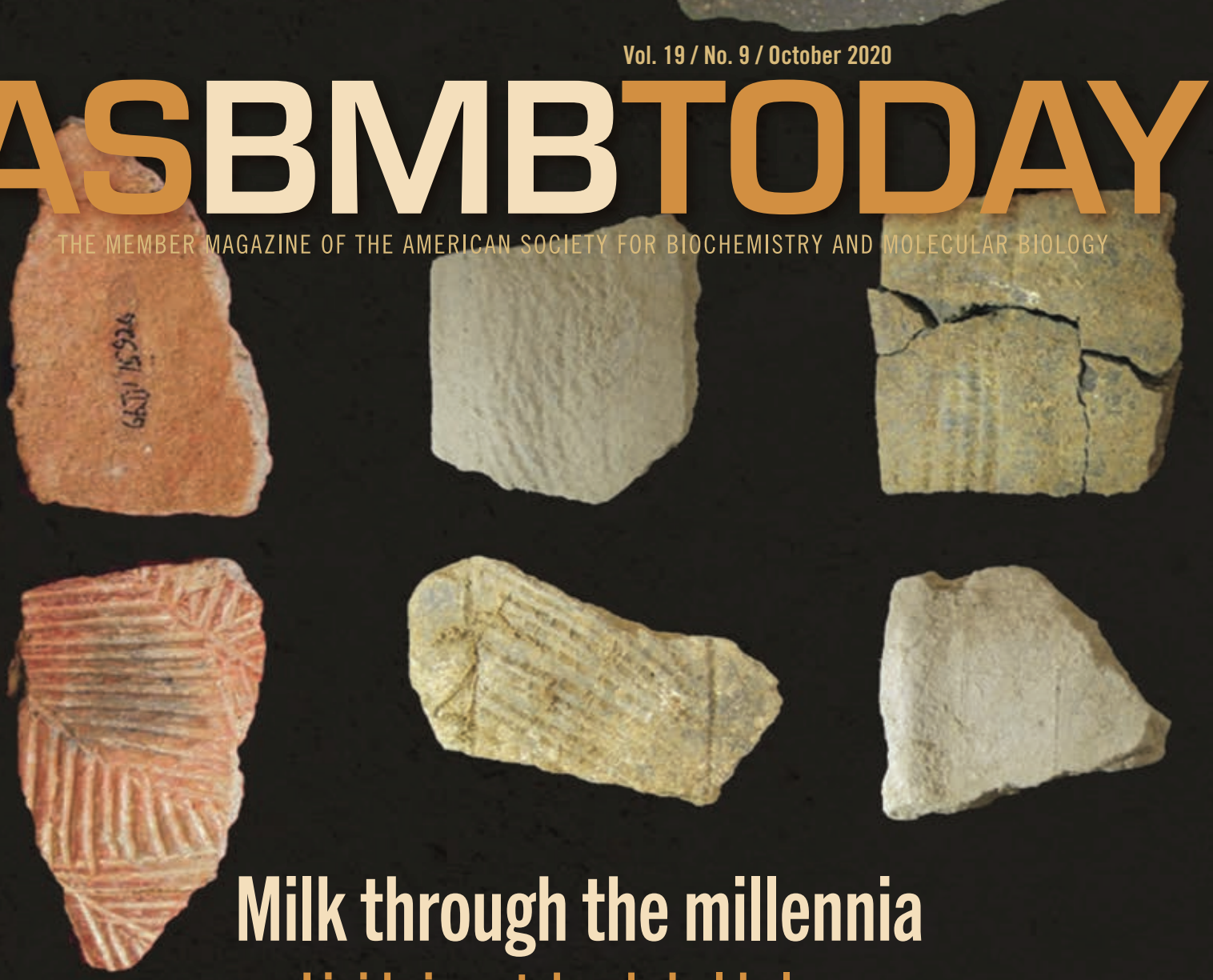
Vol. 19 / No. 9 / October 2020

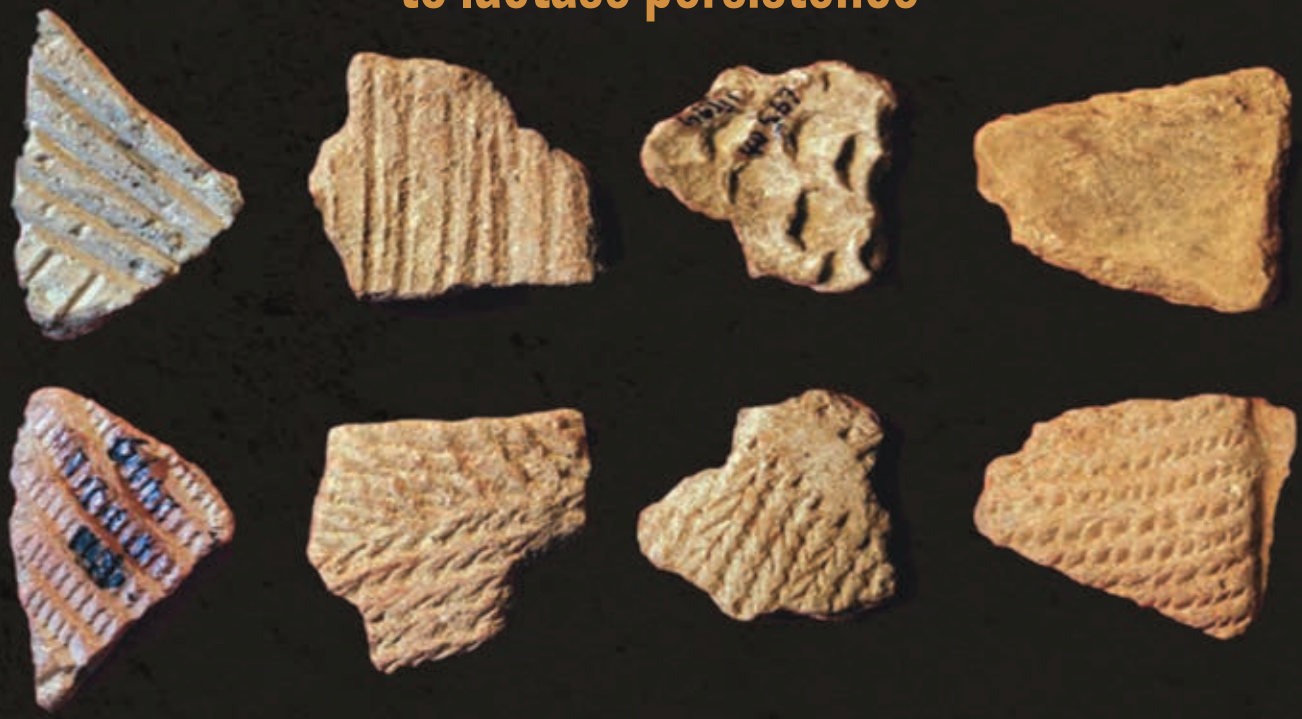
ASBMB TODAY

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



Milk through the millennia

Lipids in potsherds hold clues to lactase persistence



ASBMB '21
ANNUAL MEETING

The 2021 ASBMB Annual Meeting will be virtual!

Join us April 27–30, 2021

Learn more at asbmb.org/annual-meeting

EB
Experimental Biology

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

CONTENTS

NEWS

2
EDITOR'S NOTE
Wellness—we need it now more than ever

3
MEMBER UPDATE

6
IN MEMORIAM

9
RETROSPECTIVE
Herb Tabor (1918–2020)

15
RESEARCH SPOTLIGHT
Understanding the impact of Type 1 diabetes susceptibility genes

18
NEWS
Nobelists' former postdocs discover missing link in telomerase evolution

21
JOURNAL NEWS
21 Re-creating coagulation in a lab
22 Gut microbiome shaped by dietary sphingolipids
23 Our internal ecology
24 From the journals

FEATURES

30
MILK THROUGH THE MILLENNIA
Lipids in potshards hold clues to lactase persistence

38
PANDEMIC SNARLS RESEARCH ADMINISTRATION
Funders, grant administration offices work together to reassure anxious investigators

COVER: PHOTO ILLUSTRATION BY PATRICE GALLAGHER, BASED ON A PHOTO BY KATHERINE GRILLO

PERSPECTIVES

45
THE ART OF PAPER FOLDING AND THE SCIENCE OF PROTEIN FOLDING

48
THE UPS AND DOWNS OF TEACHING IN A PANDEMIC

50
NATIONAL CERTIFICATION EXAM AS FACULTY DEVELOPMENT EXERCISE
Applying large-scale assessment ideas to small classes

51
"IT ALL COMES DOWN TO WHERE WE PLACE OUR BETS"
5 questions for Mark Harpel

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

www.asbmb.org/asbmbtoday
PRINT ISSN 2372-0409

Wellness – we need it now more than ever

By Comfort Dorn

For six weeks, from mid-March to late April, I slept with a thermometer on my nightstand. And I did not sleep well. I woke up regularly between 2 and 3 a.m. Sometimes I went back to sleep. Sometimes not. I'd scroll on my phone for hours, checking the latest news. Every time I coughed, I took my temperature. I had whooping cough many decades ago when I was teenager; as a result, I cough a lot.

I'm lucky. I have a job I can do from home that still provides me with a steady paycheck. I can control my contact with other people. I don't have to worry about supervising children or caring for elderly relatives. But I'm still kind of a mess.

In the age of COVID-19, wellness has taken on a new meaning. Many of us are grappling not only with a scary virus but also with social isolation, uncertain job and money prospects, the need to care for and educate our children at home. We don't want to get sick, but everything we're doing to avoid getting sick might be making us a little unwell.

A couple of years ago, the staff of this magazine decided to start each year with a January wellness issue. We asked our readers to share their strategies for keeping their minds and bodies healthy in the pressure-cooker world of scientific research. We received wonderful, varied, heartfelt responses that we shared in these pages.

The third iteration of the ASBMB Today wellness issue is coming up in 2021, and as we slog our way through what feels like an endless pandemic, wellness is an ever more important topic. Beyond protecting ourselves from COVID-19, we need to stay physically and mentally strong. For many of us, the aspects of our lives that used to provide the life part of work–life balance, such as home and family, now overlap with our work. So where's the balance?

Now, when I wake up at 2 a.m., I no longer look at the latest news on my phone. I keep a soothing book and a few Sudoku puzzles on my nightstand instead of a thermometer. I don't always go back to sleep, but I'm calmer.

What about you? How are you coping? How are you keeping yourself, your colleagues, your students well in body, mind and spirit? We want to hear from you, and we want to share your stories and strategies in the January issue. Please send your submissions to asbmbtoday@asbmb.org or via our website by Nov. 2.

And, as always, I wish you well.

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

De La Cruz appointed chair at Yale


DE LA CRUZ

Enrique M. De La Cruz became chair of the Department of Molecular Biophysics and Biochemistry at Yale University in July.

De La Cruz, an associate editor for the American Society for Biochemistry and Molecular Biology's Journal of Biological Chemistry, studies the actin cytoskeleton, molecular motor proteins and nucleotide signaling enzymes.

In August, De La Cruz was appointed to the advisory board for the ASBMB Maximizing Opportunities for Scientific and Academic Independent Careers, or MOSAIC, program. He is a member of the society's Minority Affairs Committee and Meetings Committee. He previously served on the Publications Committee.

De La Cruz was tapped to lead Yale's Branford College in 2017 and won the Biophysical Society's Emily Gray Award in Education in 2018.

Cambridge gives Walker honorary degree

Molecular biologist **John Walker** is one of eight individuals that Cambridge University presented with honorary degrees this year.


WALKER

Walker, who shared the 1997 Nobel Prize for chemistry with Paul D. Boyer and Jens C. Skou for "elucidation of the enzymatic mechanism underlying the synthesis of adenosine triphosphate," was awarded an honorary Doctor of Science.

Walker has been emeritus director and professor at Cambridge's Medical Research Council Mitochondrial Biology Unit since 2015. His current work focuses on understanding the molecular mechanism of how ATP is made, specifically, how the rotation of ATP synthases is generated and how these synthases differ in humans and bacteria in their structure, function and regulation, with the goal of devising drugs that can kill pathogenic bacteria without harming humans.

A fellow at Sidney Sussex College at Cambridge and an honorary fellow at Oxford's St. Catherine's College, Walker was knighted in 1999 for services to molecular biology. He is a fellow of the Royal Society and a foreign associate of the National Academy of Sciences. In 2012, he was awarded the Copley Medal.

Developmental biologists Edith Heard and Elizabeth Robertson and mathematical physicist Roger Penrose were also nominated for honorary degrees in science this year. The 2020 awards ceremony was canceled due to the coronavirus pandemic.

Parker to head BioFrontiers Institute

Biochemist **Roy Parker** is the new director of the BioFrontiers Institute at the University of Colorado Boulder. He has taken over after eight years as

Ma wins astronaut foundation scholarship

Stella Ma, an undergraduate at the University of Wisconsin–Madison, has won a scholarship from the Astronaut Scholarship Foundation.

Now a fourth-year student in the biochemistry department, Ma spent summers as a rising high school senior and incoming undergraduate in Emery Bresnick's lab at UW-Madison, studying molecular mechanisms underlying hematopoietic stem and progenitor cell development and differentiation. In 2019, she won funding from the provost's office to work in the lab of Anna Huttenlocher, where she studies immune interactions with wounds and cancer. Also in 2019, she won a biochemistry undergraduate summer research award to work in the lab of Helen Blackwell, where she studies bacterial communication and, in collaboration with the Huttenlocher lab, how bacteria may use communication to evade the immune system. In 2020, she received a Goldwater Scholarship.


MA

The Astronaut Scholarship Foundation was started in 1986 when the founding Mercury 7 astronauts each sponsored a $1,000 scholarship and began to raise funds for future awards. The astronauts also donated proceeds from their speaking engagements, and the program now awards more than 50 scholarships each year valued at up to $15,000 each.

"I'm so grateful to the Astronaut Scholarship Foundation for this honor — I'm still half-trying to convince myself it's real," Ma said "Beyond the financial support, the networking opportunities and professional development advice ASF offers are spectacular. I'm also especially grateful to my PIs and to the Biocore honors biology program faculty and my classmates for their support."

a distinguished professor at CU Boulder, succeeding Nobel laureate and fellow RNA researcher Thomas Cech.

The interdisciplinary research institute, founded in 2009, counts physics, computer science, life science and chemistry researchers among its 19 faculty and about 100 staff and trainees. "To really make progress in science today, you need to incorporate new ways of thinking and break down the silos that get built up when we all get busy," Parker said.


PARKER

Parker has spent much of his career focused on messenger RNA. After graduating from Carnegie Mellon University in Pittsburgh and earning a Ph.D. in genetics from the University of California, San Francisco, he trained briefly as a postdoc in three different labs before launching his own, studying eukaryotic mRNA turnover at the University of Arizona.

Starting from an interest in unstable mRNAs in yeast, Parker's lab described the pathways of RNA degradation involving deadenylation and decapping, as well as showing a fundamental competition between RNA degradation and translation. This work also led the lab to discover P bodies, cytoplasmic granules that contain RNA and proteins and can regulate translation. Related particles, called stress granules, can form when something is wrong in the cell, pausing translation — and their dysregulation seems to link to pathology in diseases like amyotrophic lateral sclerosis, also known as Lou Gehrig's disease.

Parker joined the faculty at CU Boulder in 2012, after 22 years at the University of Arizona. He is a fellow of the American Academy of Arts and Sciences, a member of the National Academy of Sciences and a Howard Hughes Medical Institute investigator. He served as president of the RNA Society in 2010.

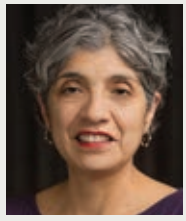
ASCB awards for Trejo, Olzmann, Farber

The American Society for Cell Biology has announced its annual awards for 2021, and three American Society for Biochemistry and Molecular Biology members are among its slate of awardees.

Joann Trejo, a professor and assistant vice chancellor for health sciences faculty affairs at the University of California, San Diego, School of Medicine, has received the ASCB's prize for excellence in inclusivity, which recognizes a scientist who champions inclusion and diversity in science with a $5,000 award to further their inclusion activities. In addition to studying protease-activated receptor and G-protein–coupled receptor signaling in vascular inflammation and breast cancer progression, Trejo is dedicated to mentoring of both faculty and trainees; the award is the latest in a series of mentoring and inclusivity awards recognizing her work from ASCB, ASBMB and UCSD.

James Olzmann, an associate professor at the University of California, Berkeley, has received the Günter Blobel Early Career Award, which honors a researcher less than seven years into an independent career. (The ASCB recently renamed the award in honor of Blobel, a cell biologist and Nobel laureate who died in 2018). Olzmann's lab studies lipid droplet function with special interest in the proteins that regulate lipid storage and mobilization from inside these organelles. He also won a 2019 Presidential Early Career Award for Scientists and Engineers.

Steven Farber, a principal investigator at the Carnegie Institution for Science embryology department and adjunct professor in the Johns Hopkins University biology department, shares this year's Bruce Alberts Award for Excellence in Science Education with Jamie Shuda. Farber and Shuda are the co-creators of an outreach educational program, Project BioEYES, which has used hands-on experiments with zebra fish to teach science to more than 130,000 students in grades 4 through 12. Farber's lab studies digestive organ physiology in developing zebra fish larvae with a focus on the cell and molecular biology of lipids.


TREJO


OLZMANN


FARBER

ASM career awards for Wickner, Moss

The American Society for Microbiology has announced the recipients of its 2021 awards, including American Society for Biochemistry and Molecular Biology members Sue Wickner and Bernard Moss among the honorees. Both are distinguished investigators who lead laboratories at the National Institutes of Health in Bethesda.

Sue Wickner, head of the DNA Molecular Biology Section at the National Cancer Institute, has received the ASM award for Basic Research, which recognizes a scientist "whose discoveries have been fundamental to advancing our understanding of the microbial world." Her work focuses on heat-shock proteins, a family of ATP-dependent molecular chaperones that participate in protein folding and proteolysis in both prokaryotic and eukaryotic cells. Her lab found that these chaperones can also participate in protein disaggregation, helping cells respond to stress. Wickner is a member of the National Academy of Sciences and a fellow of the American Academy of Arts and Sciences.

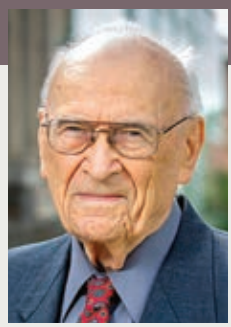
WICKNER

Bernard Moss, head of the genetic engineering section of the National Institute for Allergy and Infectious Disease, was honored with a Lifetime Achievement Award, which recognizes a career of sustained contribution to the field of microbiology. Moss, a virologist and former president of the American Society for Virology, is known for research into viral mRNA capping; immune evasion through expression of proteins that resemble host cytokines; and the use of vaccinia-based vectors for vaccines. He is a member of the National Academy of Sciences and a fellow of the American Academy of Arts and Sciences.

MOSS

IN MEMORIAM

Harold Scheraga



Cornell University professor emeritus of chemistry Harold A. Scheraga died Aug. 1 in Ithaca, New York. He was 98.

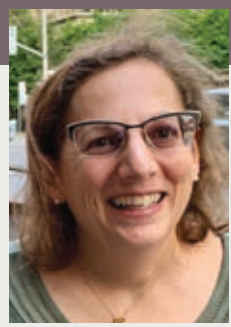
Over his seven-decade career, Scheraga pioneered the application of physical chemistry to protein science — what is now known as protein biophysics — to decipher how amino acid sequences influence the three-dimensional folding pathway, thermodynamics and biological activity of proteins. He published more than 1,300 papers about protein chemistry, the most recent of which appeared in June.

Scheraga was born Oct. 18, 1921, in Brooklyn to Samuel and Etta Scheraga. He grew up in Monticello, New York, but the family moved back to Brooklyn after his father lost his radio and musical instrument store to the 1929 economic crash. Scheraga later credited the Great Depression and the severe financial strain it put on his family with shaping his outlook and career aspirations.

After earning a bachelor's of science from City College of New York in 1941 and a Ph.D. from Duke University in 1946, Sheraga was awarded a one-year postdoctoral fellowship at Harvard Medical School. The following year, he was hired as an instructor teaching quantitative analysis at Cornell. He became an assistant professor in 1950, an associate professor in 1953 and a full professor in 1958. In 1965, he was named the Todd professor of chemistry. He served as chair of the chemistry department from 1960 to 1967, during which time he led the department's expansion into materials science and molecular biology, as well as initiated construction of the S.T. Olin Chemistry Research Laboratory.

Scheraga's wife of 76 years, Miriam, who died in January, worked for the Cornell University Library for 30 years. Scheraga is survived by his brother, David; three children; five grandchildren; and four great-grandchildren.

Deborah Zamble



Deborah Zamble, a professor at the University of Toronto, died July 6 following a brain hemorrhage.

Zamble was born in 1971 and grew up in Kingston, Ontario. She earned her bachelor's degree at the University of Toronto, where she conducted undergraduate research with Bibudhendra Sarkar on zinc-finger proteins. She went on to earn a Ph.D. in 1999 at the Massachusetts Institute of Technology, where she worked with Stephen J. Lippard studying the anticancer drug cisplatin. She completed a postdoctoral fellowship in the lab of Christopher T. Walsh at Harvard Medical School, where she studied the zinc-containing protein component of the antibiotic microcin B17 synthetase.

Zamble started her lab at Toronto in 2001 and focused on how pathogenic microorganisms use nickel.

The chemistry department at Toronto tweeted a thread after her death that said, in part: "Deborah gave tirelessly, supporting co-workers and students in their research, advancing our department and the bioinorganic chemistry community. She was also a highly skilled, caring and enthusiastic instructor. We are diminished as a department because of her loss."

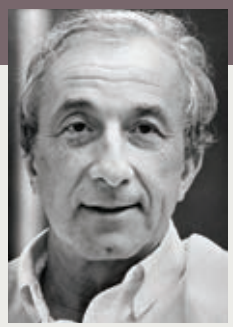
Zamble served as a member of the editorial board of the ASBMB's Journal of Biological Chemistry, on the council of the Society of Biological Inorganic Chemistry and on the executive board of the Royal Canadian Institute.

In a remembrance, the RCI noted that Zamble valued science outreach: "Deborah was passionate about making science available to everyone, particularly people outside of the scientific and academic community, and especially kids. She was always available to help ensure everything went smoothly at our events, often bringing her own young family. At our family programs in particular, Deborah made sure that all of the children attending found something fun and interesting to do."

Friends and colleagues said she enjoyed cooking, reading and gardening in her free time.

Zamble is survived by her husband, Brian Murray; children, Matthew and David; her parents, a sister and a niece and nephew.

Norbert Swislocki



Biochemist Norbert I. Swislocki died at his home in Grand View-on-Hudson, New York, on June 21 after a long illness.

Swislocki was born in 1936 in Warsaw, Poland. He and his mother fled in 1939 to Vilnius, Lithuania, where they met up with his father, a journalist following the Polish Army. In Vilnius, the family obtained a visa from the Japanese diplomat Chiune Sugihara, who helped as many as 6,000 Jews escape the Nazi regime, and crossed the Soviet Union to reach Kobe, Japan. From there, they took a boat to Shanghai, where they remained throughout World War II.

In 1947, Swislocki's family moved to the United States, settling in Los Angeles, where he would obtain his bachelor's, master's and doctoral degrees in biochemistry from the University of California, Los Angeles. Swislocki then completed a postdoctoral fellowship at Brandeis University.

Swislocki took a position at Memorial Sloan Kettering Cancer Center in New York, where he conducted research on red blood cells and aging. He was later appointed chair of the department of biochemistry at the University of Medicine and Dentistry of New Jersey, which in 2013 merged with Rutgers University to become the Rutgers School of Biomedical and Health Sciences.

Although he never hunted, Swislocki was an excellent marksman, according to his obituary in a Palisades, N.Y., newsletter, and made it to the Olympic trials in target shooting.

Swislocki is survived by his wife of 29 years, Jane Lattes–Swislocki; his brother, Arthur; children, Madeline and Mark; four stepchildren, Jain, Lisa, Abigail and Conrad; and 14 grandchildren.

George Ronald Williams

University of Toronto Scarborough professor emeritus and former principal George "Ron" Williams died in July.

Born in 1928 in Liverpool, England, Williams attended Merchant Taylors' School and earned his Ph.D. from the University of Liverpool. After pursuing postgraduate work at the University of Toronto, the University of Pennsylvania and the University of Oxford, he became a faculty member at the University of Toronto in 1956.

Williams chaired the department of biochemistry from 1970 to 1977. Under his leadership, the department expanded undergraduate instruction in biochemistry to include students in other disciplines as well as larger numbers of biochemistry specialist students. During his tenure as chair, members of the department received Canadian Biochemical Society Ayerst awards on three occasions.

Williams served as the sixth principal of what was then known as Scarborough College from 1984 to 1989. He loved to hike, and combined his passion for biochemistry with concern for the environment in a book published in 1996, "The Molecular Biology of Gaia," about the stability of the Earth's environment.

Williams loved the arts, including chamber music, opera, theater, the visual arts, poetry and novels: "His joy flowed from professional artists, but also from local amateur groups and, especially, children," according to his obituary.

Paul Gooch chaired the division of humanities at the University of Toronto from 1977 to 1982. "Ron Williams was a dear and lovely man, always positive, interested in all the world has to offer," Gooch said in a remembrance. "He had the mind of a scientist and the heart of a humanist."

Williams is survived by his wife, Joyce; children, Geoff, Glynis, and Tim; grandchildren, Jeremy, Dave, and Jano; and great-grandchildren, Nia and Lila.

IN MEMORIAM

Danica Dabich

Danica Dabich, professor emeritus of biochemistry at the Wayne State University School of Medicine, died June 20. She was 89.

Born August 6, 1930 in Detroit, Dabich received her bachelor's degree in chemistry from the University of Michigan in 1952 and a master's of science from Ohio State University in 1955. She earned a doctoral degree in philosophy from the University of Illinois in 1960.

Dabich began her career as an analytical chemist at Phillips Petroleum Co. in 1952, then worked as a research assistant at the E.B. Ford Research Institute for Medical Research. She was a postdoctoral fellow at the University of Freiburg in Germany before taking a position as a research associate at Wayne State in 1961. She became an assistant professor in 1966 and was promoted to associate professor in 1970.

Throughout her research career, Dabich explored the biochemistry of early mammalian development, working primarily with pre-implanted mouse embryos.

Dabich was a member of the American Chemical Society. In her spare time, she enjoyed reading, gardening and music.

She is survived by her sister, Lyubica Dabich, and brother, Sam Dabich.

Soll Berl

Soll Berl, a neurochemist, psychiatrist and professor emeritus of neurology at Mount Sinai Medical Center, died June 7 at his home in Pittsboro, N.C., five days before his 102nd birthday.

Born in Brooklyn in 1918, Berl earned degrees from St. John's University School of Pharmacy and the University of Wisconsin before World War II. During the war, he served as an Army medical technician and was part of a research effort to mass-produce penicillin for Allied troops. He attended medical school at Case Western Reserve University after his discharge, then did a residency at New York University Bellevue Medical Center, and a National Institutes of Health postdoctoral fellowship at the New York State Psychiatric Institute.

Berl began his career as an assistant professor and later associate professor of neurology and neurosurgery at Columbia University's College of Physicians and Surgeons. He also maintained a private part-time practice as a psychiatrist. He joined the department of neurology at Mount Sinai in 1974 and retired in 1989 as professor emeritus. He co-authored more than 100 papers with a research focus on brain amino acid and protein metabolism.

In retirement, Berl and his wife ran a bed-and-breakfast for 20 years in the Hudson Valley of New York. They later traveled extensively, spending time in Amagansett, N.Y., Vermont and North Carolina. An amateur artist, Berl also loved tennis, literature and the theater. He was admired for his cooking and was known to enjoy a very dry martini, especially on the beach at sunset, according to an obituary.

He is survived by his wife, Terry, four children and one granddaughter.

Herb Tabor (1918–2020)

By F. Peter Guengerich

On Aug. 20, the biochemistry community lost one of its giants with the passing of Herb Tabor at the age of 101. Herb was a unique individual, and he definitely will be missed.

Others knew him better than I did, but he outlived most of his contemporaries, so I was asked to write this Retrospective. I met Herb at a Journal of Biological Chemistry editorial board meeting when I joined the board for the first time in 1984, and we became acquainted later during my time on the American Society for Biochemistry and Molecular Biology council. I got to know him better after 2006, when I became an associate editor at JBC.

Herb was one of the finest individuals I have known in this field. Several obituaries already have appeared, and a detailed autobiographical account of Herb and his late wife, Celia, appeared in the 1999 Annual Review of Biochemistry. I will try not to repeat too many things. I will write about my experiences with Herb and what I know about him.

Herbert Tabor was born in New York City on Nov. 28, 1918, which he told me was Thanksgiving Day that year. World War I had just ended, and there was a viral pandemic then too. I do not know much about his childhood, but obviously, he was a real prodigy, attending the City College of New York for two years and then Harvard College, graduating from Harvard at the age of 18. He obtained an M.D. from Harvard Medical School at the ripe old age of 22 in 1941.

During his last year of medical school, Herb worked in the lab of A. Baird Hastings and developed his passion for research. His first paper in JBC was published in 1943 on this work, measuring the ionization constant of magnesium phosphate. His last JBC paper (which I acted as associate editor for) was published in 2015, 72 years after his first. I doubt this record ever will be eclipsed.

ASBMB

After he retired as editor-in-chief of the Journal of Biological Chemistry, Herb Tabor continued with the title of co-editor and helped assign manuscripts even after his 100th birthday.

Herb's medical degree did not lead to a long clinical career, but while an intern at Yale in 1942, he was the first individual to inject a new antibiotic called penicillin into a patient. The patient's recovery from severe streptococcal septicemia was remarkable, and this and other successes led to the scaling up of fermentation and use of the drug in the war effort. Herb also spent time during World War II as the only medical officer on a U.S. Coast Guard cutter ship, part of convoys in the North Atlantic. Despite a scare or two, he said, he did not have to do any surgeries.

In 1943, Herb was transferred to the U.S. Public Health Service, at first working under the direction of Sanford Rosenthal, beginning his 77-year career at the National Institutes of Health. He became a lab chief and continued in that role until 1999, when he was succeeded by Reed Wickner, who had trained with him. In the early 1940s, the NIH was new, and the NIH intramural program was small, located in Bethesda, Maryland. There, Herb and Celia Tabor began their pioneering research on polyamines, a topic that is still very interesting and was featured in a special collection in JBC edited by Tony Pegg to celebrate Herb's 100th birthday.

In the early days at the NIH, a group of what were to become stellar scientists would meet to eat lunch daily over presentations and lively discussions of current literature in the growing field of biochemistry. The

COURTESY OF ED MARKLIN

This photo of a young Herb and Celia Tabor hung in the kitchen of the duplex the family lived in since 1949 on the National Institutes of Health campus. The couple met on a Boston streetcar in 1940 and were married in 1946.

group included Herb Tabor, Arthur Kornberg, Leon Heppel, Bernard Horecker, and later others such as Earl and Thressa Stadtman, Christian Anfinsen, Alton Meister, Osamu Hayaishi and Bruce Ames. I would have loved to be part of that exciting time. Today, our field, in part because of its success, has become so broad that it is difficult if not impossible for an individual scientist to follow everything in any detail.

Herb and Celia were essentially free of most administrative responsibilities at the NIH. There was no grant writing, teaching, attending faculty meetings or serving on committees, and they relished this. Herb routinely did much of his own lab work. Late in his life, at one of our JBC associate editors' meetings, some editors were comparing problems with their eyeglasses. Herb said he was having problems in the lab with his own glasses when he was transferring bacteria, which meant he was doing the work himself. I also recall an account (not from Herb) of an NIH investigator in the 1980s who went to Herb's office to complain about a JBC submission that had been declined. He wound up having to follow Herb all around the lab because Herb was in the middle of some work, transferring rotors. The author finally felt embarrassed about bothering him.

Herb and his family lived at the NIH starting in 1949 in one of the duplexes built for staff. The big advantage was the ease of getting to and from work. Herb told me he used to walk home for breakfast (presumably, he went to the lab early). He lived in the same house at the NIH until his death. Living on the NIH campus is not so attractive today due to the security checks needed to enter; trust me — it's like the airport.

Herb was elected to the U.S. National Academy of Sciences in 1977, and in 1995, Herb and Celia received the ASBMB William C. Rose Award. I was asked to provide comments on his research program for an NIH intramural review. That was a humbling experience — how could I critique this great man? I was asked how his success compared with his contemporaries, but he had outlasted all of them.

In 1961, Herb joined the editorial board of JBC, and he became an associate editor in 1969. By today's standards, JBC was still a small enterprise, although it was certainly a premier journal in the field. When Bill Stein developed health issues, Herb took over as acting editor-in-chief and then as editor-in-chief in 1971, a job he would hold until 2010.

If you knew Herb, you could only be impressed by his organizational skills, his work ethic and his dedication to fairness. During his nearly 40-year tenure as editor-in-chief, JBC grew tremendously. Herb assigned all of the manuscripts out for review by himself, with the average rising to more than 50 per day at the peak of our submissions. In line with what he construed was his obligation to his job at the NIH, he did none of this during the workday — and it was much harder to do the necessary editorial work in the pre-electronic era. Assistants from the JBC office would leave a big sack of paper manuscripts at the back door of his house every evening. Sometimes, he would use the pay phone at the NIH lab to call the JBC office (during his lunch break), have titles read to him and make assignments (an early effort at e-communication). He handled

If you knew Herb, you could only be impressed by his organizational skills, his work ethic and his dedication to fairness.

complaints from authors and manuscript controversies on the weekends. In addition, he hosted three associate editor meetings each year.

As JBC grew, in the late 1980s, we heard pessimistic forecasts at our editorial board meetings regarding whether we could ever deal with the growing page volume. The JBC did not make too many mistakes during Herb's tenure, but one was the attempt at "miniprint" (go back to some 1980s JBC papers if you are too young to remember that). The issue later was resolved by instituting electronic publishing, where JBC led the field. Although Herb was no longer a young man, he adapted well to the electronic systems with his Mac and really pushed this new venture. As an associate editor, I knew that my new assignments (now electronic) would start rolling out every evening at about 6 p.m. Eastern time, when Herb got home from work. Even through the heavy submission years, Herb was a hands-on editor, and he assigned papers to himself for review as well as to the associate editors. He did delegate aspects of the JBC operations to Barbara Gordon and later to Nancy Rodnan, the ASBMB publications directors, both of whom he greatly admired. However, Herb was a nuts-and-bolts guy who drove the journal.

Herb worked well with the associate editors. He invited our input and was supportive in any problems we encountered dealing with authors, although he certainly wanted to be fair to the authors too. At the associate editors' meetings, he let us all have our input but was able to reach a consensus and then to make us all feel that we had been part of his final decision ("I think you will all agree with me that …").

As he indicated in his Annual Review of Biochemistry article, his objective for JBC was not to restrict publication to the most exciting research areas; we had a policy of

REMEMBRANCES

I was very fortunate to be a postdoc down the hall from Herb from 1989 to 1995. I warmly recall Herb and Celia eating lunch during our weekly seminar series. She would open up their lunch bag, hand him half a sandwich and take the other half. When that was finished, she would then take out a piece of fruit, cut it in half and give him his half. It was so wonderful to see their love for one another. And fortunately, one of his postdocs, David Balasundaram, and I cooked up a collaboration that ended up as a couple of papers. To be a co-author with Herb was a great honor. Herb always had an open door and an open ear, and he asked the best questions. He was a force of nature.

Jonathan D. Dinman, University of Maryland

After our first publication on a key enzyme in polyamine biosynthesis, Herb was among those whose comments encouraged me to shift much emphasis in my lab toward the study of polyamines. In the subsequent 10 years, I met many good friends and colleagues at stimulating and entertaining meetings in the U.S., Europe, Japan and Israel. Eventually, mitochondria regained my attention. Thus, I have not seen many of my "polyamigos" for some time, but I retain wonderful memories. Herb stands out among them as a giant role model in research and service to science.

Herb also was responsible for my selection to the editorial board of the JBC. The 10 years I spent on the board were challenging but most rewarding and satisfying.

Immo Scheffler, University of California, San Diego

In the fall of 2009, Herb Tabor phoned to ask if I would write the National Academy of Sciences biographical memoir of the biochemist Mahlon Hoagland (1921–2009). I think he was doing so as chair of NAS Section 21 at the time. He quickly added, "You are in a unique position to do this." Sensing my puzzlement, he said, "You are still alive."

We both laughed, and I accepted of course. But what added to the combined poignancy and comedy of this phone call was that Herb himself was in his early 90s at the time. From this experience — in which I felt his vigor, intelligence, kindness and sense of humor — I hoped that he would be around for much longer, and indeed he was.

Thoru Pederson, University of Massachusetts Medical School

COURTESY OF F. PETER GUENGERICH

Herb Tabor, left, poses with ASBMB Publications Director Nancy Rodnan and F. Peter Guengerich. Tabor would delegate aspects of the JBC operations to Rodnan, but he was a nuts-and-bolts guy, Guengerich writes.

accepting all manuscripts that made a substantial biochemical contribution. That is, we wanted to publish exciting papers but not at the expense of solid contributions that are important for the development of science. He resisted pressure to allow exceptions to our policy of considering all manuscripts equally, without any preselection or commitment for expedited publication of favorite authors or subjects. Some JBC Classics papers, for example, might not have seemed exciting when published, but they stood the test of time and had great impact.

After retiring as editor-in-chief, Herb continued with the title of co-editor and was helping assign manuscripts even after his 100th birthday.

After retiring as editor-in-chief, Herb continued with the title of co-editor and was helping assign manuscripts even after his 100th birthday. We sometimes would talk about assignments of problematic manuscripts or whether a submitted paper really fit our journal best — his instincts were almost always right. I never have heard anyone say anything bad about Herb, although there must have been some complaints; when you are an editor, you cannot accept all the papers, and he must have annoyed someone along the way. Publishing is changing rapidly today, and I doubt if any editor will ever match the 40-plus years Herb ran JBC.

I was privileged to know and work with Herb Tabor. He was in essence a humble man. Beyond his family, he focused everything on science and JBC. The ASBMB and the entire biomedical science community will miss him. Herb was truly a person to emulate. The ASBMB already has recognized him with the Herbert Tabor Research Award for excellence in biological chemistry and molecular biology and contributions to the community of scientists and the JBC Herbert Tabor Early Career Investigator Awards given to first authors of exceptional JBC papers.

Herb was preceded in death by his wife, Celia White Tabor, in 2012. He is survived by his four children, Edward, Marilyn, Richard and Stanley, as well as 10 grandchildren and six great-grandchildren.

So long, Herb. You are really missed. Thanks for the memories, on behalf of all of your admirers.

F. Peter Guengerich (f.guengerich@vanderbilt.edu) is deputy editor of the Journal of Biological Chemistry and the Tadashi Inagami chair in biochemistry at Vanderbilt University.

REMEMBRANCES

Herb Tabor was one of a kind. When he took hold of the JBC, it was already an iconic institution, but he took it so much farther. I value the three years I spent on the ASBMB Publications Committee, where I treasured my interactions with Herb. His wisdom was much appreciated when I had to handle a couple of ethics issues. The JBC has stayed on a high plane, but Herb was indispensable in getting it there and keeping it there.

My first research publication, as a third-year graduate student, was in the JBC, as was my last, as a long-retired professor. The JBC, and Herb, enriched my career and my life.

Christopher K. Mathews
Oregon State University

Herb Tabor was a unique and deeply memorable person — gracious leader, dedicated scientist, visionary with deep insight, devoted husband and father, and above all exceptionally kind and generous. In my years as an associate editor, his ability to guide a group of independent (and sometimes fractious) editors ever so clearly and yet gently into the best decisions was amazing. His daily dispersal of all incoming JBC submissions with just the right connection to each of the associate editors seemed an impossible task — but he always did it. Herb Tabor's personal ethos is reflected in the JBC today in a way that I hope will be transmitted into the future as a living memorial of his contributions. And even more amazing, his commitment to his own research and students thrived in the midst of these responsibilities. He mentored a multitude of students and colleagues with his quintessential example that brought together exceptional brilliance, dedication and kindness. His absence in our world is our great loss, but his example is forever before us.

Kathleen S. Matthews, Rice University

Herb's achievements in polyamine research in health and disease were substantial and significant. As the editor-in-chief of JBC for 40 years, his accomplishments set a golden mark on the scientific community. I suspect that no other scientist has had as much influence on the scientific community as he has. In 2004, he and Celia participated in the International Polyamine Conference held in Chiba, Japan, and after the meeting they visited Osamu Hayaishi (president of Osaka Bioscience Institute at that time, now deceased), who had been a close friend since their NIH era. Herb and Celia came to visit me also, and he presented an excellent lecture at Osaka University. Many of our researchers were impressed by his talk.

I remember when I met Herb at a JBC editorial board meeting, and I was amazed to learn that he personally handled over 400 submitted manuscripts to JBC and assigned each paper to a suitable associate editor. He was 81 years old at that time.

I think that he is now renewing his friendship with Professor Osamu Hayaishi in Heaven.

Tani Naoyuki Taniguchi, Osaka University and Osaka International Cancer Institute

Not only was Herb a brilliant and dedicated scientist, but he was a gentleman, who taught me a few lessons way back when I was a graduate student about how to conduct yourself when facing a not-so-friendly audience. Also, he was a devoted husband and father. His legacy is as multifaceted as his contributions and the extent of peoples' lives he touched.

We will hold his memory and his family in the Light.

Ed Eisenstein, University of Maryland

REMEMBRANCES

Herb and the JBC were a huge part of my professional career. Since he was editor-in-chief throughout my career, I think of JBC = Tabor. Here are some highlights:

• When I was a graduate student with Sidney Udenfriend, I felt I had finally made it when I published in the JBC, which was considered the gold standard.

• My postdoc from 1970 to 1973 was in the lab of Bob Schimke who himself had been a postdoc in Herb's lab. Because of this, I always thought of Herb as my scientific grandfather and reminded him of this every time I saw him. My first paper with Bob Schimke was in the JBC.

• When I was a faculty member at University of Kentucky Medical Center, my quest for tenure was substantially aided by publication of another JBC paper.

• My first two graduate students, Lee-Yun Chu and Larry Malek, published their major findings in the JBC.

• My career received a major boost when I was appointed to the editorial board of the JBC in 1990. I suspect this was one reason I was hired as head of biochemistry and molecular biology at Louisiana State University Health Sciences Center in 1992, a position I held for over 21 years until I closed my lab and went from active to emeritus faculty status.

• One of the best papers by one of my postdocs, Barry Lamphear, was in the JBC.

• Being on the editorial board drew me into service on the ASBMB Publications Committee, which I chaired for a year or two. There I saw up close and personal how the JBC functioned and what made it great.

I am grateful for Herb's outstanding service editing one of the premier scientific journals. It is inconceivable how many lives he touched and how many careers he promoted.

Bob Rhoads, Louisiana State University Health Sciences Center

During the time when JBC was trying to decide if they were going to go online or not, Herb was undecided and argued for quite a while not to go online until he could be convinced that it would be good for the journal and the readership. One day when he was in his office, he went to look up an article in a bound volume of past issues. The volume was so heavy that it slipped out of his hands and fell on his foot. It broke a toe and helped him make the decision to move the journal online.

Herb loved to tell that story as an example of higher authorities (like gravity) sometimes being needed to help make important decisions.

Charles Craik, University of California, San Francisco

Mentoring and metabolism

Sharifa Love–Rutledge studies the impact of Type 1 diabetes susceptibility genes and supports young scientists

By Kerri Beth Boggs

COURTESY OF SHARIFA LOVE– RUTLEDGE

Indications from her graduate and postdoc studies that an overlap existed between Type 1 diabetes and prediabetes inspired Sharifa Love–Rutledge's research focus at the University of Alabama at Huntsville.

When Sharifa Love–Rutledge was a little girl in Moss Point, Mississippi, her brother received a science kit for Christmas. She convinced him to let her help make borax bouncy balls from the kit, and seeing simple ingredients transformed into a tangible product changed her life.

"I hadn't done any science demos up to that point," she said. "It was exciting to have something that worked come from the experiment."

She wanted to do more.

In fifth grade, Love–Rutledge joined her school district's gifted program, which provided an outlet to explore her interest in science. She thought about becoming an ophthalmologist and designed a papier-mache eyeball to present in class. Though she sometimes tried to avoid attention, the teachers in the program helped Love–Rutledge find her voice.

"In some classes, I wanted to fade into the background. My eighth-grade science teacher, Mrs. Stevenson, made me feel seen," she said. "She encouraged me to ask questions and participate. I felt like I was valuable in that space."

Guardian angels

Love–Rutledge's teachers put her on a path to pursuing a biology degree at Tougaloo College in Hinds County, Mississippi, but she struggled with rote memorization in her freshman biology class. She decided to leave the department of natural science, and her professors, who had noticed something special in her, wondered why she disappeared.

"They saw something in me that I didn't see in myself," she said.

Fate stepped in when Love–Rutledge returned to the department to take an organic chemistry class in her sophomore year. She found her niche studying chemical mechanisms and using analytical problem solving. Her professors recognized her talents and decided to make a long-term investment in her success.

"Once I came back, they weren't going to let me leave," she said. "I had several professors that would strategically check in on me. My organic chemistry professor still checks in on me now!"

Love–Rutledge also found mentors through the National Science Foundation's Louis Stokes Alliance for Minority Participation and the U.S. Department of Education's McNair

She found her niche studying chemical mechanisms and using analytical problem solving. Her professors recognized her talents and decided to make a long-term investment in her success.

Scholars Program, both designed to help underrepresented minority students achieve academic success.

"Those two programs working together was really great," she said. "I was able to pool two sets of resources that helped me reach my end goal."

Becoming the angel

Love–Rutledge graduated from Tougaloo with a degree in chemistry and went on to pursue a Ph.D. in biochemistry at the University of Alabama.

She stepped into unfamiliar territory in her first-year biochemistry course. The students gave presentations and offered feedback to each other, but the competitive environment caught Love–Rutledge off guard. Some students put others down to make themselves look better. Love–Rutledge, who already questioned if she should be in graduate school, felt like an imposter.

Once again, her mentors came to the rescue, helping her break free from the paralyzing lies of imposter syndrome so she could blossom as a scientist. Though she sometimes wanted to give up, Love–Rutledge said that her "guardian angels" encouraged her to stick with her path.

As a graduate teaching assistant, Love–Rutledge came face-to-face with her own challenges while working with undergraduates. She watched students become defeated by their science classes and give up on themselves. She managed to help save some of them, but others slipped through the cracks, beyond her grasp.

"Now that I'm a professor, I have the ability to save more students that have the potential to succeed," she said.

Love–Rutledge learned that many students, particularly those in minority groups, struggled to believe in themselves and find their potential. She recognized the need for students to see people like themselves in the positions they hoped to reach one day.

"I hadn't met an African American female with a Ph.D. until I was in graduate school," she said.

Rats, humans and diabetes

In 2014, Love–Rutledge completed her graduate work on chromium nutrition and its relation to Type 2 diabetes. She was the first Black woman to earn a Ph.D. in chemistry from the University of Alabama.

At Michigan State University, she completed a postdoc in the physiology department, studying a virus-inducible Type 1 diabetes rat model. She saw changes in the rats that resembled the Type 2 diabetes models she had worked with in graduate school. She began to wonder if an overlap existed between Type 1 diabetes and prediabetes.

These observations inspired her research focus at the University of Alabama at Huntsville, where she is now an assistant professor in the chemistry department.

Continued work with the rat model from her postdoc showed that the animals are susceptible to Type 1 diabetes when they are young through an immune-driven event. As the animals age, they develop prediabeteslike symptoms. Love–Rutledge's research suggests that these changes are connected to a Type 1 diabetes susceptibility gene that is associated with kidney disease in African Americans and cancer risk. She plans to explore the role of this susceptibility gene in aging and lipid metabolism. Since this gene can make humans and rodents susceptible to Type 1 diabetes, it may also enhance their susceptibility to other pathologies.

Love–Rutledge's lab uses biochemical techniques to correlate the metabolic changes at multiple stages of life due to the susceptibility gene to find translational biomarkers linked to increased diabetes susceptibility. They also study the proteins expressed from Type 1 diabetes susceptibility genes to understand how they affect pancreatic beta cells and insulin-sensitive tissues such as the liver, skeletal muscle and fat.

Giving back

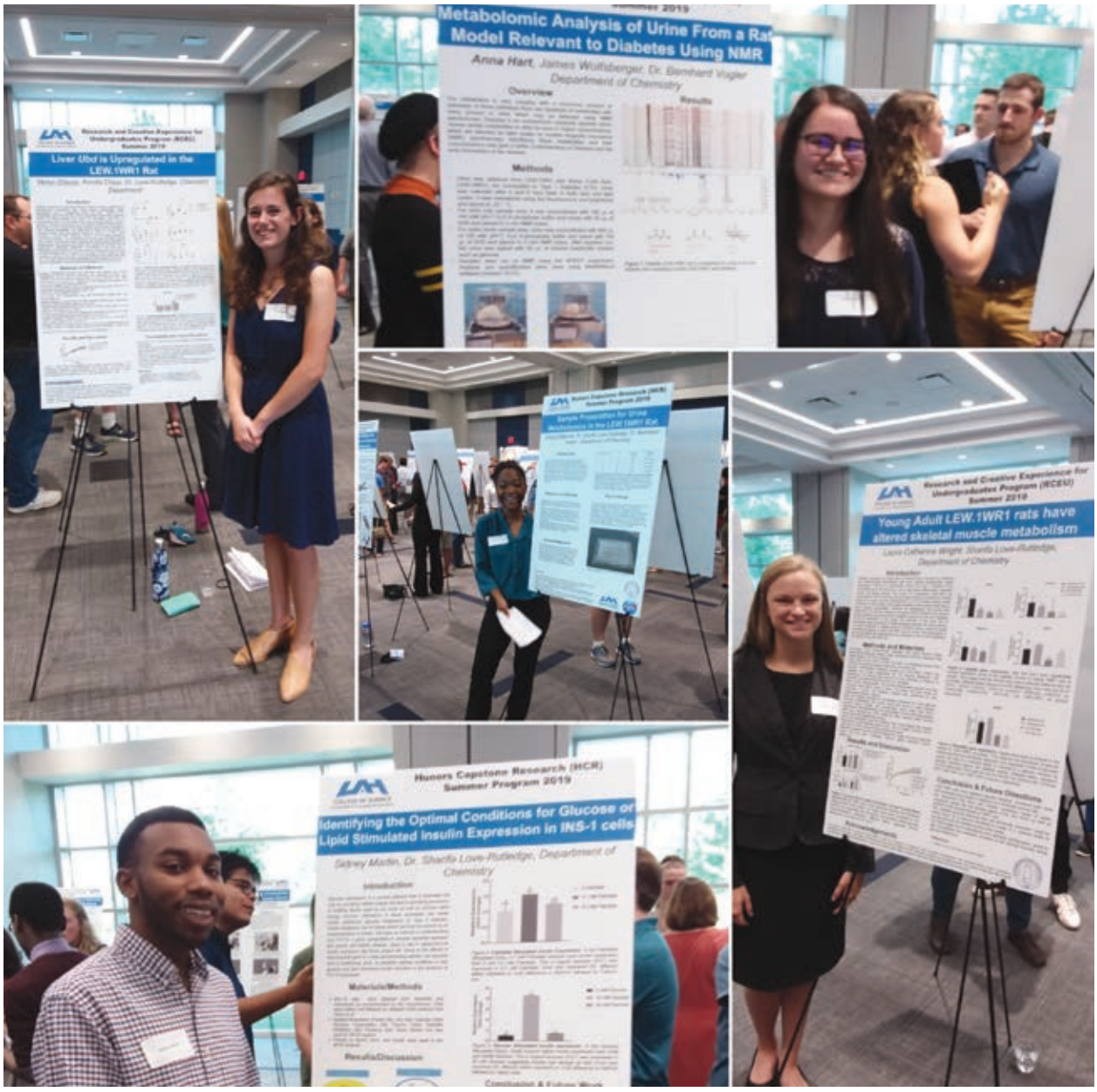
Outside the lab, Love–Rutledge serves as a mentor for students through her church and a youth symposium program where she organizes science demonstrations and programming. She wants to expose young students to science and be a resource for them as they think about their education and career options.

"Kids' choices are often limited to

About the Research Spotlight

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

COURTESY OF SHARIFA LOVE- RUTLEDGE



Members of the Love-Rutledge lab display their research: top, left to right, Helen Gibson and Anna Hart; center, Jamya Patterson; bottom, left to right, Sidney Martin and Laura Catherine Wright.

what they're exposed to. They may never get to leave their hometown," she said. "I want to help them realize that the world is bigger than what they've seen."

Love–Rutledge hopes to make a difference in the lives of young scientists, just like the mentors who never gave up on her. She reminds her mentees that Rome wasn't built in a day.

"It takes time to build all the accolades you see for the people around you," she said. "It's easy to place unrealistic expectations on yourself. Be okay with gradual changes and gradual improvement. Pace yourself. You can't force things to happen."

Kerri Beth Boggs is a graduate student in the biochemistry department at the University of Kentucky. Follow her on Twitter @KB_Boggs

Nobelists' former postdocs discover missing link in telomerase evolution

By Nivedita Uday Hegdekar

COURTESY OF DOROTHY SHIPPEN

At work in the Shippen lab at Texas A& M are, left to right, Dorothy Shippen, first author of the recent paper Jiarui 'Gerry'Song and Claudia Marcela Castillo-Gonzalez.

In 1983, Carol Greider and her Ph.D. advisor, Elizabeth Blackburn, discovered telomerase, the enzyme that replenishes telomeres. For this, they were awarded the 2009 Nobel Prize in physiology or medicine, and their seminal work opened the gateway for decades of work that has advanced our understanding of aging and human lifespan — including new research by their own former postdocs.

Those postdocs, Dorothy Shippen and Julian Chen, knew each other long before their first collaborative project, a study published in Proceedings of the National Academy of Sciences.

"Julian and I came out of Carol Greider and Elizabeth Blackburn's research labs, respectively," said Shippen, a university distinguished professor and regents fellow in Texas A&M's department of biochemistry and biophysics. "Due to our similar research interests, we kept crossing paths at various research conferences for many years. Our respective research groups used different tools to answer fascinating questions about telomerase, and Julian and I developed a mutual admiration for each other's work."

At the 2019 Cold Spring Harbor Telomeres and Telomerase Meeting, members of Shippen's group met up with Chen's lab team (Chen is a professor of biochemistry at Arizona State University), and they discussed their ongoing research projects. Those conversations resulted in a collaboration that led to a pivotal discovery about telomerase RNA.

About telomerase

Telomeres are repetitive DNA sequences that safeguard the ends of linear chromosomes. Healthy somatic cells have a limited replicative lifespan, and as they age, their telomeres shorten, leading to eventual cellular senescence and/or apoptosis. However, the ribonucleoprotein enzyme telomerase counteracts this shrinking process and helps lengthen telomeres by adding short DNA repeats, thus extending the life of the cell. The level of telomerase activity is crucial in determining telomere length, particularly in aging cells.

Many researchers have focused on the use of telomerase in cancer and anti-aging treatments. However, much is unknown about the telomerase, particularly its evolution. The enzyme is markedly different across various kingdoms, making it important to understand the components that contribute to these evolutionary differences and their role in telomere maintenance.

Telomerase complexes contain two core components: a catalytic protein subunit and an RNA subunit. The catalytic protein subunit — telomerase reverse transcriptase — has been well characterized. The RNA subunit serves as a template for the addition

of new telomeric DNA repeats by the reverse transcriptase. Researchers first isolated it in 1991 in ciliates and later discovered its homologs in yeast and humans.

Uncovering a missing link

"The telomerase RNA in these three different kingdoms — ciliate, yeast and humans — are very different with regard to transcription machinery, sequence, etc.," Chen said. "A long-standing question in the telomerase biology field is, how did these various telomerase RNAs evolve so differently?"

Researchers tried for years to isolate telomerase RNA from plant species. They included Shippen, who believed the plant kingdom held the key to unanswered questions in telomerase evolution.

"Plants often evolve unique solutions to fundamental biological challenges," she said. "Plant telomerases may tell us something new about longevity and aging and how human telomerase could be regulated. Hence, it was essential to discover this missing subunit."

Shippen previously had identified the reverse transcriptase subunit in plants. In 2019, her team, led by graduate student Jiarui Song, successfully isolated telomerase RNA from the thale cress plant, Arabidopsis thaliana. To isolate this telomerase RNA, termed AtTR, the researchers used a protein purification approach using deep sequencing of RNAs associated with telomerase activity.

"Our investigations began with some genetic and phylogenetic analysis of AtTR," Shippen said. "We then decided to follow up by further characterizing this subunit and finding new homologs. This is where Dr. Chen and his team played a crucial role."

> "Plant telomerases may tell us something new about longevity and aging and how human telomerase could be regulated."
>
> DOROTHY SHIPPEN

Chen and his team worked with the Shippen lab to determine the structure, perform functional analysis of the isolated AtTR and identify its homologs in many other plant species.

These analyses, coupled with studies in cells and animal models, uncovered a startling revelation: The plant telomerase RNA was an intermediate between telomerase RNA from humans and from lower eukaryotes. The subunit contained signature marks from both animal and protist kingdoms.

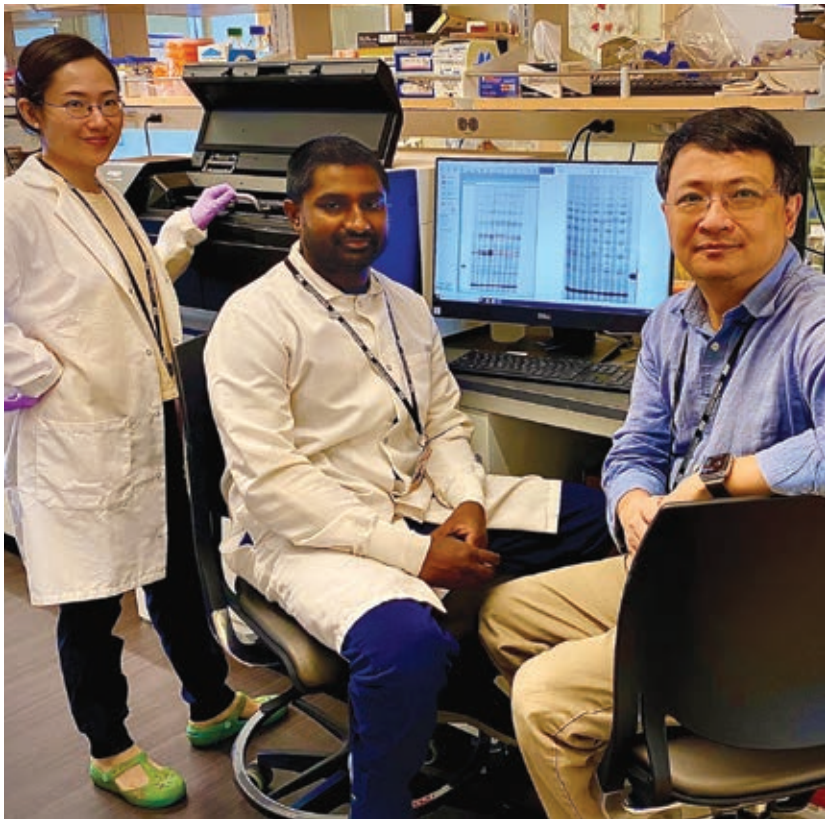
"We called this intermediate plant telomerase RNA the 'missing link' between ciliates and vertebrates," Chen said. "It significantly expanded our knowledge about telomerase evolution."

Delving deeper, moving forward

The complete identification of plant telomerase allows researchers to study telomerase evolution in a new way. While ciliate and plant telomerase RNA are transcribed by RNA polymerase III, vertebrate and fungal telomerase RNA are transcribed by RNA polymerase II. How did telomerase RNA evolve to be transcribed by two different RNA polymerases, and how did they make this transition?

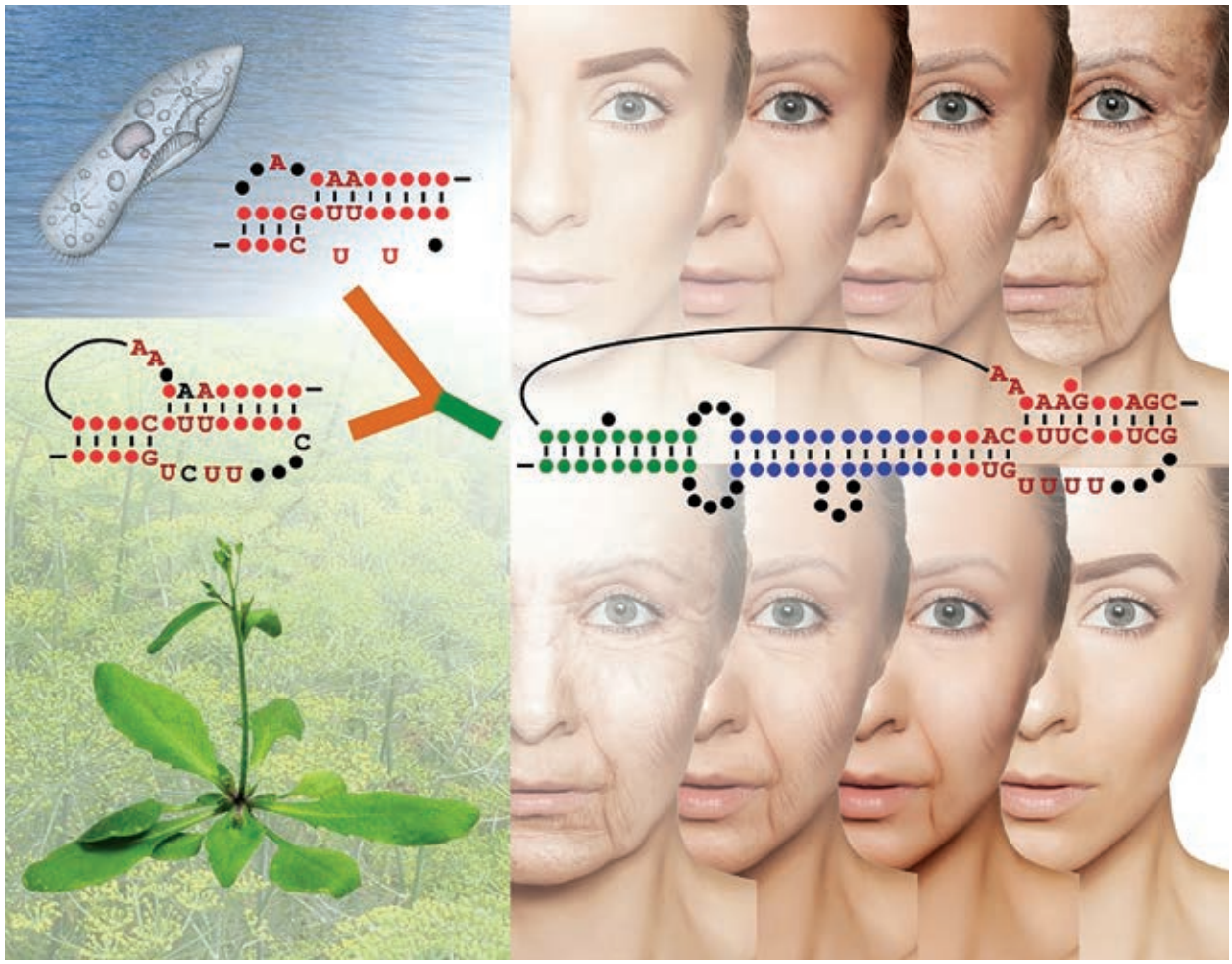
To answer this question, Chen said, "Our next step will be to study

VANAE GOHEEN-HOLLAND



Pictured in the Chen lab at Arizona State are, from left, Yang Li, a research assistant professor; Dhenugen Logeswaran, a postdoctoral fellow; and Julian Chen. All were authors on the recent PNAS paper.

COURTESY OF JULIAN CHEN



This image represents the relationship between aging and telomerase. The structure and function of a missing component of telomerase enzyme from plants hold promise for aging and cancer research.

telomerase RNA in several ancestral plant species to characterize their structure and determine which RNA polymerase they were transcribed by. Hopefully, we will soon have a comprehensive picture about how telomerase RNA has evolved along different eukaryote lineages."

Shippen wants to delve deeper into the telomerase ribonucleoprotein complex. She believes that a different group of proteins associate with the reverse transcriptase to make it functional in plants.

"By uncovering these accessory components," she said, "we will gain insight into the interface between the canonical telomerase function and other cellular functions such as metabolism."

Shippen and Chen will continue collaborating to study plant telomerase. They expect future research into the plant system to have translational application in humans, particularly for cancer and anti-aging treatments.

While plant and human telomerases differ, understanding the plant telomerase mechanism and its evolution might help researchers engineer new strategies to regulate and manipulate human telomerase. For example, higher levels of telomerase immortalize cancer cells, enabling them to live and grow much longer than normal cells. Targeted inhibition of telomerase in cancer might have therapeutic benefit.

Chen and Shippen believe that applications of their findings in humans are years away, but they are optimistic about the future of telomerase research.

"We see a lot of opportunities ahead," Chen said. "This is indeed an exciting time to be working in the field of telomere biology and telomerase evolution."

Nivedita Uday Hegdekar (nivedita.hegdekar@umaryland.edu) is a graduate student at the University of Maryland working toward a Ph.D. in biochemistry and molecular biology and an M.S. in patent law. Follow her on Twitter @NiveditaHegdek1.

Re-creating coagulation in a lab

A positive step for the horseshoe crab

By Kian Kamgar-Parsi

KALDARI/WIKIMEDIA COMMONS

The horseshoe crab has been around for 450 million years and is more closely related to spiders than other crabs. Use of horseshoe crabs' blue blood (called hemolymph) for medical tests threatens a species already pressured by environmental change and human development.

When considering modern medicine's fight against infections, a horseshoe crab is likely not the first thing that comes to mind. However, the dwindling number of these ancient arthropods is cause for concern in the biomedical industry.

Bacterial lipopolysaccharide, or LPS, is a toxic molecule that can cause life-threatening infectious reactions in humans. Horseshoe crab hemolymph (a blood equivalent) is extremely sensitive to LPS, coagulating in response to even trace amounts. Due to this property, hemolymph is used in the Limulus test, a critical tool to ensure medical devices and drugs are free of LPS contamination. Unfortunately, the harvesting of hemolymph pits medical and conservation interests against each other.

Shun-Ichiro Kawabata, a researcher at Kyushu University in Japan, seeks a solution to this conflict. "(The) raw materials of Limulus test are totally dependent on the limited natural resource," he said. "As an alternative approach, we have been doing studies to develop a next-generation Limulus test using recombinant (engineered) proteins."

Recent research published by Kawabata and his colleagues in the **Journal of Biological Chemistry** represents an important step toward a hemolymph-free Limulus test.

In their study, Kawabata's team focused on the main catalytic pathway of hemolymph coagulation: three zymogens (inactive enzyme precursors) called proC, proB and proCE. In the presence of LPS, proC is activated into an enzyme called alpha-chelicerase C that converts proB into chelicerase B; chelicerase B in turn activates proCE into the clotting enzyme that coagulates the hemolymph. Kawabata previously engineered functional proC and proB; in this new research, his lab also made a functional proCE without the use of hemolymph for the first time.

"We have overcome several difficulties in preparing these recombinant proteins, and now we have (all) three recombinants: proC, proB, and proCE," Kawabata said. Using these three proteins to reconstitute the coagulation cascade, the team discovered that specific regions and amino acids in proB and proCE are key for activation. Now they are using their set of recombinant zymogens and these recent data to improve on nature's designs.

"We are pushing this work forward to prepare more effective and stable recombinants of the protease zymogens applicable for the detection of LPS," Kawabata said.

Challenges remain before a fully synthetic hemolymph substitute can be used for the Limulus test. While the proteins developed by the team represent the core components, three proteins alone cannot mimic hemolymph perfectly. "Some cofactors, environmental proteins or some preservatives must be indispensable," Kawabata said.

It is also important to ensure that the cascade cannot be triggered by other environmental substances, something that will require further testing and optimization.

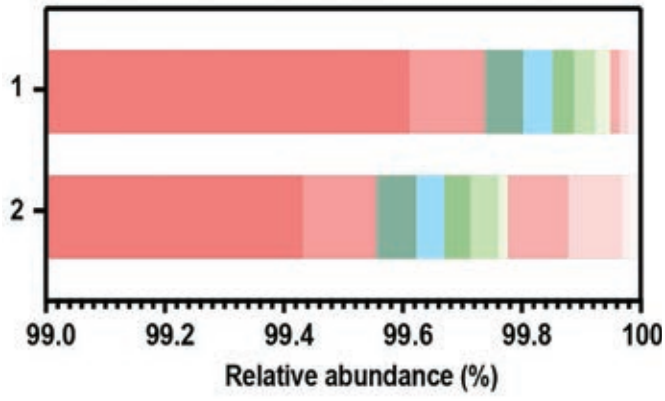
Although questions remain, Kawabata and his team already are working with companies in Japan "to make a more sensitive and convenient test … and ensure a continuous supply of the best materials," he said.

In time, the proteins developed in the Kawabata lab could bring medical and conservation concerns into harmony, protecting the horseshoe crab population while providing a powerful tool to prevent infections.

Kian Kamgar-Parsi received a Ph.D. in biophysics from the University of Michigan and works as a consultant for the pharmaceutical industry.

Gut microbiome shaped by dietary sphingolipids

By Nivedita Uday Hegdekar



This bar graph shows the sphingolipid interactors of the microbiome in decreasing order from left to right, with Bacteroides, Prevotella, Lactobacillus and Bifidobacterium being the top four interactors.

The gut microbiome comprises trillions of symbiotic microorganisms that reside in our gastrointestinal tract and perform biochemical functions that affect metabolic health. Each microbiome is unique, and microbiome imbalance is associated with disorders such as inflammatory bowel disease and celiac disease.

Diet influences gut microbiome composition, and macronutrients such as carbohydrates, protein and fats are key mediators of this influence. Lipids are a major macronutrient, yet scientists know little about how individual classes of dietary lipids interact with the microbiome.

Elizabeth Johnson studies sphingolipids, a class of lipids that consist of a sphingoid backbone attached to a fatty acid via an amide bond. Sphingolipids not only are present in most foods and synthesized from scratch by the host tissue but also are produced by gut microbes themselves. This raises some questions: How do dietary sphingolipids interact with the microorganisms that do and do not produce sphingolipids? Are they assimilated into the microbiome? If so, how do they influence microbial metabolism?

The Johnson lab developed a method called bioorthogonal labeling-sort-seq-spec, or BOSSS, for identification and fate-mapping of dietary sphingolipids in the gut microbiome. The researchers synthesized and fed alkyne-tagged sphingolipids (distinguishable from the body's sphingolipids and those in the host microbiome) to mice and conjugated fluorescent dyes to the tagged metabolites using click chemistry. Fluorescence-activated cell sorting and 16S rRNA gene sequencing isolated and identified microbes that took up the alkyne-tagged sphingolipid metabolites and those that did not.

The team found that the dietary sphingolipids largely were taken up by Bacteroides and Prevotella spp., two key players in the human gut microbiome. Metabolomic analysis revealed that non–sphingolipid-producing microbes such as Bifidobacterium, a major microbiome component, could process the sphingolipids in ways similar to the sphingolipid-producing microbes such as Bacteroides and also in unique ways.

Because the foods we eat are assimilated by our microbiomes, this work could have consequences for health and, importantly, in development of the infant microbiome. Sphingolipids comprise approximately 0.2% to 1% of the total lipids in human milk. In breastfed infants, human milk and microbiome development are intimately related in the first six months of life. Johnson and her group hypothesize that sphingolipids in milk could influence positively the development of the infant microbiome.

Min-Ting, is first author on the paper published in the **Journal of Lipid Research**.

"We will next investigate the molecular consequences of sphingolipid consumption in infants and in our mouse models," she said. "Furthermore, we will be using our BOSSS methodology to investigate how other lipids, for instance cholesterol, can shape the microbiome."

Such work has implications for microbiome-related nutrition, Johnson said.

"By determining how the microbiome might be interacting with different metabolites, we can ultimately use diet to positively influence our microbiome composition. This way we can really revolutionize the field of precision medicine."

DOI: 10.1194/jlr.RA120000950

Nivedita Uday Hegdekar (nivedita.hegdekar@umaryland.edu) is a graduate student at the University of Maryland working toward a Ph.D. in biochemistry and molecular biology and an M.S. in patent law. Follow her on Twitter @NiveditaHegdek1.

Our internal ecology

Ecosystem models help explain the diversity of the gut microbiome

By Laurel Oldach

According to a recent estimate, if you sample enough humans' intestines, almost 40,000 types of microbe can be found. Any individual may have 100 trillion individual micro-organisms in one or two thousand taxonomic groups. How does the microbiome maintain such diversity?

One model to explain the enormous variety borrows from studies of larger ecosystems. A well-known theory in ecology, nonequilibrium coexistence of competitors, suggests that as an environment fluctuates, different species gain an edge over neighbors — but their ascendance rarely lasts long.

Intestinal nutrients fluctuate as the human host eats and excretes, in time with the physiology of sleep–wake cycles, and along the length of the gut. A layer of mucus that protects host cells from commensal microbes introduces new oligosaccharides as a fuel source and also separates microbial communities into mucosal and luminal niches. As conditions change, species in the microbiome shift in abundance and jockey for survival, and the constantly changing competitive edge keeps the ecosystem diverse.

According to University of Ottawa postdoctoral fellow Leyuan Li, the time is ripe for microbiome studies to apply population modeling and systems dynamics from macroecology to this more intimate ecosystem.

"Most of the time we study the gut microbiome as a whole: We sequence one sample as if it were representative of our whole gut," said Li. "The gut is actually a heterogeneous system … so we need to start thinking about the gut microbiome like a rainforest."

LEYUAN LI

Macro- and microecosystems may have more in common than we might think.

Li, who conducted her Ph.D. studies building artificial ecosystems, now studies gut microbiome dynamics in health and diseases such as inflammatory bowel disease in the lab of Ottawa professor Daniel Figeys. In a recent review in the journal **Molecular & Cellular Proteomics**, the pair offer an introduction to microbiome ecology.

The review highlights the potential for metaproteomics, which characterizes the proteins of whole communities of microbes, to describe microbial function. Most microbiome studies use metagenomics, ribosomal RNA sequencing of the mixed population of a microbial community, to identify the bacteria, fungi and archaea that are present. Li thinks metaproteomics also may help researchers road-test increasingly popular ex vivo experimental models of the microbiome to make sure they match up to the real thing.

"Using metagenomics, you know who are there and what they can do," Li said. "With metaproteomics you know who are there and what they are doing."

DOI: 10.1074/mcp.R120.002051

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

From the journals

By Nuala Del Piccolo, Latavia Hill & Anand Rao

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

Risk factors for metabolic disease

Following a meal, the human body rapidly converts extra calories into triglycerides. These fatty acids then are stored in the bloodstream and fat cells, where they serve as an accessible source of energy. Dysregulation of triglyceride metabolism and storage is associated with metabolic diseases, including Type 2 diabetes. Age also increases the risk for metabolic disease. The combined impact of these two factors rarely is considered.

In a recent **Journal of Lipid Research** review paper, Kathryn Spitler and Brandon Davies of the University of Iowa summarize the current literature on the relationship between aging and triglyceride metabolism/storage. They write about studies that link aging to an increase in plasma triglyceride levels, a decrease in the activity of enzymes that break down triglycerides, changes in the distribution of fat cells in the body, and alterations in inflammation-associated lipid storage and release processes.

The authors assert that supplementing the existing literature with mechanistic studies at the molecular, cellular and physiological levels will answer open questions about how aging and triglyceride metabolism/storage cause metabolic disease and

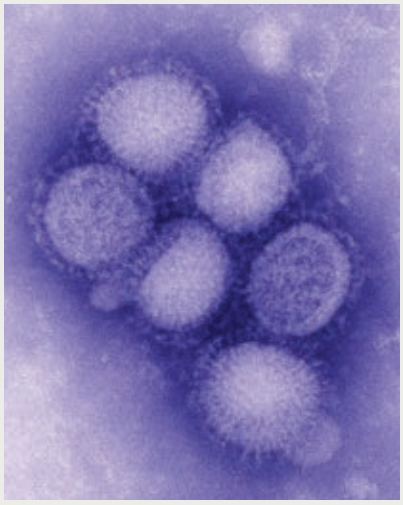
Pinpointing the proteases that make flu go viral

There are four main types of influenza viruses — A, B, C and D — and nearly every winter in the U.S. the influenza A and B viruses cause the disease epidemic known as flu season. Globally, influenza A and B account for over 300,000 deaths and 3 million to 5 million cases of severe respiratory illness each year, according to the World Health Organization.

Hemagglutinin, or HA, is a glycoprotein located on the surface of influenza viruses. HA is activated by cleavage by host cell proteases and is essential for initiating the entry of influenza virus into host cells. Understanding the mechanisms of HA protein cleavage is important for development of flu therapies, but the proteases involved in the activation of many viral strains remain unknown.

In a recent paper published in the **Journal of Biological Chemistry**, Anne Harbig of Philipps-University Marburg and an international team revealed a collection of proteases that process HA and govern protease functionality against specific HA glycoproteins. Using RNA sequencing, infection of mouse cell lines and plaque assay analysis, the authors analyzed the collection of proteases present in mouse lower airway tissues and identified four candidate proteases responsible for influenza A and B HA activation: hepsin, prostasin and two transmembrane serine proteases, or TMPRSSs, known as TMPRSS4 and TMPRSS13.

CENTERS FOR DISEASE CONTROL INFLUENZA LABORATORY



Researchers are studying the proteases responsible for cleaving the influenza A and B glycoprotein hemagglutinin, found in viruses such as H1N1 influenza, shown here in a colorized image.

The researchers used protease inhibitors alongside transfection of TMPRSS13, hepsin and prostasin in double-knockout Tmprss2-/-Tmprss4-/- cells to identify differences in HA reliance on protease cleavage. They found that HA proteases overlap in the two influenza viruses but demonstrate functional differences. Finally, the authors extended their work from mouse airway tissue to human tissue, finding that human orthologs of hepsin and prostasin cleave influenza B HA extensively but not influenza A HA.

The researchers' data suggest that influenza A and B strains have overlapping sets of proteases that cleave HA differently and that protease activity differs in mice and humans. Identifying the factors responsible for influenza HA activation has both basic science and potential therapeutic applications.

DOI: 10.1074/jbc.RA120.012635

inform strategies to mitigate these risk factors.
DOI: 10.1194/jlr.R120000922

Ribosomes don't rewire protein folding reactions

To function properly, proteins must adopt and maintain specific conformations. They typically reach their final structure by cycling through preferred intermediate conformations, a process that starts during protein synthesis. But how the ribosome affects protein folding remains unclear.

Using a ribosomal force-profiling assay, Madeleine Jensen of the University of California, Berkeley, and collaborators at the University of Cambridge showed that ribosomal interactions have little impact on the folding pathways of RNase H, suggesting that the ribosome does not influence protein folding. Additionally, the authors found that the ribosome promotes RNase H unfolding while the growing protein chain is close to the ribosome, which may limit the detrimental effects of RNase H misfolding and assist in folding fidelity.

These results, reported in a recent paper in the **Journal of Biological Chemistry**, provide new insights into how ribosomes affect the folding of nascent proteins.
DOI: 10.1074/jbc.RA120.013909

A new way to study Parkinson's

Parkinson's disease is a progressive, neurodegenerative disorder that causes involuntary loss of control over some body functions. The causative agents of some Parkinson's cases are mutations in the leucine-rich repeat kinase 2, or LRRK2. These changes lead to increased kinase activity, which enhances the phosphorylation of an important protein known as Rab10 involved in disease manifestation. Recent work published in the journal **Molecular & Cellular Proteomics** by

HELENE HOFFMAN

Male iguanas secrete substances from their femoral glands to attract female mates.

Immune function of femoral glands in marine iguanas

Femoral glands play a key role in chemical signaling in many lizards and amphibian species, including marine iguanas. Male iguanas secrete substances from their femoral glands to attract female mates, and researchers hypothesize that certain lipids in these secretions aid in territory marking and male quality communication. Recently, Fredrick Tellkamp, Franziska Lan and a team of German researchers published a paper in the journal **Molecular & Cellular Proteomics** that focused on identifying the function and identity of proteins found in femoral gland secretions using a comprehensive proteomic approach.

The researchers developed the first transcriptome data set and used this information to identify various phospholipase isoforms in marine iguanas. They used prediction software to characterize unidentifiable proteins and learned that two of the 15 candidates were enriched in femoral gland secretions. Next, they used several biochemical methods, including mass spectrometry analysis, to characterize these compounds further. This analysis revealed several thousand hits, and further experimentation identified epidermis-specific proteins, lipid-binding proteins and immune-responsive proteins.

The work also yielded femoral gland proteins that have antimicrobial properties. This finding led to the generation of a library of antimicrobial peptides, and the researchers selected 17 AMPs for analysis. Of these 17 AMPs, peptide 4 showed strong antimicrobial effects against E. coli and Bacillus subtilis in growth rate reduction experiments. The researchers speculate that AMPs and immune cells in femoral gland secretions provide protection against bacterial infection and degradation when the femoral gland opens during male iguana territory marking, which is crucial to survival.
DOI: RA120.001947

How does CETP modulate cholesterol transport?

Plasma lipoproteins are particles that make lipid-based nutrients and waste products soluble for transport in the bloodstream. They are critical for transporting triglycerides, or TGs, and cholesteryl esters, or CEs, throughout the body. TGs are an essential fuel source, and CEs are the dietary form of cholesterol, which is a necessary component of healthy cells. Each class of plasma lipoprotein is responsible for a specific function, which can include transport of CEs or TGs from the intestines to peripheral tissues or removal of excess CE from the tissues and bloodstream through the liver.

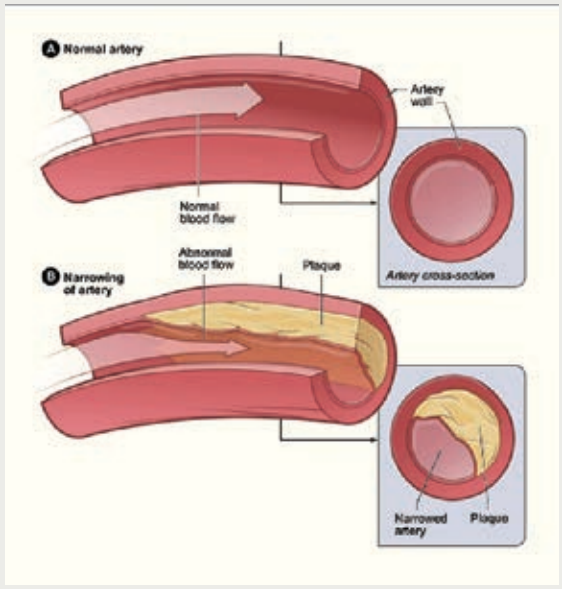
Cholesteryl ester transfer protein, or CETP, is a bidirectional lipid transfer protein that catalyzes the transfer of CE from lipoproteins that bring nutrients to peripheral tissues to lipoproteins that clear excess material through the liver; it also can catalyze the transfer of TG in the reverse direction. An excess of CE in lipoproteins that provide tissues with nutrients (or a paucity of CE in lipoproteins that remove waste) has been linked to atherosclerosis and other cardiovascular diseases in humans. Based on its ability to modulate the dynamic equilibrium among plasma lipoproteins, CETP has emerged as an enticing therapeutic target.

A new study reported in the **Journal of Lipid Research** examines how CETP's preference for TG or CE affects plasma lipoproteins. The report takes advantage of the natural difference in human and hamster CETP's preferences for CE and TG cargo, respectively. Richard Morton and Yan Liu of the Cleveland Clinic overexpressed each gene in hamsters and then probed the utility of the new model system by assessing the distribution and content of plasma lipoproteins.

In animals overexpressing human CETP, the lipoproteins that provide tissues with nutrients carry more CE. At the same time, the concentration of lipoproteins that remove waste is reduced drastically, and these particles carry less CE and more TG. Further, hepatic expression of genes involved in cholesterol uptake and metabolism is reduced. In contrast, in animals overexpressing hamster CETP, analyses of plasma lipoproteins and gene expression matched wild-type measurements.

These findings highlight the central role of CETP — specifically, its cargo preference — in plasma lipoprotein-mediated cholesterol transport and inform the design of future CETP-targeted therapies.
DOI: 10.1194/jlr.RA120000691

NATIONAL HEART, LUNG AND BLOOD INSTITUTE



Dysregulation of cholesterol transport by plasma lipoproteins increases a person's risk for atherosclerosis.

Ozge Karayel of the Max Planck Institute of Biochemistry and an international team focused on determining the stoichiometry of Rab10-Thr73 in Parkinson's patient samples.

The researchers developed a highly sensitive, mass spectrometry–based assay, mxSIM, to show that Rab10 phosphorylation is a direct readout for LRKK2 activity. Using mxSIM coupled with in-gel digestion, the researchers detected small differences in LRRK2 activity in mouse fibroblast cells. Next, they tested Rab10 levels before and after LRRK2 inhibition in both human peripheral blood and Parkinson's patients and found increased Rab10-Thr73 phosphorylation levels in the patients as compared to healthy controls. Overall, this work provides new knowledge about the role of Rab10-Thr73 in LRRK2-associated Parkinson's. Furthermore, these findings can aid the development of new medications that will treat disease progression, not just the symptoms. Lastly, the mxSIM technology can be used to study other diseases.
DO: RA120.002055

An adaptor protein prompts membrane protrusion

Invadopodia — protrusions from the membranes of cancer cells that are rich in the cytoskeletal protein actin — are essential for metastasis. The role of transforming growth factor beta, or TGF-beta, in metastasis has been well established, but how TGF-beta signaling is linked to cancer cell motility as well as its relation to invadopodia remain unknown.

Alex Kiepas of McGill University and collaborators at Laval University revealed that Src-homology/collagen adaptor protein initiates the dynamic adhesion complexes necessary for invadopodium formation in a TGF-beta–dependent manner.

These findings, published in a recent study in the **Journal of Biological Chemistry**, further researchers' understanding of cancer metastasis and open new avenues for cancer drug discovery.
DOI: 10.1074/jbc.RA119.011903

Enzymes collaborate to synthesize phospholipids

The lipid composition of membranes is essential to cell function, affecting everything from membrane protein activity to cellular homeostasis. Hence, lipid composition in cells is orchestrated carefully through constant synthesis, degradation and recycling of lipid species. Cellular synthesis of ethanolamine phospholipids, or PEs, the second most abundant lipid in human cells, takes place through the phosphatidylserine decarboxylation and cytidine diphosphate-ethanolamine pathways. The latter is the focus of a new study reported by Yasuhiro Horibata and a team of researchers from Dokkyo Medical University.

Their **Journal of Lipid Research** paper characterizes the two enzymes — EPT1 and CEPT1 —that catalyze the last step of the cytidine diphosphate-ethanolamine pathway, in which ethanolamine phosphate is transferred to a lipid acceptor. The authors show that EPT1 is localized in the Golgi apparatus, synthesizes PE species (including plasmenyl-PE) with long fatty acid chains, and prefers the lipid acceptor 1-alkyl-2-acyl-glycerol, or AAG. CEPT1, on the other hand, is found in the endoplasmic reticulum, synthesizes PE species with short fatty acid chains, and prefers the lipid acceptor 1,2-diacylglycerol, or DAG. The findings identify complementary roles for the CEPT1 and EPT1 enzymes in PE synthesis and provide a basis for future studies into maintenance of PE species in mammalian membranes, including why mutations and loss of exons in EPT1 are linked to neurodegenerative diseases.
DOI: 10.1194/jlr.RA120000898

Measuring glycosylation in influenza A

Influenza A is an RNA virus that affects birds and mammals. Strains of this virus caused the 1918 Spanish flu pandemic and the more recent 2009 H1N1 swine flu outbreak. This virus has a high mutation rate, which ultimately helps it to evade the host immune response. This is why researchers create new flu vaccines annually. Influenza vaccine development takes advantage of antigenicity of the influenza A envelope protein hemagglutinin, or HA, and its glycosylation state.

Recent work published in the journal **Molecular & Cellular Proteomics** focused on determining if there is a difference in glycosylation at the protein level in two related influenza strains, using a statistics-based approach. Deborah Chang of Boston University and a team of U.S. researchers used the Tanimoto similarity metric and determined the hemagglutinin glycosylation similarities for the wild-type SWZ13 strain versus a SW13 mutant. The mutant strain contained the same sequons as the wild type, but at the whole glycoprotein level the two strains were measurably distinct in glycosylation due to alteration of head group glycosylation. The researchers concluded that the Tanimoto similarity metric is useful for determining alterations in glycoprotein glycosylation from bottom-up glycoproteomics data. This work will aid future vaccine production.
DOI: RA120.002031

Lab-grown amyloidosis model measures up

Systemic amyloidosis is a rare hereditary disorder that commonly manifests in heart, kidney, liver and nerve complications, sometimes leading to organ failure. Systemic amyloidosis is caused by misfolded proteins, such as transthyretin, resisting the body's catabolic processes and building up outside cells. Studies seeking to identify the biological mechanisms underlying this condition require clinically relevant disease models.

In recent work published in the **Journal of Biological Chemistry**, Sara Raimondi of the University of Pavia and an international team compared the characteristics of fibrils generated experimentally with natural transthyretin fibrils to assess their value as a model for systemic amyloidosis. The authors found that the experimentally generated fibrils are thermodynamically and structurally similar to naturally occurring amyloid fibrils.

These results show that laboratory-grown transthyretin fibrils are a useful model for investigating the pathophysiology of amyloidosis.
DOI: 10.1074/jbc.RA120.014026

Sorting out sensor domains to inhibit MRSA

Infections by methicillin-resistant Staphylococcus aureus, or MRSA, bacteria are notoriously difficult to treat due to the bacteria's resistance to several antibiotics. Contributing to MRSA's antibiotic resistance are two integral membrane proteins, BlaR1 and MecR1.

In a recent paper published in the **Journal of Biological Chemistry**, J. Andrew N. Alexander of the University of British Columbia and colleagues at the University of Maryland and San Francisco General Hospital solved the X-ray crystallographic structures of the BlaR1 and MecR1 sensor domains in complex with avibactam, a beta-lactamase inhibitor that blocks the activity of the beta-lactamase enzyme produced by S. aureus.

These findings reveal the presence of a secondary sulfate-binding pocket that could be exploited in the design of future inhibitors capable of treating MRSA.

DOI: 10.1074/jbc.RA120.013029

Nuala Del Piccolo (ndelpiccolo@ucdavis.edu) is a postdoctoral scholar in the biomedical engineering department at the University of California, Davis. She earned her Ph.D. in materials science and engineering at Johns Hopkins University.

Latavia Hill (lataviahill@ku.edu) is a graduate student studying microbiology at the University of Kansas.

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

Connect your community with a virtual scientific event

Interested in hosting a virtual event? The ASBMB is here to help. The ASBMB provides a platform to share scientific research and to discuss emerging topics and technologies in an interactive, virtual setting.

When you host a virtual event with the ASBMB, your event will:

- accommodate up to 500 attendees
- be marketed to the ASBMB's 11,000 members
- reach the ASBMB's network of journal authors and meeting attendees

Learn more about how to submit your proposal at asbmb.org/meetings-events

ASBMB
American Society for Biochemistry and Molecular Biology

Milk through the millennia

Lipids in potsherds hold clues to lactase persistence

By John Arnst

FIONA MARSHALL/WUSTL

This Pastoral Neolithic bowl from the Bromshead archaeological site in Kenya's portion of the Great Rift Valley is an example of Elmenteitan pottery, a lithic and pottery tradition. The bowl is housed in the Fitzwilliam Museum at Cambridge University and was photographed by Fiona Marshall, an anthropologist at Washington University in St. Louis.

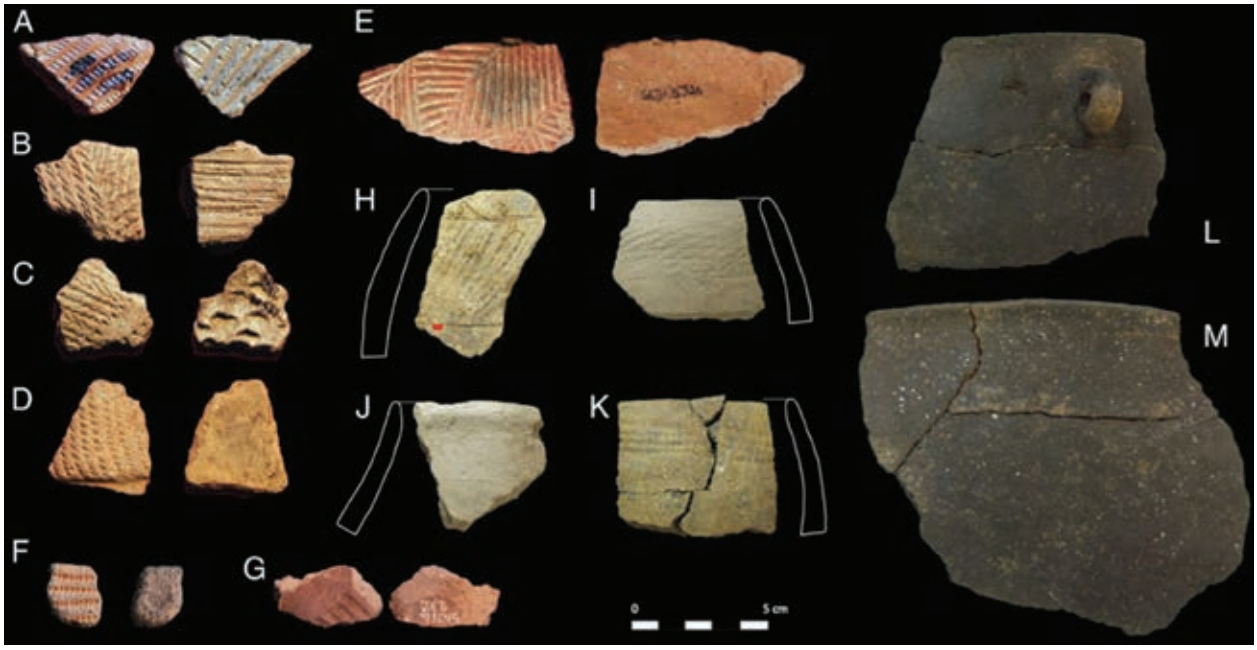
Sixty-six million years ago, primitive animals with mammary glands managed to ride out a mass extinction event, with the eventual result that today humans have to pay bills and ponder our own mortality. However, we are the only mammals that can digest lactose into adulthood and blunt these pains with industrial quantities of cheddar cheese, so the verdict is out on whether this situation is a net positive or negative.

But for nearly two-thirds of adults worldwide who are lactose intolerant, milk, cheeses and other dairy products cause a different kind of pain. In the absence of lactase, the enzyme that cleaves lactose into glucose and galactose once the sugar enters our small intestines, lactose passes through whole and becomes food for the microbes that live in our large intestines, whose byproducts then cause bloating, nausea, stomach pains and diarrhea. Moreover, digesting the milk protein casein in adulthood releases insulin growth factor-1, a hormone that can, in excess, cause cystic acne. Production of lactase also can fall off suddenly in adulthood, although the role that diet — say, eating a brick of feta cheese every day for lunch for several months — may play in this is unclear.

The persistence of lactase in 35% of adults is due to single nucleotide polymorphisms in the gene that codes for the enzyme. Several thousand years ago, the ability to continue digesting lactose was such a strong evolutionary advantage in pastoralist societies that alleles for it independently developed in human populations in both Northern Europe and Eastern Africa, with subgroups from the latter — in what are today Tanzania, Kenya and Sudan — developing three distinct polymorphisms.

Genetic analyses of modern pastoralists have helped revise our understanding of where lactase persistence developed, but they give a broad range— 6,800 to 2,700 years before the present day — for when those traits emerged.

K. GRILLO/UNIVERSITY OF FLORIDA



K. GRILLO/UNIVERSITY OF FLORIDA

To pinpoint when humans began consuming milk in East Africa, researchers, including anthropologist Katherine Grillo and organic geochemist Julie Dunne, looked for lipid residues on 125 pottery shards, or sherds, that were found at archaeological sites in Kenya and Tanzania and are similar to these. Sherds A–E come from the site Jarigole, while sherds F and G come from the site Dongodien, both of which are located in the Turkana basin in Kenya. Sherds H–K come from the site Luxmanda in north-central Tanzania. Sherds L and M, which come from the site Ngamuriak in the Great Rift Valley in southwestern Kenya, are examples of Elmenteitan pottery.

By analyzing the lipid residues on 125 fragments of ceramic pots recovered from sites in Kenya and Tanzania, scientists at the University of Bristol, the University of Florida and the University of Dar es Salaam have uncovered cultural contexts behind the genetic phenomenon that date its emergence in East Africa to approximately 5,000 years ago.

"Advances in ancient DNA recovery and processing have really helped us pinpoint when we think selection for these alleles appeared and evolved. We now know from the genetic record that this probably happened during a key time period known as the Pastoral Neolithic, which roughly dates to between 5,000 and 2,000 years ago in East Africa," said Katherine Grillo, an anthropologist at the University of Florida. "But what we didn't understand previously is the context in which selection for those alleles actually happened."

Atomizing pottery

That context is provided by gas chromatography–mass spectrometry. Chromatography first was used to analyze residues in archaeological samples in 1976 when French scientists used gas chromatography to detect trace amounts of fatty acids — byproducts of oil — in fragments of jars used to transport goods in the ancient Mediterranean. Their work appeared in the journal Archaeometry.

Today, Julie Dunne, an analytical chemist at the University of Bristol uses GC–MS to examine the lipids embedded in the matrices of ancient shards of pottery.

"If you think about an unglazed ceramic pot, and if you had to put some milk in it, or even meat, and just boil it up, what you would actually see is fat globules floating on the top," Dunne said. "Those globules of

JULIE DUNNE

fat, lipids, absorb into the unglazed ceramic matrix during cooking."

Unlike proteins, which are too large to fit in ceramic matrices, lipids are small and can survive in the matrices of ceramic pots for more than 10,000 years.

"They sit very nicely in the pot until people like me come along and grind up broken potsherds, which are generally only what survives anyway," Dunne said. "I've analyzed pottery from Europe and Africa which is nearly 10,000 years old, and there is actually pottery in Japan that goes back more like 15,000 to 17,000 years and has yielded lipids."

In 2008, the leader of Dunne's research group, Richard Evershed — who developed the field of organic residue analysis — helped determine that the earliest date that pastoral societies in Anatolia, now Turkey, began consuming processed dairy was 9,000 years ago. This predates the 5,000 year-old pottery that she and Grillo recently analyzed.

"If milk is being processed in the pots, we know humans are consuming milk," Dunne said. "And once you start processing it and reduce the lactose content, then it makes it much easier for humans to digest. So that's happening in the Near East around about 7000 B.C."

From serendipity to eureka

The pottery sherds that Grillo and Dunne recently analyzed came from four sites across Kenya and Tanzania that are together representative of the breadth of Pastoral Neolithic sites in the region. While samples from the three sites located in Kenya — Dongodien, Jarigole and Ngamuriak — were obtained from museum collections in collaboration with Karega–Munene, an anthropologist at the United States International University in Nairobi, sherds from the fourth site were products of serendipity.

In 2012, Grillo and her colleagues had been searching for new archaeological sites in northern Tanzania when a collaborator, Agnes O. Gidna from the National Museums of Tanzania in Dar Es Salaam, took a short trip home to her family's farm near the town of Luxmanda on the Mbulu Plateau, farther south in north-central Tanzania.

"We had spent weeks and weeks surveying for new sites much farther north, and towards the end of a field season, Dr. Gidna said, 'You know what? I'm just going to go home for a few days. I'll be back,' and she went. Then she calls us and she said, 'there's some pottery.' And pretty soon realized we discovered that she had discovered the biggest Pastoral Neolithic site in East Africa," Grillo said. "It's in her mother's yard."

After the researchers recover a small, two- to three-centimeter sherd like those Gidna first found at the Luxmanda site, they clean its surface to remove the oils of more recent human lives — lotions, sunscreens and sebum — and pulverize the pottery into dust. They then use an acid extraction to separate the lipids from the sherds.

ELIZABETH SAWCHUK/MAX PLANCK INSTITUTE FOR THE SCIENCE OF HUMAN HISTORY

Katherine Grillo, an anthropologist at the University of Florida, co-directs two major field projects in East Africa: one examining the social significance of monumental "pillar sites" built by the region's earliest herders in the Turkana Basin in northwestern Kenya, and another examining the largest Pastoral Neolithic settlement site in eastern Africa farther south at Luxmanda, Tanzania.

JJ HARRISON

Feta is a softer cheese made from sheep's milk or a mixture of milk from sheep and goats.

"Sometimes when we come to the end of the extraction, you can actually see the fat in the little vial coming from the animals cooked in the pots thousands of years ago, which is quite amazing," Dunne said.

The scientists then run those lipids through a gas chromatograph, which lets them know whether the lipids are animal fats and whether they are too contaminated to be interpretable. The process most often yields fats from animals, but it also can reveal byproducts of plants and insects, such as bees, where lingering traces of wax will indicate that a population likely harvested honey. After then running the lipids through an isotope mass spectrometer, the researchers are able to differentiate whether they came from a ruminant — cattle, sheep or goats — or nonruminants, such as pigs, chickens and donkeys.

"Then we can also differentiate, most crucially, between milk and meat," Dunne said. "And that was our eureka moment in our lab, probably 20 years ago now, that's really enabled such a body of work on exploiting milk and the evolution of lactase persistence."

By applying these techniques to the sherds from the four sites, Dunne, Grillo and their colleagues were able to obtain the first direct evidence that herders in ancient eastern Africa were consuming milk 5,000 years ago. Whether the gradual reduction in lactose content by fermentation ended up driving populations to consume more lactose-heavy, however, is a more elusive question.

"The development of widespread lactose persistence in herding societies through gene-culture coevolution is a topic now preoccupying scientists worldwide," Grillo said. "Selection for lactase persistence may have become stronger as herders became even more specialized and dependent on livestock later on."

Milk markets

Today, the reduction of lactose levels in processed dairy foods means someone who is lactose intolerant and no longer can eat softer cheeses like feta without first swallowing Lactaid might be able to eat a sharp block of cheddar that has almost all of its lactose removed.

According to Andrea S. Wiley, a medical anthropologist at the University of Indiana at Bloomington who studies the relationship between milk consumption and child health in the U.S. and in India, consumption of cheese, butter and similar products was the status quo of dairy production in the U.S. until the late 1800s.

ANDREA S. WILEY

"The late 19th century is really when milk consumption starts to become more common, other than just dairy products, and mostly as food for children as a breast milk substitute," she said.

Over the ensuing decades, milk producers, working with the National Dairy Council, began pitching milk

as a source of nutrients for children.

"The Dairy Council was formed in 1915, and that's when they take the lead role in identifying what is the best food for children, and milk is a central part of that message," Wiley said. "(They) tried out different nutrient messages, that milk is a good source of X, Y or Z. And the prevailing way, certainly beginning in the 1930s and on, was that milk has been understood nutritionally as a source of calcium. And that's where the link to the strong bones matches up very nicely."

That messaging stuck for decades. Take, for example, the "Got Milk?" ad campaign of the 1990s, which infiltrated billboards, magazines, airwaves, televisions and lunchrooms for more than 20 years to sell a generation and their parents on the belief that milk builds strong bones in children.

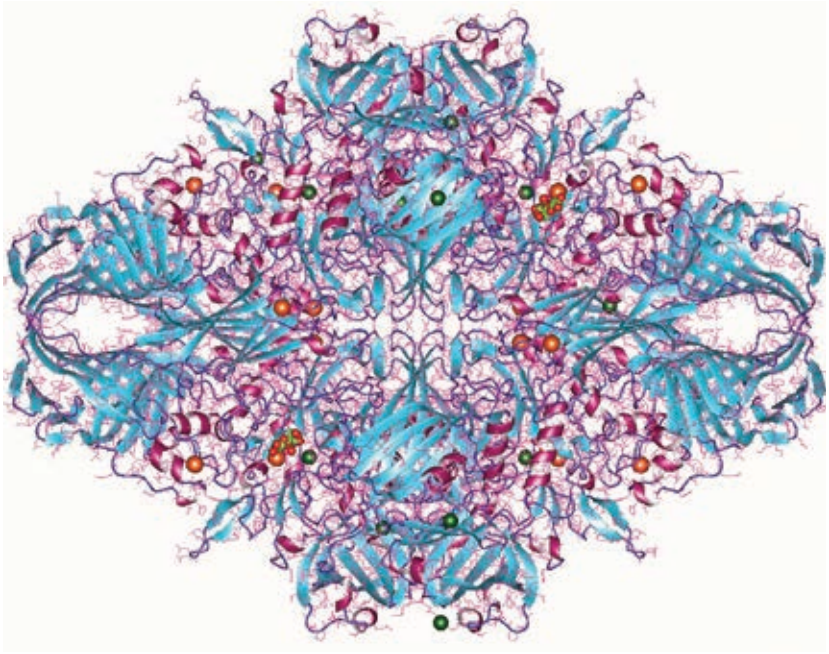
While the link between cow's milk and strong bones is dubious, the connection does have a scientific basis in breast milk: In infancy, breast milk acts as a source of calcium, and its whey and casein proteins act as growth promoters.

But a wildly successful ad campaign couldn't reverse a downward trend that started after World War II, which marked the high point for American production and consumption of milk. The dairy industry today is in dire straits, with more than 2,700 dairy farms having gone out of business in the last two years and the amount of liquid milk consumed per capita plummeting more than 40% since 1975.

"We're really back to where we were around the early 20th century in terms of milk consumption in the U.S.," Wiley said. But despite the plummet in overall consumption of cow's milk, she thinks milk as a substance still inspires a certain cultural reverence.

"Milk has always been positioned, I think, as a very special food. And, you know, in one way, it really is," Wiley said. "Milk is what mammals produce, or female mammals produce, and it sustains infants when it's all they consume."

JUERS, D.H., MATTHEWS, B.W., ASTROJAN/PDB, WIKIPEDIA



Lactase, an enzyme found in the small intestines of mammals, splits the sugar lactose into glucose and galactose.

Lactase emergence

Over the past two decades, our understanding of lactose intolerance as an enzymatic matter also has been transformed and revised, according to Sarah Tishkoff, a geneticist at the University of Pennsylvania's Perelman School of Medicine who studies genetic variation in East African populations.

SARAH TISHKOFF

In 2002, the geneticist Leena Peltonen and her colleagues created a map of genetic variants in Finnish families that were lactose intolerant, a rarity in Northern Europe. This discovery was essential to understanding the genetic mechanisms of lactase persistence.

"They thought of lactose intolerance like a disease, basically," Tishkoff

MARION_SMITH / ISTOCKPHOTO.COM

Herd of African cattle grazing on Masai Mara plains, Masai Mara, Kenya.

said. "It was interesting because (the mutations) were not in the lactase gene, they were upstream in front of a neighboring gene. And at that time, very little was known about gene regulation. It was a rare example of finding a regulatory mutation that influences this well-known common trait."

Four years later, Tishkoff and her colleagues, working with Tanzanian, Kenyan and Sudanese ethnic groups, found that lactase persistence evolved at least four times in human populations. They described this convergent evolution of lactase persistence in the journal Nature and expanded upon it in 2014 in the American Journal of Human Genetics.

"We saw this very strong genomic footprint of selection," Tishkoff said. "And that was one of the earliest genomic signatures of selection, and still one of the strongest signals in the human genome."

Lipid whispers

Today, pastoralist societies in Eastern Africa still rely on milk and milk products from cattle, sheep, goats or camels; some groups are estimated to derive up to 60% or even 90% of their total calories from milk products, which they complement with meat, maize, beans and seasonally available plants.

While the digestive chemistry of humans has changed over the past 10,000 years, the enzymatic activity of bovine stomachs has not, making modern cows proxies for the ancient cattle of pastoralists past. A plant that passes through a cow's stomach in significant quantities today will make the same subtle imprint on the chromatographic character of its milk that its identical ancestor did millennia ago.

This has yielded insights that cattle and assorted mammals in ancient Europe tended to eat very temperate vegetation known as C3 plants, named after the number of carbon molecules in the first compound formed by the Calvin cycle of carbon fixation, but African mammals tended to eat more arid-friendly C4 plants like sorghum and amaranths.

"We see, for example, the animals were eating lots of C4 grasses, and so we think in East Africa at this time, there were some environmental shifts happening," Grillo said. "Even if people weren't able to be farmers because of unpredictable or patchy rainfall, they may have had milk or something like it."

By providing glimpses into past periods of climate and habitat disruption, forces that will continue to shape the lives of pastoralists in coming decades, Grillo hopes the long-preserved lipids may make the case for a more resilient lifestyle.

"It's getting harder to be a herder in many areas (that are) drying out, but it's actually much easier to be a herder when the climate is getting really unpredictable and arid than it is to be a farmer," Grillo said. "We can build a much more holistic picture of what life was like for these people because of the residue analysis."

John Arnst (jarnst@asbmb.org) is an ASBMB Today science writer. Follow him on Twitter @arnstjohn.

Pandemic snarls research administration

Funders, grant administration offices work together to reassure anxious investigators

ERIC KUONG/STANFORD MEDICINE

Tenure-track, but not yet tenured faculty like Creed Stary of Stanford University have expressed concerns about keeping their labs funded through the pandemic.

By Laurel Oldach

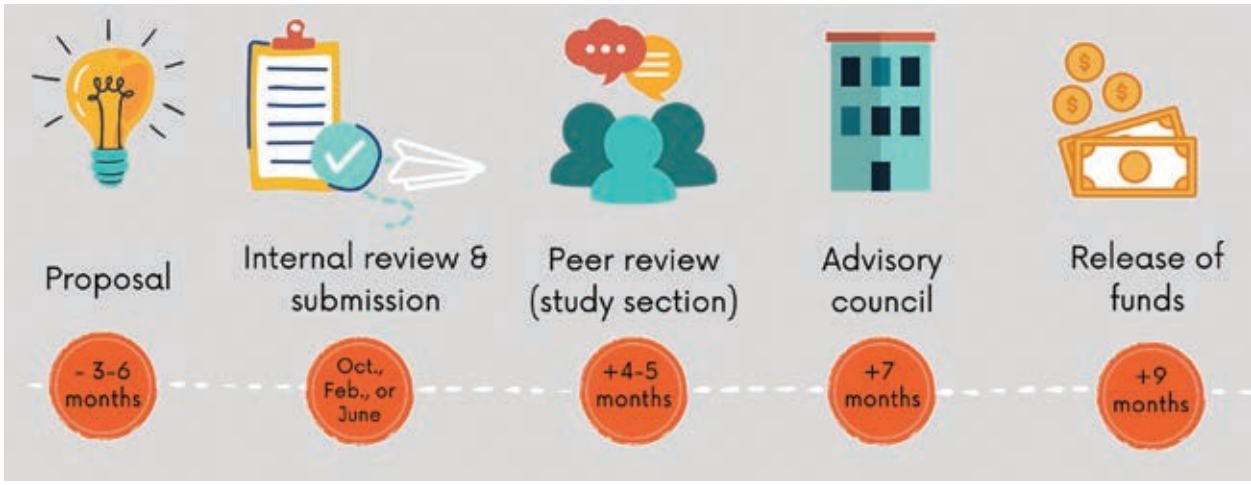
Creed Stary was in a difficult position. As his research lab at Stanford gradually reopened, the physician–scientist realized he had to choose which of two grant proposals to focus on; his team wouldn't have enough time to complete both on schedule.

Stary's lab of two technicians and two postdocs is supported by an R01, a five-year grant of about half a million dollars from the National Institutes of Health, along with smaller individual grants to the postdocs. He needs to show the NIH continued annual progress on that major grant. In the meantime, hedging his bets, Stary also had submitted an application for a second R01 in February of this year. The pandemic upset his plans to revise that grant in response to reviewers' concerns and resubmit it in October.

"We have to try to get the data for our existing R01, try to get the data for our new R01 revision, try to get the data for my postdoc's grant that he's finishing up, and also try to get the data for a new grant he's submitting this fall," Stary said. With limited time in the lab, his team couldn't run all of the experiments to collect all of the data they needed on the timeline he had hoped for.

Stary wasn't the only PI scrambling to rework his funding strategy. As the pandemic continues to beleaguer the U.S., in most of the country lab work has remained slow, stripped to the minimum hours required to keep critical research going. Now, as research-

LAUREL OLDACH/ASBMB TODAY



For principal investigators at research universities, R01 grants are a major source of funding. Most PIs spend several months developing a research proposal and budget and work with university grant administration offices to compile and submit the complex proposal packages. There are three annual deadlines to submit an R01 application: early in October, February and June. Four to five months after the application deadline, a study section of peers who have read a group of applications meets to review and score applications. Funding decisions, based on reviewers' scores and institutional priorities, are determined at the next NIH advisory council meeting. After those decisions are finalized, several more months can pass before funds are transferred.

ers and administrators prepare for the next set of major grant application deadlines in early October, many are especially concerned about principal investigators like Stary — relatively young, pre-tenure and vulnerable to a serious disruption if just one grant application should be denied.

The big picture

Funding to the NIH has not faltered during the pandemic. "There is a lot of money available if you're doing research on SARS-CoV-2," explained Ben Corb, the American Society for Biochemistry and Molecular Biology's public affairs director, during a recent webinar hosted by the society. "If not, there is continued funding available at the same levels, and we expect an increase in fiscal year 2021."

The Coronavirus Aid, Relief and Security or CARES Act, passed in March, included about $1.65 billion in additional funding for the NIH for COVID-19 research. As of mid-September, fiscal year 2021 budget proposals from the White House and House of Representatives call for maintained funding; and additional proposed legislation, called the Health and Economic Recovery Omnibus Emergency Solutions or HEROES Act, would add over $4 billion in supplemental research spending to the NIH's budget if passed.

However, gaining access to that money can be a challenge. Winning research grants is a complex and time-consuming task. Up to a year can pass from when an applicant submits an investigator-initiated grant to when — if the application is successful — the funds are released. About 79% of all applications for R01 grants across the NIH are unsuccessful. Too many consecutive unsuccessful applications can force a researcher to close a lab and walk away from a research career despite decades of training.

Principal investigators spend months preparing applications and years learning grantsmanship, the unwritten rules for success in the federal funding system. They also spend significant time planning ahead to keep their labs funded continuously. Many, like Stary, are concerned about the effect of research disruptions on their funding.

As the pandemic continues to beleaguer the U.S., in most of the country lab work has remained slow, stripped to the minimum hours required to keep critical research going.

Working below full capacity, researchers are trying to focus on doing the work that's most important while also taking care to avoid starting monthslong experiments that might have to be abandoned if local public health mandates change.

Federal officials at the NIH stress that they are sensitive to these concerns and are working hard to find solutions. In a statement, the Office of External Research wrote, "We are deeply concerned and mindful about how the spread of COVID-19 has affected the biomedical research enterprise and we have implemented various administrative flexibilities."

Some of those flexibilities, like extended deadlines to submit grants in the spring, were short-term. Others, like relaxation of strict rules for career-stage grants for postdocs and early-career independent investigators, have continued.

Research down, grant writing up

When university campuses closed across the country in March, many researchers turned to writing, data analysis and other projects to stay productive while shut out of their labs. Bill Sonntag, who directs a research center at the University of Oklahoma Health Science Center, said, "I tell the faculty in my department … 'While we're shut down and you have to be home, can you write a grant?'"

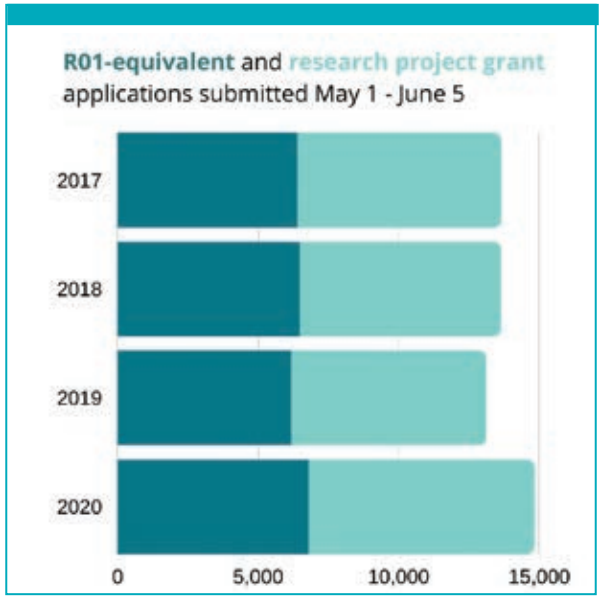
That flurry of writing is reflected in submission systems. Renee Gonzales, director of the Office of Sponsored Research and an assistant vice president for research at the University of Texas at Austin, said that even as other support staff faced furloughs and layoffs, her office has worked harder from home, handling expedited requests for COVID-19 research funds along with an uptick in non–pandemic-related grant applications.

Likewise, the NIH reported a 10% increase in the number of grant applications received from May to June in 2020 compared to the same funding cycle in previous years.

Phased reopenings have brought researchers back into once-shuttered labs slowly. Not all researchers were able to return to work full-time (see 'The parent trap' on page 41). For those who could, reagents were back-ordered, animal colonies had to be reestablished, and laboratories are operating at restricted capacity to prevent crowding. The slowdown may last many more months.

Working below full capacity, researchers are trying to focus on doing the work that's most important while also taking care to avoid starting monthslong experiments that might have to be abandoned if local public health mandates change.

"Starting out the year, you have these grand plans about planning out experiments," Stary said. But this year, "you don't have the luxury of all that labor that you were relying on."



LAUREL OLDACH/ASBMB TODAY

According to a blog post by NIH Deputy Director for External Research Mike Lauer, R01 and research project grant applications were both up by about 10% over previous years in the June 2020 application cycle.

Reporting progress

At the end of each year of a funded grant, the principal investigator must submit a progress report explaining what work has been done, what money has been spent and any unexpected interruptions. University and federal program officers review that report before disbursing the next year's funding.

Renee Gonzales' staff typically reviews progress reports for two red flags: investigators giving less effort than expected or spending less than

Scientists with young children lost more time than their childless peers, and mothers of young children lost more time than fathers.

The parent trap

A study published in the journal Nature Human Behavior in July confirmed what many scientists report anecdotally: The cost of the pandemic to research time isn't equal across fields or life stages. Scientists with young children lost more time than their childless peers, and mothers of young children lost more time than fathers.

School districts across the country remain closed for in-person classes. Daycare facilities are providing a fraction of their normal enrollment to limit crowding and the risk of spreading the virus. (Campus daycare options often are overbooked already, with yearslong wait lists.) And many grandparents, who can be at heightened risk from infection, are sitting out this round.

Some large universities, such as Yale, the University of California system and the University of Chicago, have invested in or beefed up backup childcare benefits for their faculty and staff and sometimes also trainees. These programs subsidize an in-home caretaker for days when a normal care plan falls through unexpectedly. However, hammering out that normal care plan is a significant challenge; young parenthood overlaps with the precarious early-career stage that lasts well into most researchers' forties; and many are concerned that the result will squeeze parents, especially mothers, out of science altogether.

LYNNE MAQUAT

"I have one very productive postdoc who decided not to come back (to the lab) in the end," said Lynne Maquat, a professor and director of the RNA biology center at the University of Rochester. Concerned about taking care of children and two sets of aging parents, the researcher reduced his hours to one day a week, conducted remotely, to focus on care responsibilities and begin consulting as a freelancer. Others in the lab have picked up the project he was working on.

three-quarters of the annual budget. This year, she said, both problems are commonplace.

OLEG BARSKI

Oleg Barski, a program officer in biochemistry at the National Institute for General Medical Sciences, said repeatedly in an interview that the NIH has no intention of penalizing funded researchers for disruptions caused by COVID-19.

"These projects, and these PIs, were carefully selected through a very rigorous process," Barski said. "We are here to do everything possible to ensure the success of these scientists, not to punish them for the delay."

The progress report form leaves PIs an opportunity to explain why they made less progress or fewer purchases than planned and how they plan to address the setback. But the current environment makes it difficult to plan. Gonzales said that progress reports are full of statements such as, "'I don't know when I can get back up to (full) spending; I don't know if I'm going to be able to complete the project.' There are just so many unknowns."

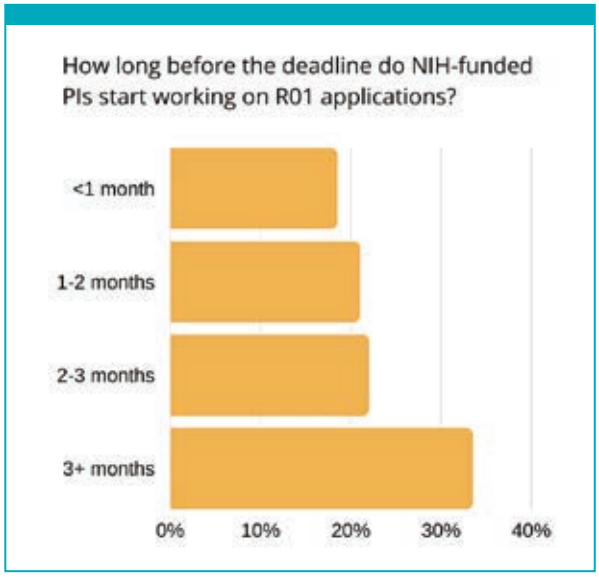
As the pandemic continues, Gonzales thinks the NIH should consider retooling the progress report. "If I feel this way in my office, I can imagine what they feel like when they get thousands and thousands of these reports. What's the point of asking the question (about plans) when there's no answer?"

Early in the pandemic, Gonzales said, her office frequently fielded questions about whether researchers could keep paying their staff and their trainees (see 'Can I pay my technicians?'on page 44). Later, other questions rose to prominence — such as what to do if money runs out before a lab can return to working at full capacity.

Even with labs closed, PIs have continued to pay personnel costs such as stipends, tuition and benefits, and most universities still charge overhead to keep lights and freezers on and pay support staff such as Gonzales' team. Gonzales said that some researchers have expressed concern that those fixed costs, which, unlike experiments, were not interrupted, might drain grants, which could make it impossible to complete the full scope of work once their labs are back to full capacity.

If time runs out on a grant before a lab can complete the project, the investigator can apply for more time. If the money runs out, the NIH plans to make supplementary funding available — but current guidance suggests that researchers wait to apply for that boost until the pandemic's full cost to their labs is clear.

LAUREL OLDACH/ATODAY



A plurality of 130 NIH-funded principal investigators polled start their R01 applications three months or more in advance, but many start closer to the deadline. Respondents were polled via Twitter in September 2020.

Landing new grants

Meanwhile, the NIH continues to shepherd grants through the review process, including this spring's bumper crop of new grants for research projects not related to COVID-19. For these new applications, some concessions were made to the pandemic. For example, researchers can submit

additional preliminary data after otherwise finalizing a grant.

So far, only the round of grant applications submitted, like Stary's, before the full effects of the pandemic were felt in the U.S. have been reviewed. Stary has to convince peer reviewers, organized into a study section, that his proposed project is scientifically interesting and poised to succeed.

"They were locked at home, reading a stack of grants," Stary mused. "I wonder if they took that into consideration, in terms of saying 'He should do this, this and this before resubmitting'?"

According to Barski, study sections have not changed dramatically, even as they've gone from meeting on the Bethesda campus of the NIH to videoconferencing via Zoom. Reviewers, he said, have received instructions "to assume that issues resulting from the pandemic will be resolved prior to the award — and to show understanding that everybody has been affected."

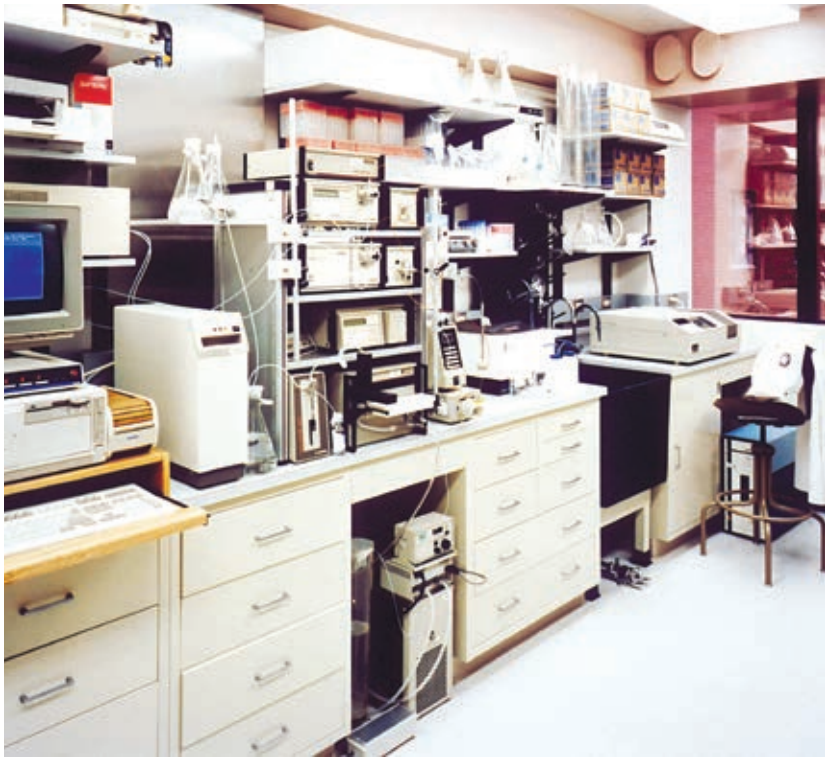
At the same time, reviewers are asked to be rigorous. Barski reminds researchers that they should submit the very best grant application they can muster, which may mean delaying submission by one or more cycles.

"Reviewers are still tasked to determine if the premise and feasibility of the project are solid," Barski said. "It's unfortunate, but if that crucial experiment, for example showing proof of principle, has not been done — and therefore the feasibility or the premise of the project is questionable — I think the PI should wait until they're able to submit the best proposal possible."

Reviewers generally have the prerogative to request more experiments to bolster the preliminary data that PIs present. Collecting those data can pay off; in 2019, only about 17% of grant proposals were funded after first being submitted, whereas about 33% of resubmissions made the cut after a second round of review. The study section that reviewed Stary's grant had questions that would require more experimentation. While he initially had hoped to submit a revised application in November, he has had to accept that the lab will be unable to get it all done in time.

Meanwhile, Stary also spent time this summer reviewing grants submitted during the spring cycle. "I know how difficult it's going to be to get the data that I would like to see," he said a week before his deadline to submit his appraisals. He said he planned to ask himself, "What's the absolute most critical thing they need to address here?"

According to a study section member who preferred to remain anonymous, reviewers are in a confusing position. They are not well equipped to determine how the pandemic might have affected an individual lab's ability to collect preliminary data. Many also are concerned about whether the pandemic's impact on different fields of research and regions can be mitigated fairly.

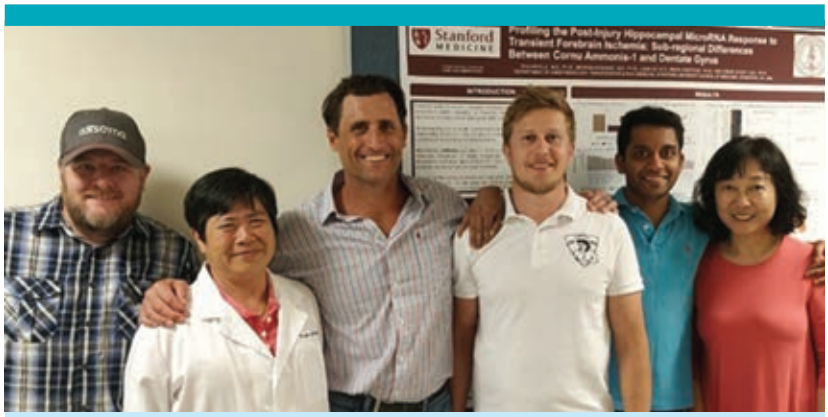


HTTPS://UNSPLASH.COM/PHOTOS/MAQHDUSSMNO

Labs across the country sat empty for months, and many still are working at less than full capacity.

Barski reminds researchers that they should submit the very best grant application they can muster, which may mean delaying submission by one or more cycles.

COURTESY OF CREED STARY



Stary's lab includes two postdocs and two technicians.

"Can I pay my technicians?"

In June, the National Institutes of Health passed on guidance from the federal Office of Management and Budget stating that, if grant-funded workers couldn't work on the funded projects, universities needed to use up other sources of funding before applying grant funds to continue paying salaries.

For some researchers, this was not a problem. "My people were busy," said Lynne Maquat of the University of Rochester. Even among the scientists who were not involved in keeping animal colonies and other essential functions running, "I never had anyone furloughed in the sense that they weren't working. We wrote commentaries, we wrote reviews, we wrote fellowships, we worked on manuscripts."

The guidance did not apply to researchers supported by training grants, even if they could not work directly on the projects outlined in their grants. For professional staff, such as technicians and lab managers, funded from a federal source, guidelines applied across the federal government demanded that they be paid from other sources, such as laboratory startup funds, until those other sources were exhausted.

According to Stanford professor Creed Stary, the announcement was a challenge, especially since it applied retroactively. Startup money in his department generally comes from hospital income. With elective and nonemergency surgeries canceled for months, that revenue evaporated.

"The hospital was losing millions of dollars a month," Stary said. "That profit sharing that the department can normally rely on … was essentially gone. So, suddenly everyone was very nervous about being able to support their staff."

As far as he knows, no one working in a lab at Stanford was laid off or furloughed. But he's concerned about year-end accounting and the effect on his lab's startup fund, a source that many PIs rely on as a sort of savings account against a gap in funding.

Ensuring continuity

Some universities have stepped in to help their professors make it through. For example, Yale and the University of Pennsylvania have introduced recovery grants up to tens of thousands of dollars to help researchers whose funding was interrupted by the pandemic or doesn't cover costs of closing down and starting back up again.

Just how great those costs will be has yet to be seen. Kathryn Kirkland Snider, a grants administrator at the University of Colorado Boulder, said, "Given that we still don't really have a good clear image of what the economic impact of COVID will be long term on the economy … I think it's going to be a while before we really know the full impact (on research)."

"I've found that NIGMS-funded PIs are an extremely resilient and an extremely creative group," said Barski. "Yes, I hear concerns, of course. But what I see more, is not 'what are we supposed to do?' but 'what we are going to do in order to do the best possible science in the situation.'"

Although the future is uncertain, Stary, Maquat and other researchers said, in light of the economic hardship the pandemic has caused, they feel fortunate to be in a relatively stable situation for now.

"There's a lot of heartache out there," Stary said. "We're among the lucky ones."

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

The art of paper folding and the science of protein folding

By Sudha Neelam

SUDHA NEELAM

The author's son Nikhil gets started on an origami project. Precise measurements are key to successful paper folding.

In a world where we glorify busyness, slowing down can be a challenge. In recent months, an invisible enemy has forced many of us to slow down and shut down our usual routines. As the parent of a teenager, I've had my own set of challenges. Kids, especially teens, need to be engaged, motivated and entertained.

When we were brainstorming ways to make the most of our time during the spring lockdown, an origami jumping frog on the internet caught our attention. We were drawn to the simplicity of origami; all we needed was paper and some basic folding skills. We turned to what we thought was the only reliable source to help us learn about it — YouTube — and found numerous tutorials on how to fold paper. These videos got my teenager hooked. Our floors soon were covered in large sheets of paper as we learned about precreasing, folding, collapsing and all sorts of other origami tidbits.

This activity has kept my son Nikhil engaged. He spends hours trying to get accurate measurements on a square of paper; a fraction of an inch off will make him start all over again. He insists that the success of an origami structure lies in the precision with which the paper is measured and folded. Watching him meticulously measure, fold, collapse and shape paper made me think of our own biological origami and the science of

SUDHA NEELAM

Titled "Walking in the rain," this origami structure folded by the author's son Nikhil portrays a woman carrying an umbrella. The author and Nikhil like being able to fold people depicting feelings and emotions.

protein folding. Proteins, the essential building blocks of life, can only function if they are folded properly. This idea piqued my scientific curiosity and I wanted to explore the similarities between paper folding and protein folding.

A brief history of origami

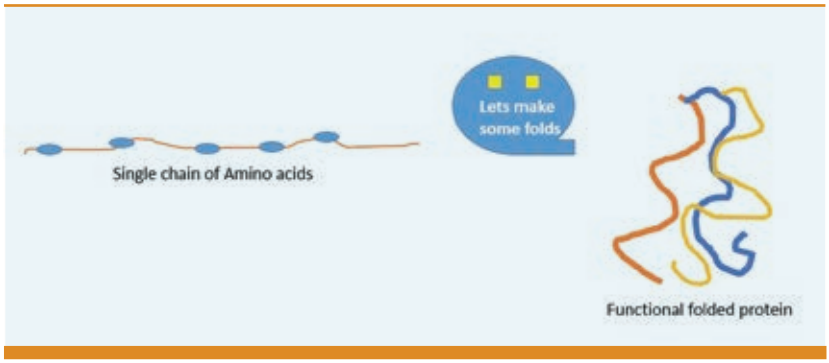
Origami, the ancient Japanese art of paper folding, has entertained generations with its beautiful simplicity. Origami used to be called orikata. The word "origami" comes from two Japanese words; "oru" means "to fold," and "kami" means "paper." Paper was invented in China around 105 A.D., and Japanese origami originated when Buddhist monks carried paper from China to Japan sometime in the sixth century. Origami paper was difficult to make and therefore expensive. In Japan, handmade paper was a luxury used only on specific religious occasions.

Before the invention of paper, people did recreational folding with materials such as cloth or leather. As with most art forms, new techniques have evolved. Origami is no longer folded exclusively with origami paper. People use printer paper, wrapping paper, old newspapers, junk mail and even scrapbook paper. Unlike traditional origami, modern variations involve cutting, shaping and even using glue to make the structure more sturdy and stable.

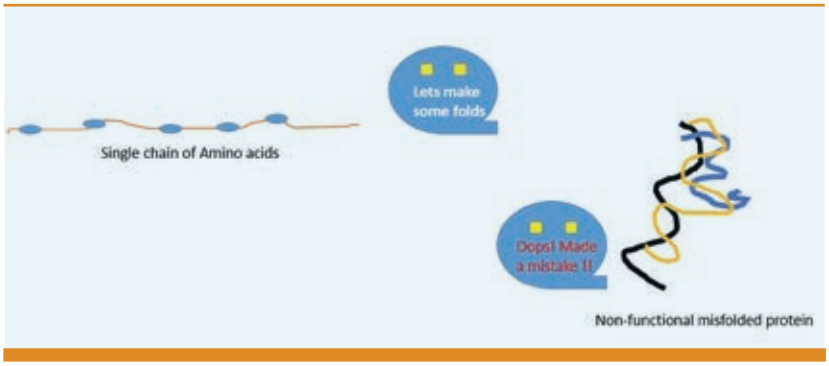
Proteins: Our own biological origami

Proteins, the building blocks of life, also are folded. However, in the case of proteins, they fold spontaneously based on a series of codes in the form of amino acids, which are akin to the crease patterns and folds of origami. This biological origami depends on the correct genetic code, accurate assembly of amino acids and the precise folding of the amino acids into a functional protein.

SUDHA NEELAM



These PowerPoint images depict how protein folding affects the function of the protein. The single chain of amino acids must be folded into 3D structures to create functional proteins.



Changes or mishaps in the folding of the single chain result in a misfolded or nonfunctional protein.

Initially, proteins are synthesized as a long chain of amino acids. The sequence of amino acids and their properties determine how the proteins are folded. Proteins are at the core of all the biological and molecular machinery in our bodies. They must be synthesized, assembled and folded accurately to perform the critical functions that keep us alive.

Misfolded, unfolded or inaccurately folded proteins are nonfunctional, and they form a sticky, gooey mess. The sticky, misfolded, obsolete protein becomes a hindrance to our bodies' normal functioning.

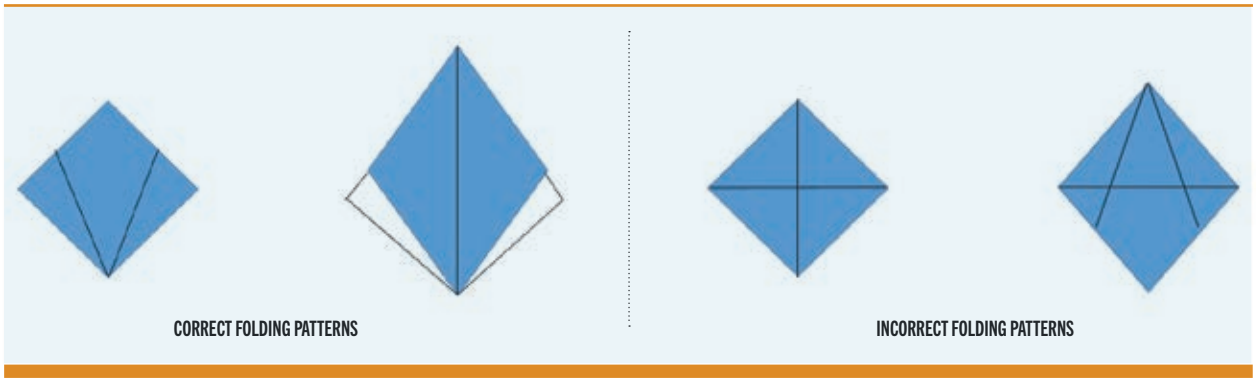
The yin and yang of folds

Each type of fold in origami has its own distinct pattern and purpose. For example, the popular origami crane starts with a bird base. This structure has a square base and petal folds. If we make a mistake in one of the folds or switch a petal fold for a mountain fold, we will end up with an unstable, inaccurate and perhaps disfigured crane.

Robert Lang, an origami pioneer, creates incredible design patterns from plain paper. I find it fascinating to look at his crease patterns and envision how one particular diagonal crease will be folded into the tentacles of a bug, or how one mountain fold or valley fold will become the base of a 3D structure.

Similarly, our DNA carries crease patterns in the form of a genetic code that determines the type and sequence of amino acids. Like origami crease patterns and folds, our biological origami depends on folding the correct sequence of amino acids into pristine

SUDHA NEELAM



Similar to protein folding, mishaps or mistakes in origami folding can result in mismatched structures. These PowerPoint images show correct and incorrect folding patterns for an origami crane and how each affects the final structure.

functional proteins. A group of disorders known as proteopathies occur when the proteins are misfolded due to incorrect assembly of the amino acids, genetic changes or abnormal folding patterns. In neurodegenerative diseases such as Alzheimer's and Parkinson's disease, the proteins are misfolded and become nonfunctional. Knowing the structure and folding patterns of proteins is vital to understanding their functions, and this in turn will help in designing therapeutics for these diseases.

Folds of life and art

A protein starts off as a flat sheet before being folded into a 3D structure. The protein sheet is similar to origami paper. Both need to be measured and folded accurately. Precision, perfection and patience are of utmost importance in creating the simple yet beautiful, pristine folds of life and art.

As scientists continue to explore protein folding, and while Nikhil and I experiment with the art of paper folding, I can't help but wonder if origami is a mirror reflecting the invisible folds of our life.

Sudha Neelam (neelam.sudha@gmail.com) is a research scientist in the field of cell biology. She is interested in studying the mechanisms of protein synthesis, how misfolded proteins cause diseases and how therapeutics can correct damage caused by misfolded proteins. She also loves to cook, which she believes is a form of science.

The ups and downs of teaching in a pandemic

By Victoria Del Gaizo Moore

I am an associate professor in the chemistry department at Elon University. I teach undergraduate students and have an undergraduate research lab. We currently are operating on campus.

The university has put protocols in place for faculty, staff and students: wearing masks on campus when indoors or outside if we are unable to maintain 6 feet or more distance, wiping down work stations when we finish, limiting student numbers in a classroom or lab based on the size of the room. Wipes and hand sanitizer stations are in every classroom, and most classrooms are upgraded with cameras to record or livestream class through Zoom or Webex.

The university is administering COVID-19 tests at random each week and posting results on a dedicated website. On that website we also can find total numbers of student and faculty cases, how many students are in quarantine (at least one entire dorm is dedicated to quarantine) and how many days' supply of wipes, hand sanitizer and other supplies are on campus. We get a weekly update from the vice president of communications with info about the situation.

The administration instructed the faculty to set up our courses so we could pivot quickly to fully remote, if needed, and encouraged hybrid or flipped classrooms. The Center for the Advancement of Teaching and Learning and the teaching and learning technologies department staff provided several three-day online sessions in late July and early August for faculty to learn about best practices for hybrid and remote teaching, and faculty were incentivized to participate with a small stipend.

COURTESY OF VICTORIA MOORE

In Victoria Moore's lab, student Seth McKee, pictured at the cell culture hood, is investigating chemoresistance in pancreatic cancer, and Maggie Canavan, pictured with Moore at the microscope, is studying chemosensitivity in acute myeloid leukemia.

Due to limits on how many students can be in a classroom, many faculty can have only half of their class in person at a time. I have adapted my class to be hybrid, with half the students attending on Monday, the other half attending on Wednesday; we are all remote and meet during class time on Zoom on Fridays. I prerecord lectures using an electronic white board and post 20- to 25-minute lectures of material on Moodle and then use in-class time to answer questions and dive deeper into the material. I record and post each in-person session so the other half of the class can view later what occurred. I don't use the whole class periods on Monday and Wednesday, because the students have video lectures to watch and other projects to work on for our Friday meetings, which usually are reserved for group work and presentations.

I am framing my entire medicinal and pharmaceutical chemistry course around COVID-19. For example, instead of looking at random clinical trials, we are using COVID-19 clinical trials to learn about trial phases. Also, one topics project is centered on COVID-19 topics, and I will introduce major principles of pharmacokinetics and dynamics using drugs that

are being used to treat COVID-19 patients. I also adopted a grading contract policy with less emphasis on points and more emphasis on doing a good job and learning the material. Students will take all exams synchronously online through Moodle.

We are teaching the general chemistry lab sections in pods — groups of nine students that cycle through in-person labs, virtual prerecorded lab videos with data analysis and off weeks so we can get all the students in person for a few hands-on labs.

I had to purchase my own voice projector/microphone, as the university did not supply one. It is absolutely necessary when trying to teach with a mask on. All office hours are through Zoom.

I have one lecture student who is completely remote; students with health concerns could apply for this option but had to be vetted through a committee. I assigned this student an in-person buddy. I also have one virtual lab student who uses prerecorded video lectures for all the labs — the chemistry department paid a few student workers to run through all of the fall semester general chemistry labs and record them for virtual students or in case the entire university has to transition to all remote.

The upside

My research lab is forging ahead as usual but with masks on and limiting the number of people in the research space at any given time. We are interested in understanding chemoresistance and chemosensitivity in different types of cancer, specifically looking at apoptosis and mitochondrial metabolism. I'm grateful that this aspect of the fall semester is undisrupted.

Committee work has been reduced to essential work only. Curriculum committees are reviewing proposals for new courses to be taught this academic year but not taking on programmatic review or five-year planning that ordinarily would be done. All committee meetings are online.

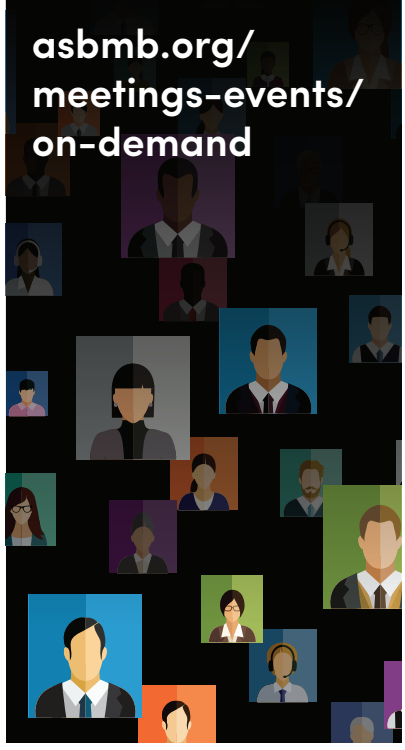
After taking the initial extra time and effort to figure out how I would teach hybrid courses, the fall semester has been a little easier than normal for me, being a mom of two school-aged children. I can record lectures whenever and from wherever I want. With office hours on Zoom, I don't have to go to my actual office; I can be at home with my kids after school hours. The same holds for committee meetings — I can be at home and be working.

My prerecorded lectures allow me to focus on student understanding when we are in person rather than just delivering the concepts, which is actually really nice from a pedagogical standpoint. I also don't feel the pressure to give a performance, because I am sharing small snippets of material. I can have all of my notes and the textbook laid out in front of me, and I always can pause the recording if needed.

We never would have explored these new ways of conducting the semester had there not been the pandemic. We have learned we don't need to be together physically to be productive, which offers flexibility to working parents. Once we are back to normal (not wearing masks and without a strictly limited number of students in the classroom), I hope that we can retain some of the practices we've put in place. I certainly will consider continuing the flipped lecturing and grading contracts for my courses in the future.

Read more COVID-19 on campus essays at asbmb.org/asbmb-today.

Victoria Del Gaizo Moore (vmoore3@elon.edu) is an associate professor in the chemistry department at Elon University.



National certification exam as faculty development exercise

Applying large-scale assessment ideas to small classes

By Brian Chiswell

If you are considering volunteering to serve on a team involved in the American Society for Biochemistry and Molecular Biology certification exam, I strongly recommend it based on my own experience.

Five years ago, I helped to score a single question for the ASBMB certification exam, which is offered to college juniors and seniors enrolled in ASBMB-accredited programs and is designed to test their understanding of the core competencies in biochemistry and molecular biology. Little did I know the effect this activity would have on my thinking and the impact it would have on my own test question writing. Since that time, I have worked each year on small committees of bright, motivated faculty to write new questions for the ASBMB exam and to create and refine rubrics for existing questions.

Working with the ASBMB has allowed me to take a hard look at three important components of written assessment: writing questions, writing rubrics and scoring answers. My classroom instruction is guided mainly by how I want students to think their way through an answer. Without each component of the written assessment aligning and synergizing with the others, there is a risk that the questions are not fair, not actually assessing what I had hoped or not requiring the students to think. Working on these exam committees has changed my mindset, so I am more aware of these issues when working on my own exams.

I have learned a few things from colleagues who are members of or work at the ASBMB. These lessons ensure fairness to the student, promote consistency in grading, and bring deserved attention to question and rubric details.

LESSON 1: The person or committee that writes an exam question ideally should not be the one to write the rubric or score the answers. When we write a question, we are already biased toward an answer.

LESSON 2: The exam should be anonymous when graded, especially if you know the student.

LESSON 3: Exams should be scored by more than one scorer and interrater reliability should be calculated and addressed.

LESSON 4: Questions should be reevaluated and improved after each time the test is administered.

LESSON 5: Each question should be graded from all exams at the same time.

LESSON 6: Questions should target different levels of Bloom's taxonomy to create an exam that also can be a useful teaching diagnostic tool. We should aspire to teach students to analyze, evaluate and create, so categorizing questions in this manner will diagnose how well we are teaching these skills.

The ASBMB in each of the last two years scored almost 1,000 exams, so it is a large-scale process. The ideas above can be applied on a smaller scale in your department. For example, choose your toughest question to grade and ask a few colleagues to score an answer to check if interrater reliability is an issue. Instead of asking a peer to take one of your exams, ask them to take a five-question quiz containing the five new questions you are vetting for this year's final. Also, another professor teaching the same subject could help you with a rubric to make sure it is objective, not overly biased toward what you remember saying in lecture.

Written assessments are difficult to develop, and we should develop them together.

ASBMB

The ASBMB in each of the last two years scored almost 1,000 exams. Here, ASBMB staff members Quira Zeidan, Kirsten Block and Stephanie Paxson prepare the exams for mailing.

Brian Chiswell (brian.chiswell@touro.edu) is an associate professor at Touro College in Manhattan. In his undergraduate research lab, students study the molecular detail of cell signaling in stomach cancer oncogenesis. Follow him on Twitter @BPChiswell

"It all comes down to where we place our bets"

5 QUESTIONS WITH MARK HARPEL

By Laurel Oldach

Drug discovery involves coming up with a safe and effective molecule — but first, you have to figure out what part of the cell you can mess with to get your desired result in disease. Mark Harpel of GlaxoSmithKline is a scientific leader in a unit that does exactly that.

1 You work on novel human genetics. What does that mean?

One of the most important parts of drug discovery, at least in terms of investment, is getting the target right. We draw on genetics to pick targets that have a disease basis in actual human data.

Our research unit evaluates targets that come out of genetic analyses and advances them through validation into a discovery program and, if we're successful, to the point of early clinical studies.

It all comes down to where we place our bets. We use genetics to help us select targets, but then build the package to understand them and identify the early kill experiments that could stop us from investing in something that ultimately will not work out.

2 What's a kill experiment?

Any experiment that would let us say whether the hypothesis is good or bad moving forward. That could be working with human cells to reduce expression of a protein. It could also be down the road: If we run a high-throughput screen and we don't get anything out, we've either run the wrong screen or the target's no good.

3 Tell me about a day in your life.

Primarily, I'm a matrix program leader for one particular program. I set the strategy and get it approved, make sure we have the appropriate resources and handle the day to day. I also evaluate new targets — so a lot of my day is spent reading journal articles and talking to people — and provide expertise on business development opportunities.

4 What traits do you look for in a potential employee?

It has to go beyond the resume. What's most important to me is a genuine sense of interest and excitement; the other skill I look for is adaptability. There's no guarantee that what we're doing today will be of interest three months from now. If we find a reason why we should not be working on something, we'll walk away from it. There has to be an understanding up front that that could happen.

5 When has networking really worked for you?

I had an opportunity to join either DuPont Pharmaceuticals or DuPont Basic Research — my contact was someone at Basic Research that I knew well from various meetings. He brought me in to interview for his enzymology group, but he made sure my resume made its way up to DuPont Pharma, and I had a dual interview. I ended up not working with him directly — but what he did really speaks to people wanting to do good things for other people.

Mark Harpel

CURRENT POSITION
Scientific leader, novel human genetics, GlaxoSmithKline

CAREER PATH
Ph.D., University of Minnesota, 1990
Postdoctoral research: protein engineering, Oak Ridge National Lab

FIRST JOB OUTSIDE OF ACADEMIA
Chemical enzymologist, DuPont Pharmaceuticals

FAVORITE MOLECULE OR PROTEIN
"Non-heme iron containing oxygenases, the first enzyme I purified … or RuBisCo: it's a dog of an enzyme."

Read an extended version of this interview at asbmb.org/asbmbtoday.

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

Online teaching: Practices and resources

asbmb.org/education/online-teaching

Access a collection of best practices on:

- Organizing course materials
- Collaboration and peer review
- Online assessments
- Online lab work

These resources were collected by a group of dedicated educators and ASBMB members.

To submit resources to the collection, visit **asbmb.org/education/online-teaching** and fill out the form.

ASBMB

ASBMB
American Society for Biochemistry and Molecular Biology

ASBMB Today call for submissions

ASBMB Today is accepting submissions for two upcoming special issues.

The wellness issue

January 2021
Deadline: November 2, 2020

With our lives upended by a worldwide pandemic, how have you kept yourself well? If you are a professor, investigator or supervisor, how have you looked after your students' and workers' wellness? Write about the physical and mental challenges you faced and overcame in 2020.

The reimagining issue

June/July 2021
Deadline: March 15, 2021

When the world reopens after COVID-19, it will be a different place. It's a good time to reimagine ways the scientific enterprise could be more sensible and just. We want your ideas for how to do that. Think about the systems around you. Can they be improved? Should they be replaced? Tell us what you would do to make them better.

For information, email asbmbtoday@asbmb.org or go to asbmb.org/asbmbtoday and click SUBMIT.

CLASSIFIEDS

Senior Scientist, Cell Therapy
Simcere Innovation, Inc.

Simcere Innovation is one of the internal innovation arms of Simcere Pharmaceutical group with focuses on the discovery and development of novel cell therapies for oncology and immunology indications. We believe that the pharmaceutical and venture capital global community needs a new way to explore and facilitate R&D in the ever-changing field of medicinal science. We provide an environment where all the talents can pursue and foster their aspirations outside the traditional organization box. Our disruptive operation model can help scientists tackle challenging scientific problems, while minimizing risk. Together, we aim to develop a truly transformative model that would benefit our patients and revolutionize scientific society.

The Senior Scientist will participate in early drug discovery and development projects with a focus on immuno-oncology. The candidate will characterize and develop large and small molecules in close collaboration with partner lines as an integral member of drug discovery teams. Ideal applicants will employ and develop new cutting-edge in vivo mouse and human cancer models. The individual will provide technical and scientific expertise in in vivo pharmacology to the Cancer Immunology Discovery department to enable target identification, validation, prioritization and efficient drug discovery. Ideal applicants will be collaborative and team-oriented, possess excellent communication, leadership and organizational skills, critical problem-solving abilities, and a commitment to excellence.

careers.asbmb.org/job/senior-scientist-cell-therapy/54764024/

Postdoctoral Associate
Weill Cornell Medicine

The Postdoctoral Associate position (available immediately) is for a full-time researcher to work on molecular identification of lipid transporters for protein glycosylation' using biochemistry, chemical biology and cell biology approaches. The project is a collaboration between the Menon laboratory at Weill Cornell Medical College in New York City, and the Bütikofer and Häner laboratories at the University of Bern, funded by the Swiss National Science Foundation. The main approach will be to use available photoclickable analogs of dolichyl phosphate to capture and identify lipid transporters (scramblases) involved in the flip-flop of dolichol-linked oligosaccharides and monosaccharides across the endoplasmic reticulum (ER) membrane for protein N-glycosylation. Scramblase candidates captured by photoclick chemistry will be identified by quantitative proteomics, and their role will be validated by biochemical and genetic approaches. The Menon laboratory was the first to demonstrate the scramblase activity of a purified membrane protein and provides an excellent environment for this project.

The ideal candidate will have first author publications and direct experience in biochemistry, chemical biology and/or cell biology. The candidate should be self-motivated, able to work independently as well as part of a collaboration, possess reasonable quantitative skills and a strong attention to detail. Prior experience with protein purification, biochemical reconstitution, and/or yeast genetics would be beneficial.

careers.asbmb.org/job/postdoctoral-associate/54664256/

Associate/Sr. Associate, Assay Development and Quality Control Analytics
Cepheid

Cepheid is a leading molecular diagnostic company that is an operating company within Danaher Corporation's Diagnostics platform. Cepheid is dedicated to improving healthcare by developing, manufacturing, and marketing accurate yet easy-to-use molecular systems and tests. By automating highly sophisticated and time-consuming manual procedures, the company's solutions deliver a better way for institutions of any size to perform sophisticated molecular diagnostic testing for organisms and genetic-based diseases. Through its strong molecular biology capabilities, the company is focusing on those applications where accurate, rapid, and actionable test results are needed most, such as managing infectious diseases and cancer.

The successful applicant will work as a member of the Protein Reagent Development and Production Department to develop and manufacture recombinant protein reagents including recombinant enzymes. He/She will mainly contribute to protein reagent assay development and quality control analytics.

careers.asbmb.org/job/associatesr-associate-assay-development-and-quality-control-analytics/54763578/

Assistant Professor of Biology
Augustana University

Augustana University, a selective, private, liberal arts institution invites applications for a tenure-track Assistant Professor position in the Department of Biology beginning September 2021. A Ph.D. is expected; postdoctoral experience is preferred.

Duties typically include teaching 2 lectures and 2 labs each semester and a January term course. These will include a team-taught genetics course and a molecular biology course in alternating semesters, as well as other courses based on the needs of the department and qualifications of the applicant.

While teaching is a major component of the position, productive research involving undergraduates is expected and is a long-standing tradition in the department. The college is situated in an area experiencing rapid growth in biomedical, biotech, agricultural, and environmental research, offering collaboration opportunities in various research areas. A research startup will be provided as well as access to extensive existing research equipment ($1,350,000 in new purchases in the department over the last decade).

careers.asbmb.org/job/assistant-professor-of-biology/54764154/

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

ASBMB
American Society for Biochemistry and Molecular Biology

ASBMB FELLOWS

Call for nominations: the first class of ASBMB fellows

DEADLINE: JAN. 4, 2021

Selection as a fellow of the American Society for Biochemistry and Molecular Biology is an honor to be bestowed upon our most distinguished members. Fellows will be recognized for their meritorious efforts to advance the molecular life sciences through sustained outstanding accomplishments in areas such as scientific research, education, mentorship, commitment to diversity and service to the society and scientific community.

The ASBMB Fellows Program encourages nominations that reflect the breadth and diversity of the society's membership.

Nominees must be regular, industry or emeritus members of the ASBMB.

asbmb.org/about/asbmb-fellows