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ASBMB TODAY

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

FIRST CLASS

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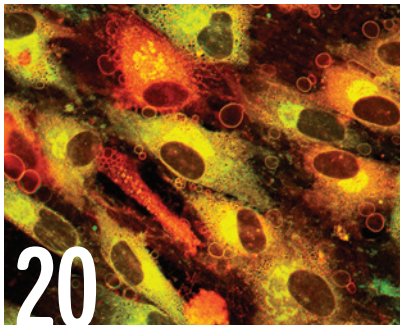
CONTENTS

NEWS



FEATURES

PERSPECTIVES

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

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'Share your aha moments!'

By Allison Frick

I'm not a scientist. My background is in broadcast journalism. When I came to the American Society for Biochemistry and Molecular Biology in 2015, it was from a local TV station, where I covered high school sports online and worked with reporters and producers on related TV elements. Biochemistry and molecular biology were a far cry from Friday night lights. I was nervous to enter a new realm of content, but, more importantly, I was excited for a new challenge.

The thing that I absolutely love the most about working in communications is hearing people's stories. I love learning about how they've navigated life. In fact, when I was a kid, I really wanted to grow up to be an actress. My logic: I'd never have to choose just one job. I could try everything if I was an actress. It turns out performing is not my forte, but I never lost that passion for storytelling and learning about the human experience.

Once I got to the ASBMB and began working as a multimedia content specialist and sharing articles from ASBMB Today on our social media channels, I started getting to know our members and the scientific community. I quickly learned that scientists have fascinating stories. From their personal experiences to their research, they are inspired to figure out how this world works. I knew I was going to hear some amazing stories working here, and I have.

Fast-forward to January 2021, when ASBMB's journals made the transition to gold open access. Papers published in the Journal of Biological Chemistry, the Journal of Lipid Research, and Molecular & Cellular Proteomics were going to be published immediately and be permanently available for everyone to read, download, copy, distribute and reuse. In preparation for the change, our marketing and communications teams were tasked with coming up with a plan to share the news.

Last fall, Joanna Kotloski, then our digital and content marketing manager; Anand Rao, our publications department's science communicator; and I all hopped on Zoom one afternoon and started brainstorming. We wanted to come up with a fun way to encourage scientists to share their discoveries in ASBMB journals. I love these brainstorming sessions and admire Joanna and Anand for their creativity. As we talked about what motivates us to connect with organizations and remember content, TikTok came to mind. Then Joanna remembered one of her favorite commercials from Southwest Airlines, and as the ideas kept coming, we landed on the slogan "Share your aha moments!" That was the beginning; we'd make a TikTok-inspired video with our members passing papers to one another and a second video with words of encouragement about the opportunities offered by publishing in an ASBMB journal.

ASBMB

Ngee Kiat "Jake" Chua encouraged his fellow ASBMB members to share their aha moments.

We recruited help from our journals' associate editors and JBC's early-career reviewers. They showed up and went above and beyond to bring this to life. I have to thank Ray Blind, Craig Cameron, George Carman, Courtney Chandler, Ngee Kiat "Jake" Chua, Michel Geovanni Santiago–Martínez and Catherine Goodman for graciously appearing in these videos. Their performances were outstanding! You can see for yourself on the ASBMB's YouTube channel.

From there, another element of the "Share your aha moments!" project came to life, and for this, we have Angela Hopp to thank. She created an essay contest, asking our members to reflect on their careers or those of scientists they respect and to write about the aha moment that sparked a shift in their work. It could be any kind of revelation that changed the trajectory of their research or life. We received dozens of submissions. Wow. Thank you to all who contributed. It wasn't easy to select the winners. We're publishing the winning essays in this issue, starting on page 44. We hope you enjoy them as much as we did.

When I reflect on my own career, I realize my first few months at the ASBMB were huge for me. Before starting here, I'd taken steps toward changing fields. I wasn't sure communications was right for me, but my experience at the ASBMB reminded me how much I love storytelling and multimedia. It was career-changing. Working here was my aha moment, and to this day, not a month goes by when I'm not reminded I'm in the right place. This month, that's thanks to these essays. Thank you for sharing your stories and aha moments with us and reminding me just how grateful I am for mine.

We're publishing the winning essays in this issue, starting on page 44. We hope you enjoy them as much as we did.

Allison Frick (africk@asbmb.org) is the ASBMB's multimedia and social media content manager. Follow her on Twitter @allisonfrick.

Hanawalt, Nagata and Regev named AACR fellows

The American Association for Cancer Research announced in March the new class of fellows in its AACR Academy, which recognizes scientists whose contributions have led to progress against cancer. Three American Society for Biochemistry and Molecular Biology members — **Philip Hanawalt, Shigekazu Nagata** and **Aviv Regev** — are among the class of 25 fellows.


HANAWALT

Philip Hanawalt is an emeritus professor of biology at Stanford University. The AACR is honoring him for his contributions to DNA damage repair. He co-discovered the ubiquitous process of DNA excision repair in 1964 and also discovered transcription-coupled repair, which removes transcription-blocking damage from the template strands of expressed genes. His work has furthered our understanding of the role of unrepaired DNA damage in oncogenesis.


NAGATA

Hanawalt is a fellow of the American Academy of Arts and Sciences, a member of the National Academy of Sciences, and a past member of the AACR's board of directors. He is a senior editor for the journal Cancer Research.

Shigekazu Nagata is a distinguished professor of biochemistry and immunology at the Immunology Frontier Research Center of Osaka University in Japan. He is honored by the AACR for "categorizing crucial steps required for cellular apoptosis." Nagata and his lab described a membrane protein called the Fas receptor as a cell death receptor; after binding to its ligand, which Nagata's lab also identified, Fas initiates an extrinsic cell death pathway that is crucial for immune control of tumors.

Nagata is a member of the Japan Academy and a foreign associate of the U.S. National Academy of Sciences.

Aviv Regev has been the executive vice president of Genentech Research and Early Development since 2020. The AACR honors her for "developing and applying sophisticated computational modeling techniques and algorithms to understand molecular circuits and predict cellular behavior." While a professor at the Broad Institute and Massachusetts Institute of Technology and a Howard Hughes Medical Institute investigator, Regev led a lab that developed high-throughput single-cell sequencing technologies and conducted systems modeling to understand cells' responses to varying stimuli. She co-leads the Human Cell Atlas project, a multinational research consortium that aims to define each cell type in the human body.


REGEV

Regev is a member of the National Academy of Sciences and the National Academy of Medicine.

Strickland to hold new professorship

Sidney Strickland, a professor, dean of graduate and postgraduate studies, and vice president for educational affairs at Rockefeller University, will be the first person to hold that university's new Fisher Center named professorship for neurodegenerative disease research.

Strickland's lab studies the contribution of vascular dysfunction to the development of Alzheimer's disease; they found that beta-amyloid protein can promote clotting and inflammation in the brain by interacting with fibrinogen and activating coagulation factor FXII. The work has suggested new molecular mechanisms for the widely studied β-amyloid protein to contribute to Alzheimer's pathogenesis and has linked the disease to other common maladies of aging, such as hypertension and cardiovascular disease.


STRICKLAND

The position, funded by the Fisher Center for Alzheimer's Research Foundation, will support research into neurodegenerative diseases. It extends the Fisher Center's partnership with Rockefeller University; the university is also home to the foundation's flagship lab of 40 scientists focused on Alzheimer's disease. Strickland has been a member of the Fisher Center's neuroscience advisory committee since 2019.

Blind recognized by GSA

Raymond D. Blind, an assistant professor at Vanderbilt University, was named in early March a member of the inaugural cohort for the Genetics Society of America's Presidential Membership Initiative. This competitive program aims to diversify the GSA membership while providing professional-development programming and support for early-career scientists.

Blind's lab studies how nuclear

inositides and inositols regulate chromatin-bound proteins. He recently completed a two-year stint as a junior associate editor for the Journal of Lipid Research, an American Society for Biochemistry and Molecular Biology publication.


BLIND

Blind gave a talk titled "The acyl chains of phosphoinositides alter the structure and function of nuclear receptor steroidogenic factor-1" at a special session on lipid diversity and disease at the 2021 ASBMB Annual Meeting.

Hazelbauer pledges $1 million to high school

Gerald Hazelbauer, a curators' distinguished professor emeritus of biochemistry at the University of Missouri, plans to donate $1 million to foster innovative science teaching at Lyons Township High School in Illinois.

Hazelbauer, a 1962 graduate of the school, is making the bequest in honor of Ruth Wenner, his freshman biology teacher, according to an article in the Riverside/Brookfield Landmark.

Wenner, described by Hazelbauer as an innovative and challenging teacher who treated her students like scientists, arranged for him to accompany her to some laboratory sessions of a summer course for teachers at the Illinois Institute of Technology after his freshman year. The following year, she gave him the opportunity to be student leader of a high school research project funded by the National Science Teachers' Association through the Future Scientists of America Foundation. He went on to earn a bachelor's degree in biology from Williams College, a master's degree in biology from Case Western Reserve University and a Ph.D. in genetics from the University of Wisconsin.

Research in the Hazelbauer lab at the MU School of Medicine and the College of Agriculture, Food and Natural Resources focuses on elucidating molecular mechanisms of transmembrane receptors and sensory transduction in bacterial chemotaxis. A number of recent projects have used the emerging technology of nanodiscs to manipulate membrane proteins in a water-soluble state.

Hazelbauer is making an initial $20,000 donation to LTHS this year, which will support creative projects of several of the school's science teachers. He has pledged to give at least the same amount each year while he and his wife are alive, prior to the $1 million posthumous donation.


HAZELBAUER

A member of the American Society for Biochemistry and Molecular Biology since 1984, Hazelbauer is also a fellow of the American Association for the Advancement of Science and of the American Academy of Microbiology.

McReynolds to join faculty at Penn State

Melanie McReynolds, a postdoctoral fellow at Princeton University, will join the faculty at Pennsylvania State University's department of biochemistry and molecular biology, taking a named early-career chair, in January of next year.

McReynolds studies the metabolic changes that occur during aging, focusing on NAD^+, the essential metabolite converted into NADH during cellular respiration. NAD^+ declines with age in both mice and the roundworm Caenorhabditis elegans. When it is missing, glycolysis can slow down. McReynolds' research explores how the resulting energy deficit might contribute to cellular ageing and whether it can be reversed. She also has published extensively on mentoring and improving the equity of scientific training.

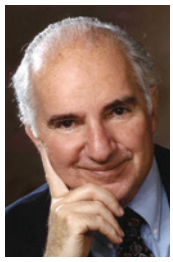

MCREYNOLDS

The move is a homecoming of sorts: McReynolds earned her Ph.D. in biochemistry, molecular biology and microbiology at Penn State in 2017. She served as the president of the Black Graduate Student Association during her time in State College. She arrived at Penn State through a Bridges to the Doctorate program with Alcorn State University in Mississippi, where she earned her bachelor's and master's degrees. Her awards as a graduate student included an award from the Alfred P. Sloan Foundation Minority Ph.D. Program; as a postdoc, she has received a Howard Hughes Medical Institute Hanna Gray fellowship and the Burroughs Wellcome Fund Postdoctoral Enrichment Program award.

Department chair Wendy Hanna–Rose was McReynolds' dissertation adviser. "Dr. McReynolds is a creative and collaborative researcher of exceptional promise," she stated in a Penn State news release. "As a graduate student, she was well known and recognized across campus for her activism and leadership."

Passano Foundation honors Goldberg

Alfred Goldberg, professor of cell biology at Harvard Medical School, won the 2021 Passano Award, which is presented by the Passano Foundation to a researcher who has made an exceptional contribution to the advancement of medical science.


GOLDBERG

Goldberg was recognized for introducing the proteasome inhibitor MG132, now very widely used as a research tool, and initiating the research that led to the development of the inhibitor bortezomib, which is used worldwide in the primary treatment of the blood cancer multiple myeloma.

Goldberg's major discoveries have concerned the biochemical mechanisms and physiological regulation of protein breakdown in cells and the importance of this process in human disease.

His laboratory first discovered the ATP-dependent system for protein breakdown, now termed the ubiquitin–proteasome pathway. They first demonstrated the involvement of the proteasomes in this process and discovered the ATP-dependent proteases responsible for protein degradation in bacteria and mitochondria.

Also of great impact have been his findings about the mechanisms for the excessive protein degradation and muscle atrophy in many disease states and their elucidation of the role of the proteasome and cellular peptidases in antigen presentation to the immune system.

Goldberg's wide-ranging work has had a major impact on many areas of biology, medicine and biotechnology.

Derbyshire named Sloan fellow

Emily Derbyshire, an assistant professor of chemistry at Duke University, is one of 128 early-career scholars who are winners of the 2021 Sloan Research fellowships.

Derbyshire earned her Ph.D. from the University of California, Berkeley, in 2008 and then held a National Institutes of Health postdoctoral fellowship in biological chemistry and molecular pharmacology at Harvard Medical School from 2009 to 2014. She was a scholar in residence in the chemistry department at Duke's Trinity College of Arts and Sciences before joining the faculty. She is also an assistant professor in molecular genetics and microbiology and an associate of the Duke Initiative for Science and Society.


DERBYSHIRE

Derbyshire's lab studies novel aspects of malaria parasite biology with the aim of identifying druggable targets. They develop phenotypic and target-based screens to discover small molecules that can be leveraged to elucidate biological pathways. Their efforts integrating biochemistry, microbiology and chemical biology have revealed parasite and human proteins that are important for pathogen infection.

Each year, the Alfred P. Sloan Foundation provides fellowships to promising scientific researchers whose achievements and potential place them among the next generation of scientific leaders in the U.S. and Canada. Winners each receive $75,000, which may be spent over a two-year term on any expense supportive of their research.

Kornfeld and Dahms named to M6P board

The Missouri-based biotechnology company M6P Therapeutics, which develops enzyme and gene therapies for lysosomal storage disorders, has appointed a scientific advisory board of geneticists and glycobiologists including two American Society for Biochemistry and Molecular Biology members, **Stuart Kornfeld** and **Nancy Dahms**.

The company is named for the sugar mannose-6-phosphate, which acts as a signal flag to promote trafficking of enzymes destined for the lysosome. Without the sugar, enzymes don't make it to the lysosome — and absence of certain enzymes can cause lysosomal buildup of their substrates. Lysosomal storage disorders are generally rare diseases but can be very serious. The company is developing a gene therapeutic approach that expresses both a missing lysosomal enzyme and a phosphotransferase that enables proper lysosomal targeting.


KORNFELD

CONTINUED ON PAGE 8

American Academy of Microbiology inducts fellows

The American Academy of Microbiology has elected 65 new fellows into its class of 2021. The academy, an honorific leadership group of the American Society for Microbiology, elects microbiologists annually through peer review. Five of this year's AAM fellows are American Society for Biochemistry and Molecular Biology members.

Julie Maupin–Furlow is a professor of microbiology and cell science of the University of Florida's Institute of Food and Agricultural Sciences. She is known for her lab's biochemical and proteomic characterization of archaeal protein turnover through the proteasome–ubiquitin system. The work, which uses extremophiles from environments like the hypersaline Dead Sea, is relevant to bioenergetic research, aiming to generate renewable fuels, as well as to astrobiological research. Maupin–Furlow is a member of the Archaeal Proteome Project, has organized Gordon Research Conferences and received her university's UF Research Foundation award in 2010.

Kenneth Marians is a professor at Memorial Sloan Kettering Cancer Center in New York and a leader in the field of DNA replication. He served as chair of the molecular biology program for 25 years and was the founding dean of the Louis V. Gerstner Jr. Graduate School of Biomedical Sciences. He is now back in the lab full time.

Mitzi Nagarkatti is Carolina distinguished professor and SmartState endowed chair of the Cancer Drug Discovery SmartState Center as well as chair of the department of pathology, microbiology and immunology at the University of South Carolina School of Medicine. Her lab pursues broad-based research on inflammatory diseases, including studying the contribution of epigenetic modifications and other regulatory genes in inflammation and seeking small-molecule treatments for several types of cancers and cancer immunotherapy. She is a fellow of the American Association for the Advancement of Science and has received numerous research awards.

Mario Feldman is a professor of molecular microbiology at Washington University in St. Louis, where he studies pathogenic Gram-negative bacteria, some of which frequently cause hospital-acquired infections. Feldman's lab works to develop new antimicrobials by better understanding bacterial secretion systems, virulence factors and outer membrane vesicles. Feldman also co-founded a biotechnology startup called VaxNewMo in 2016 and serves as chief scientific officer; the company aims to use glycoengineering to produce vaccines that more closely resemble true bacterial antigens.

Sarah Gaffen is the Gerald P. Rodnan endowed professor of rheumatology and clinical immunology at the University of Pittsburgh and the director of the Pittsburgh Autoimmunity Center of Excellence in Rheumatology. Her lab was among the first to study interleukin-17 and continues to study the role of this cytokine, and the T cells that produce it, in host defense from fungal infection and also, when unchecked, autoimmune disorders such as psoriasis.

CONTINUED FROM PAGE 6

The scientific board's chairman is also the company's co-founder, glycobiologist Stuart Kornfeld, a professor at Washington University Medical School in St Louis. Kornfeld, who has taught at WashU since 1967, has a long history of service to the field. He served several terms on the editorial board of the Journal of Biological Chemistry, including a term as an associate editor, and has served on numerous research review boards for awards and granting agencies. In 2012, he received the Herbert Tabor Research Award from the ASBMB.

DAHMS

Board member Nancy Dahms, a professor at the Medical College of Wisconsin, has studied lysosomal storage diseases since she was a postdoc in Kornfeld's lab at WashU in the 1980s. As a postdoc, she characterized mannose-6-phosphate receptors that govern lysosomal enzyme targeting. She has studied glycoproteins and their receptors ever since, becoming a leading expert in Fabry disease, a lysosomal storage disorder caused by buildup of a glycosphingolipid when a certain lysosomal glycan-digesting enzyme is mutated or absent. She is the 2021 president of the Society for Glycobiology.

IN MEMORIAM

Robert Baldwin

Robert Lesh Baldwin, a founding member of Stanford University's biochemistry department and a member of the ASBMB since 1957, died March 6 at his home in Portola Valley, California. He was 93.

"Baldwin devoted his career to studying how proteins, which begin life as linear chains of chemical building blocks, quickly assume their characteristic highly complex, functional structures," an article posted on the Stanford Medicine news website stated. "His research sped a shift in many biologists' attention from organismic biology, the study of creatures great and small, to molecular biology, which focuses on the individual biochemical reactions that underpin all living processes and on the molecules — usually proteins — responsible for catalyzing those reactions."

Born Sept. 30, 1927, in Madison, Wisconsin, Baldwin was nicknamed "Buzz" by one of his sisters. He earned a bachelor's degree in chemistry at the University of Wisconsin before attending the University of Oxford as a Rhodes scholar, where he received his D.Phil. in biochemistry. He did a postdoc in physical chemistry at the University of Wisconsin and then joined that school's faculty.

In 1958, Arthur Kornberg invited Baldwin to join a group of researchers from Washington University in St. Louis who were moving to Stanford to establish a biochemistry department. Baldwin began his tenure at Stanford as an associate professor and was promoted to full professor in 1964.

In 1965, he married Anne Norris, a postdoc in the lab of Paul Berg. (Another member of the Stanford biochemistry founding group, Berg went on to win the 1980 Nobel Prize in chemistry.) Norris had been offered a faculty position at Harvard that year but chose to stay in California.

Baldwin served as Stanford's biochemistry department chair from 1989 through 1994. He was a member of the National Academy of Sciences and of the American Academy of Arts and Sciences and a fellow of the Biophysical Society. He received the Stein and Moore Award of the Protein Society in 1992 and the Wheland Award in chemistry in 1995.

He had been an emeritus professor since 1998 and, according to Berg, continued to make major theoretical advances until the last five years of his life.

In addition to his wife, Baldwin is survived by two sons, David and Eric, and five grandchildren.

Remembering Curtiss, former JLR associate editor

By Angela Hopp

Linda Kay Curtiss, a professor at Scripps Research in California, died Feb. 23 of cancer. She was 77.

Curtiss studied plasma lipoproteins, inflammation and innate immunity in atherosclerosis. She was a former associate editor for the American Society for Biochemistry and Molecular Biology's Journal of Lipid Research, a champion of women in science, and an advocate for robust federal funding for research.

Curtiss was born in 1943 to Ruby and Glenn Curtiss in Seattle and raised in Kirkland, Washington. She attended and held leadership positions and participated in sports at Lake Washington High School, where her mother taught biology. She graduated in 1962.

Curtiss earned her bachelor's degree in zoology at the University of Washington in 1966 and then earned a master's degree in biology at the University of Colorado Boulder in 1968.

She spent six months in Europe and another six in Africa before returning to UW for her Ph.D. She finished her thesis on immunochemistry while doing a research fellowship at the Mayo Clinic in Minnesota in 1974.

For postdoctoral studies, she moved to Scripps to work on plasma lipoproteins in the lab of Tom Edgington.

"I left the Mayo Clinic in a blizzard in 1974," she said in an interview with Scripps' online weekly back in 2007. "I stepped off the plane in San Diego — those were the days when

they rolled the stairs out to meet you — the sun hit my eyes, I smelled the ocean, and I immediately thought, 'This is where I'm going to stay.'"

Indeed, she did. She won a faculty position at Scripps' immunology and microbiology department and started her own lab in 1978.

Curtiss was a committed volunteer and leader for the American Heart Association, which ultimately made her an elected fellow and gave her three awards for her body of work and her service: the Distinguished Achievement Award in 2006, the Mentor of Women Award in 2004 and the Special Recognition Award in 2000.

With the AHA, Curtiss on multiple occasions visited Capitol Hill and talked to lawmakers about her work, federal spending priorities and science policy.

For most of the 1990s, Curtiss held leadership positions on the advisory board for the Deuel Conference on Lipids. She also served on numerous National Institutes of Health study sections and review committees.

Curtiss also was committed to supporting other women in science. She was a member of the Association for Women in Science and, in the 1980s, served on the board of the San Diego chapter.

For decades, Curtiss served as an editorial board member and associate editor for the JLR.

Kerry-Anne Rye, who became JLR's co-editor-in-chief in 2020, is a longtime friend and colleague of Curtiss. She said that Curtiss was a role model for her and other women in their field.

"This is a huge loss. I'm going to miss her a lot, but I fortunately got to see her for the last time during my final pre-COVID trip to the U.S. It was just a few days before everything was locked down. Talk about impeccable timing," Rye said.

She also said that Curtiss' early love of athletics never faded.

"One of the first times I went to visit Linda in San Diego, she was in a great hurry to get to a baseball game, so we went straight there from the airport. I thought we would be spectators. That was certainly the case for me, but she was one of the players!" Rye said. "Actually, her main sporting passion was golf, which she played with huge enthusiasm for many years."

Curtiss retired from Scripps in 2014 and remained in San Diego.

She is survived by her wife of four decades, Jeanne Niosi, a sister and a brother, and many nieces and nephews.

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

FIRST CLASS

Meet the inaugural ASBMB FELLOWS

Introduction by Judith Bond & Edward Eisenstein

The title of fellow has a long history in academia and professional societies and typically designates distinguished members or partners who have contributed significantly to a field or endeavor. Over the past year, the leadership of the American Society for Biochemistry and Molecular Biology established a fellows program to recognize members of our society who have demonstrated exceptional commitment to the ASBMB and made outstanding contributions to advance the molecular life sciences.

The Membership Committee took on the responsibility of implementing the program by defining criteria and developing a process for selection of the fellows. The committee decided that fellows should demonstrate exceptional service through active participation and leadership in ASBMB programs and should personify the core values of the ASBMB through scientific achievements, educational endeavors, mentorship, commitment to diversity, and/or service to the society and the scientific community. Our objective was to select fellows who represent the breadth and diversity of the society's membership and all its missions.

A call for nominations for fellows was announced electronically to members in society publications (including ASBMB Today) and on our website. Nominations were accepted from regular, industry and emeritus ASBMB members in good standing. There was an immediate and robust response. It became obvious that our society has a very large number of accomplished members who have served the ASBMB and advanced the life sciences in many ways. A subgroup of the Membership Committee screened and assessed the candidates, the assessments were then discussed with the whole committee, and finally a list of 30 candidates (out of about 100 nominees) was submitted to and approved by the ASBMB Council. The list was announced during the 2021 ASBMB annual meeting in late April.

The 2021 fellows are indeed a distinguished group of scientists who have contributed to multiple missions of our society over a sustained period of time and enriched our world through their efforts and accomplishments. It was an honor to be part of the process to recognize this group, and their contributions make us proud to be members of the ASBMB.

Natalie Ahn, University of Colorado Boulder

Natalie Ahn is a distinguished professor of biochemistry at the University of Colorado Boulder. Her lab merges proteomics, cell biology and biophysical approaches to investigate signal-transduction mechanisms, particularly those implicated in cancer.

Ahn served as president of the American Society for Biochemistry and Molecular Biology from 2016 to 2018. Before that she was a member of the society's Council. She was nominated to be an ASBMB fellow by Ruma Banerjee, who wrote: "Natalie worked tirelessly to enhance the status of the national meeting and selected a new editor-in-chief for (the ASBMB's) flagship journal, JBC, which ushered in sweeping and positive changes. … Natalie's scientific record is stellar. … She is most deserving of the recognition that would be conferred as an ASBMB fellow."

She earned her Ph.D. from the University of California, Berkeley, and did postdoctoral work at the University of Washington.

Karen Allen, Boston University

Karen Allen is a professor and chair of the chemistry department at Boston University. Her lab uses structural biology techniques to study enzyme evolution and substrate specificity, with a longstanding focus on the haloalkanoate dehalogenase superfamily. Her lab also has designed inhibitors for several enzymes from pathogens that cause understudied diseases such as elephantiasis.

Allen is a former member of the ASBMB Council and secretary of the society and a founding member of the Women in Biochemistry and Molecular Biology Committee.

She was nominated to be an ASBMB fellow by Ann Stock and Tina Iverson, who wrote that Allen "is a superb scientist who has made fundamental contributions to the field of enzymology … has her pulse on the leading questions of the field and is an investigator with the highest integrity and values."

Allen earned her Ph.D. at Brandeis University and did postdoctoral training at the Massachusetts Institute of Technology.

Teaster Baird Jr., San Francisco State University

Teaster Baird Jr. is a professor and chair of the department of chemistry and biochemistry at San Francisco State University. A dedicated educator who has led many initiatives within and beyond his university to improve science education, Baird also maintains a research program in serine protease enzymology, examining and engineering the enzymes to modify their catalytic activity, substrate specificity and interactions with macromolecular inhibitors.

Baird has served the ASBMB as the Southwest regional director of Student Chapters for at least six years and remains the faculty adviser for his university's Student Chapter. For 10 years, he served on the steering committee that developed concept-driven teaching strategies in biochemistry and molecular biology.

He was nominated to be an ASBMB fellow by a panel of seven colleagues from SFSU and the ASBMB Student Chapters program, who wrote that "he sees potential, provides opportunities, and gives a voice to students and faculty who often are forgotten or overlooked … (and) is constantly pushing the boundaries of the way students are educated."

Baird earned his Ph.D. from Duke University and was a postdoctoral fellow both at Duke and at the University of California, San Francisco.

Ruma Banerjee, University of Michigan

Ruma Banerjee is a professor of biological chemistry at the University of Michigan whose lab studies the enzymes that metabolize and transform sulfur-containing compounds. Her work focuses especially on coenzymes, notably vitamin B12, or cobalamin.

Banerjee was nominated to be an ASBMB fellow by Tina Iverson, who wrote, "Ruma is a mover and shaker in enzymology … (who) has maintained this field-leading research program in the context of extensive service to her home institutions and the world at large."

Among her many service projects, Banerjee has served on the ASBMB Council and Minority Affairs Committee; is the founding co-PI of the society's Maximizing Opportunities for Scientific and Academic Independent

ASBMB FELLOWS

Careers, or MOSAIC, program; and is an associate editor of the Journal of Biological Chemistry. She has been the recipient of numerous awards, including, in 2019, the ASBMB–Merck Award, which recognizes outstanding contributions to research in biochemistry and molecular biology.

Banerjee earned her Ph.D. at Rensselaer Polytechnic Institute and was a postdoctoral fellow at the University of Michigan.

Suzanne Barbour, University of North Carolina at Chapel Hill

Suzanne Barbour is the dean of the graduate school and a professor at the University of North Carolina at Chapel Hill.

Barbour served on the ASBMB Education and Professional Development Committee for 12 years. She is now a member of the Minority Affairs Committee and the Council. Barbour serves on the Annual Meeting Program Planning Committee and organized scientific sessions for the 2020 annual meeting. She has been on the Journal of Lipid Research editorial board for almost 14 years.

She was nominated to be an ASBMB fellow by Sterling Bradley, who wrote that Barbour "is a recognized national advocate for many aspects of career development and the challenge facing working scientists and the coming generation of scientists."

Barbour earned her Ph.D. at Johns Hopkins University and did postdoctoral training at the University of California, San Diego. She has been a program director at the National Science Foundation and a dean at the University of Georgia.

J. Ellis Bell, University of San Diego

J. Ellis Bell is a lecturer at the University of San Diego. A dedicated educator, Bell has published extensive pedagogical research and also pursues structural biology studies in a lab jointly run with his wife, USD professor Jessica Bell.

Ellis Bell won the 2015 ASBMB Award for Exemplary Contributions to Education. That award recognized his service to biochemistry education as a long-serving member of the Education and Professional Development Committee; he led the committee that developed concept-driven teaching strategies in biochemistry and molecular biology, and he also played a key role in developing the ASBMB accreditation program.

Bell was nominated as an ASBMB fellow by Marilee Benore, who wrote, "Ellis' gift is his ability to step back and allow faculty to work within the strategic outline to create change, develop professionally and then step into their own leadership roles."

Bell earned his doctorate at Oxford University and did postdoctoral research at Duke University.

Squire Booker, Pennsylvania State University

Squire Booker is a professor and distinguished chair at Pennsylvania State University, where his lab studies the catalytic mechanisms of redox enzymes involved in natural product biosynthesis and human health. He is also a Howard Hughes Medical Institute investigator.

Booker has chaired the ASBMB's Minority Affairs Committee and was the founding principal investigator on the ASBMB Interactive Mentoring Activities for Grantsmanship Enhancement grant writing workshop. He also co-organized the 2016 ASBMB annual meeting. He now serves on the Finance and Nominating committees.

Booker was nominated to be an ASBMB fellow by Ruma Banerjee, who wrote, "Squire's work is characterized by its elegance and rigor. … His research productivity is all the more impressive given his heavy teaching load and service commitments both at Penn State and nationally."

Booker earned his Ph.D. at the Massachusetts Institute of Technology and did postdoctoral research at the Université René Descartes in Paris and the University of Wisconsin. He is an elected member of the American Academy of Arts and Sciences and the National Academy of Sciences.

George Carman, Rutgers University

George Carman is a professor at Rutgers University and director of the university's Center for Lipid Research. He has made seminal contributions to the understanding of the regulation of phospholipid synthesis using the yeast Saccharomyces cerevisiae. His group identified the molecular function of the yeast version of mammalian lipins, phosphatidic acid phosphatase enzymes that are crucial regulators of fat metabolism.

Carman is a repeat associate editor for the society's Journal of Lipid Research and is a former associate editor for its Journal of Biological Chemistry. He won the society's 2012 Avanti Award in Lipids, which recognizes outstanding research contributions in the area of lipids.

He also has served on and as chair of the society's Meetings Committee and Annual Meeting Program Planning Committee. He also has been a member of the ASBMB Council and Awards Committee and co-organized numerous society events.

Alfred H. Merrill Jr. at Georgia Tech University nominated Carman to be an ASBMB fellow. "George has made impressive contributions to science through both the discoveries of his laboratory and his assistance to others through these activities," he wrote.

Carman earned his master's degree from Seton Hall University before going on to complete his Ph.D. at the University of Massachusetts. He did postdoctoral work at the University of Texas Medical School in Houston.

Michael Cox, University of Wisconsin–Madison

Michael Cox is an endowed professor in the University of Wisconsin–Madison department of biochemistry. His lab studies DNA replication and repair and is best known for contributions to understanding the RecA and Flp recombinases, which have become widely used tools for biotechnology and developing transgenic model organisms.

Cox served as a member of the ASBMB Council and an associate editor of the Journal of Biological Chemistry; he was a member of the steering committee that developed concept-driven teaching strategies in biochemistry and molecular biology and continues to advise his university's ASBMB Student Chapter. He has served for many years as a judge in the undergraduate research poster competition at the ASBMB annual meeting.

UW–Madison colleague Aaron Hoskins, who nominated Cox as an ASBMB fellow, wrote, "Mike is a remarkable scientist. … From writing a grant to writing an exam, Mike has been an exceptional scientific role model in every way."

Cox earned his Ph.D. at Brandeis University and was a postdoctoral researcher at Stanford University School of Medicine.

Enrique M. De La Cruz, Yale University

Enrique M. De La Cruz is a professor at Yale University, where he leads the molecular biophysics and biochemistry department and Branford College. His lab studies the actin cytoskeleton, molecular motor proteins and nucleotide signaling enzymes.

De La Cruz is an associate editor for the Journal of Biological Chemistry and an advisory board member for the society's Maximizing Opportunities for Scientific and Academic Independent Careers, or MOSAIC, program. He previously served on and chaired the society's Publications Committee, served on the Meetings Committee, co-organized a 2013 annual meeting thematic session and co-organized the 2014 annual meeting.

Mark Hochstrasser at Yale nominated De La Cruz to be an ASBMB fellow. "Enrique is an active member of the ASBMB and is an exemplary scientist in his research, teaching and training, particularly of underrepresented scientists. … He has done an enormous amount of work in helping to build diversity both here at Yale and elsewhere."

De La Cruz earned his Ph.D. at the Johns Hopkins University School of Medicine and completed postdoctoral training at the University of Pennsylvania.

Edward Dennis, University of California, San Diego

Edward Dennis is a distinguished professor at the University of California, San Diego. He has made important contributions to the study of lipid metabolism and cell signaling through his research on phospholipase A2 enzymes. Importantly, he pioneered the lipidomics movement.

Dennis has been a member of the ASBMB Council and served as the first chair of the ASBMB Annual Meeting Program Planning Committee, program chair of the 1996 annual meeting, and on the society's Membership Committee, Education and Professional Development Committee, and Finance Committee. He was a member of the Publications Committee when the society started the journal Molecular & Cellular Proteomics and acquired the Journal of Lipid Research, and he went on to serve as editor-in-chief of the JLR for 15 years. He also served on the editorial board of the Journal of Biological Chemistry. He won the society's 2000 Avanti Award in Lipids and its 2020/2021 Bert and Natalie Vallee Award

ASBMB FELLOWS

in Biomedical Science.

George Carman nominated Dennis to be an ASBMB fellow. "Numerous investigators have entered the field of phospholipases and signal transduction as well as lipidomics because of the contributions of Dr. Dennis," Carman wrote. "These investigators do not even include the many graduate students and postdoctoral fellows that Dr. Dennis has mentored at the University of California at San Diego. The fact that many of his past students are now leaders in the field in their own right is testimony of his outstanding ability to train and motivate people."

Dennis earned his master's degree and Ph.D. from Harvard University and completed postdoctoral training at Harvard Medical School.

John Denu, University of Wisconsin–Madison

John Denu is a professor at the University of Wisconsin–Madison, where his lab studies enzymes responsible for adding and removing post-translational modifications. Recently, his team revealed new regulatory mechanisms that link metabolism and chromatin function, opening up new insights into diet, gut microbiota and the epigenome.

Denu has served as an editorial board member and now is an associate editor of the Journal of Biological Chemistry. He also serves on the ASBMB Nominating Committee. He has organized both scientific sessions and professional-development events for the ASBMB annual meeting.

Sharon Dent, who nominated Denu as an ASBMB fellow, wrote, "John's research is consistently trailblazing. … John is a highly productive scientist … (who) is also highly committed to teaching and mentoring."

Denu earned his Ph.D. at Texas A&M University and completed postdoctoral training at the University of Michigan.

Henrik Dohlman, University of North Carolina

Henrik Dohlman is a professor at the University of North Carolina, Chapel Hill, where he chairs the pharmacology department and studies G protein–coupled receptor signaling and desensitization in yeast. His lab was the first to demonstrate G protein regulation by GTPase-activating RGS proteins, mono- and poly-ubiquitination, and proton second messengers.

Dohlman has been an ASBMB member for more than three decades. He served multiple terms on the editorial board of the Journal of Biological Chemistry and today is an associate editor.

Jeremy Thorner, who nominated Dohlman as an ASBMB fellow, wrote, "Henrik has made numerous path-finding contributions about what are now known as G-protein coupled receptors. … Moreover, in the process, he has trained legions of his own Ph.D. students and postdoctoral trainees."

He earned his Ph.D. at Duke University and completed postdoctoral training at the University of California, Berkeley.

William Dowhan, University of Texas Health Science Center at Houston McGovern Medical School

William Dowhan is an endowed professor in biochemistry and molecular biology at the University of Texas Health Sciences Center McGovern Medical School, where his lab studies lipid–protein interactions. His lab found that lipids are involved in proper folding of membrane proteins and that changes to the lipid environment can alter membrane protein activity.

Dowhan won the ASBMB's 2005 Avanti Award in Lipids, which recognizes outstanding research contributions. He has served on the society's Meetings Committee and organized a scientific symposium for the annual meeting. He is a past editorial board member for the Journal of Biological Chemistry.

"Dr. Dowhan's success lies in successfully challenging dogma … use of evolving technology and approaches … and generating new concepts," wrote George Carman, who nominated Dowhan as an ASBMB fellow.

Dowhan earned his Ph.D. at the University of California, Berkeley, and did postdoctoral research at Harvard Medical School.

Catherine Drennan, Massachusetts Institute of Technology

Catherine Drennan is a professor at the Massachusetts Institute of Technology and a Howard Hughes Medical Institute investigator. She studies the structural biology of metalloenzymes. Her lab's targets have included multiple enzymes that depend on metal cofactors, such as ribonucleotide reduc-

tase, an early enzyme in DNA biosynthesis. Drennan was once a high school science and drama teacher, and she has remained committed to developing teaching best practices and research-based modules for students ever since.

As a postdoctoral fellow in 1997, Drennan started the undergraduate poster competition at the ASBMB annual meeting. She ran it for the next five years. She also served on the ASBMB Education and Professional Development Committee during the period when the society developed its undergraduate biochemistry curriculum recommendations. She later served on the Publications Committee. In 2013, she co-organized a themed session on catalytic mechanisms for the ASBMB annual meeting, and she is organizing one on enzymology for the 2022 meeting.

In her nomination letter, Tina Iverson at Vanderbilt University noted Drennan's "deep commitment to education and inclusivity" and her "long service to ASBMB, her contributions to training, and her stature as a world leader in the field."

Drennan earned her Ph.D. from the University of Michigan and completed her postdoctoral research at the California Institute of Technology.

Takita Felder Sumter, Winthrop University

Takita Felder Sumter is the dean of the College of Arts & Sciences and a professor at Winthrop University.

She has been deputy chair and later chair of the ASBMB Minority Affairs Committee. She was instrumental in creating the society's Marion B. Sewer Distinguished Scholarship for Undergraduates and co-led the Interactive Mentoring Activities for Grantsmanship Enhancement program. She helped organize regional workshops and other activities that ultimately led to the creation of two new mechanisms to evaluate student learning: the ASBMB degree-accreditation program and the ASBMB certification exam.

She has been a regional director for the society's Student Chapters program, and she has served for the past decade and a half as a judge for the annual undergraduate poster competition. Sumter is now on the ASBMB Council.

Heather J. Evans Anderson at Stetson University, who nominated Sumter to be an ASBMB fellow, wrote: "Taken together these efforts exemplify Dr. Sumter's exemplary mentorship skills and her commitment to service to ASBMB and the scientific community. … Overall, the products of Dr. Sumter's mentorship skills have established broad contributions and her widespread impacts will continue to influence the next generation of science education and production of scientists."

Sumter earned her Ph.D. at the University of South Carolina and completed a postdoctoral fellowship at the Johns Hopkins University School of Medicine.

Karen Fleming, Johns Hopkins University

Karen Fleming is a professor at Johns Hopkins University and a pioneer in the study of membrane-protein folding. Her lab focuses on beta-barrel proteins of the bacterial outer membrane and investigates the structural basis of chaperone interactions with unfolded membrane proteins.

Fleming is an associate editor of the Journal of Biological Chemistry and a past member of the Council. She has organized multiple meetings in protein biophysics, including events for the ASBMB, and she has been a vocal advocate for equity in scientific careers.

Cynthia Wolberger, who nominated Fleming as an ASBMB fellow, wrote, "She has worked extensively on issues facing women in STEM … and has recently expanded her efforts to confront issues that face both women and men of color."

Fleming earned her Ph.D. at Georgetown University and did postdoctoral training at Yale University.

Lila M. Gierasch, University of Massachusetts Amherst

Lila M. Gierasch is a distinguished professor and former department head at the University of Massachusetts Amherst. Her lab studies protein folding, investigating the mechanisms of molecular chaperones and the effects of misfolded protein aggregates.

She has been the editor-in-chief of the Journal of Biological Chemistry since 2016. She was the 2014 recipient of the ASBMB's Mildred Cohn Award, which honors scientists who have made substantial advances in understanding biological chemistry using innovative physical approaches.

Daniel Hebert, who nominated Gierasch as a fellow, wrote that, beyond her many accolades, "What is most special about Lila are the so many things she does that do not show up on a resume. Beyond serving as an

ASBMB FELLOWS

example of excellence and dedication, she cares deeply about her trainees and colleagues."

Gierasch earned her Ph.D. at Harvard University. She joined Amherst College as a faculty member immediately after finishing her Ph.D. and subsequently held positions at the University of Delaware and the University of Texas Southwestern Medical Center before joining UMass Amherst. Gierasch is an elected member of the National Academy of Sciences and a fellow of the American Academy of Arts and Sciences.

F. Peter Guengerich, Vanderbilt University

F. Peter Guengerich is a professor at the Vanderbilt University School of Medicine Basic Sciences. His lab studies mechanisms of activation and detoxification of chemical carcinogens and toxicants and characterizes enzymes involved in these processes. Major areas of interest include the metabolism of carcinogens and drugs by cytochrome P450 enzymes, the bioactivation of halogenated hydrocarbons, and polymerase interactions with carcinogen-modified DNA.

Guengerich has served as an editorial board member, associate editor, interim editor-in-chief and, most recently, deputy editor of the Journal of Biological Chemistry. He also has been a member of the society's Public Affairs Advisory Committee and the Council. In 2005, he won the ASBMB William Rose Award, which recognizes outstanding contributions to biochemical and molecular biological research and a demonstrated commitment to the training of younger scientists.

Lawrence J. Marnett nominated Guengerich as an ASBMB fellow, writing that his "extraordinary accomplishments in scientific research are matched only by his devotion to the ASBMB." Marnett added that his inclusion "will go far to distinguish the body of fellows as being the very crème de la crème of the august body of scholars, educators, and public servants represented by the ASBMB."

Guengerich earned his Ph.D. at Vanderbilt and completed postdoctoral training at the University of Michigan.

Heidi Hamm, Vanderbilt University

Heidi Hamm is a professor at Vanderbilt University School of Medicine Basic Sciences, where she once led the pharmacology department. Her lab is focused on G proteins' roles in protease-activated receptor signaling in the cardiovascular system and regulation of exocytosis at synapses.

Hamm served as the president of the ASBMB from 2006 to 2008. Before that, she was a member of the Council and Annual Meeting Program Planning Committee. She also has been an editorial board member for the Journal of Biological Chemistry. She won the society's 2001 Fritz Lipmann Memorial Lectureship, which recognizes conceptual advances in biochemistry, bioenergetics and molecular biology.

Tina Iverson, who nominated Hamm to be an ASBMB fellow, emphasized Hamm's commitment to advocating for science, writing that "her national contributions to science advocacy and her stature as a world leader in the field warrant her inclusion."

Hamm earned her Ph.D. at the University of Texas at Austin and did postdoctoral research at the University of Wisconsin–Madison.

William Merrick, Case Western Reserve University School of Medicine

William Merrick is a professor at the Case Western Reserve University School of Medicine. His lab seeks to identify all of the eukaryotic translation initiation factors and determine their sequential utilization in the initiation pathway as well as to characterize how the initiation pathway is regulated and the different consequences depending on the exact point of regulation.

Merrick has been an ASBMB member for almost 50 years. He served on the society's Public Affairs Advisory Committee and as the PAAC chair. He was a member of the society's Annual Meeting Program Planning Committee and a symposium chair for the 2006 annual meeting. In addition, he has served as the ASBMB representative to the American Association of Medical Colleges.

He has been a member of the Journal of Biological Chemistry editorial board, during which time he was a lead reviewer for papers on protein synthesis. He continues to serve as an external reviewer from time to time.

Thomas Dever nominated Merrick as an ASBMB

fellow, writing, "His work has established much of our current understanding of the initiation pathway for eukaryotic protein synthesis and the biochemical properties of the translation factors."

Merrick earned his Ph.D. at the University of Georgia and completed a postdoctoral fellowship at the National Institutes of Health.

Alexandra Newton, University of California, San Diego

Alexandra Newton is a distinguished professor at the University of California, San Diego, and co-director of the graduate program's molecular pharmacology track. Her lab investigates the molecular mechanisms of cell signaling and how they are deregulated in disease, with particular emphasis on protein kinase C and the phosphatase PHLPP.

Newton has served on the ASBMB Nominating Committee, the Annual Meeting Program Planning Committee and the Council. She has been an editorial board member for the Journal of Biological Chemistry and has organized numerous ASBMB symposia. She co-chaired the 2004 and 2007 International Union of Biochemistry and Molecular Biology/ASBMB congresses in Boston.

She won the ASBMB Avanti Award in Lipids in 2008. She has served as the ASBMB representative to the IUBMB general council and was elected president of the IUBMB, a role she will assume in July.

John D. Scott nominated Newton to be an ASBMB fellow, writing, "Alexandra is a thought leader in the field of signal transduction, a role model for the next generation of women biochemists, and a tireless advocate for ASBMB. … There is no question that ASBMB is a better organization as a result of (her) insights, commitment and enthusiasm."

Newton earned her Ph.D. from Stanford University and did postdoctoral research at the University of California, Berkeley.

Daniel Raben, Johns Hopkins University School of Medicine

Daniel Raben is a professor at the Johns Hopkins University School of Medicine. His lab began by investigating the molecular species of lipids generated in signaling pathways and now studies the enzymology, structure, regulation and function of lipid-metabolizing enzymes. These studies have focused some attention on the regulation and roles of these enzymes in the nervous system, particularly the central nervous system.

Raben has chaired the ASBMB Meetings Committee for the past eight years. He is also on the executive committee of the society's Lipid Research Division, which he co-founded. In the past, he chaired the ASBMB Task Force on Graduate and Medical Education and served multiple terms on the Journal of Biological Chemistry editorial board.

Michael Wolfgang, Binks Wattenberg and Jessica Ellis nominated Raben as an ASBMB fellow. Wolfgang wrote, "It is hard to imagine another ASBMB member who has contributed as much service to the society in as many capacities over the last 25 years." Wattenberg wrote, "His extensive, selfless, and underappreciated contributions to the Society are exemplary," and Ellis wrote, "His leadership skills and passion for the society are extremely evident."

Raben earned his Ph.D. from Washington University and was a postdoctoral fellow at the University of California, Irvine.

Kerry-Anne Rye, University of New South Wales

Kerry-Anne Rye is a research professor, head of the Lipid Research Group and deputy head of research in the University of New South Wales School of Medical Sciences. With expertise in high-density lipoprotein structure, function and metabolism, she and her team study signal-transduction pathways in multiple cell types to identify new therapeutic targets for atherosclerosis and diabetes.

Rye is co-editor-in-chief of the Journal of Lipid Research. She was nominated as an ASBMB fellow by Nicholas Davidson, her fellow JLR co-editor-in-chief, who wrote, "Rye has had a long and distinguished scientific career, in which she has advanced the molecular life sciences, through her own research programs as well as through her commitment to education and mentorship and as well as her service to the society." If appointed a fellow, he wrote, Rye would doubtless be "an exemplary international ambassador for the organization and a wonderful role model for successful women scientists everywhere."

Rye earned her Ph.D. from Flinders University in South Australia and did postdoctoral work at the University of Illinois at Urbana–Champaign. In 2017, she won the American Heart Association Arteriosclerosis,

ASBMB FELLOWS

Thrombosis, and Vascular Biology Council Mentor of Women Award.

Sarah Spiegel, Virginia Commonwealth University

Sarah Spiegel is a professor at Virginia Commonwealth University, where she chairs the biochemistry and molecular biology department. She is also director of the VCU Massey Cancer Center's cancer cell biology program. The Spiegel lab studies the lipid sphingosine-1-phosphate and discovered its role as a bioactive mediator in cell-growth regulation.

Spiegel has served on the editorial board of the Journal of Lipid Research for more than a decade and was a member of the Journal of Biological Chemistry editorial board from 2010 to 2018. She won the ASBMB's 2009 Avanti Award in Lipids.

Suzanne Barbour, who nominated Spiegel as an ASBMB fellow, said she "is a remarkable scientist whose brilliant career has helped to launch and sustain an entire field of biochemistry. In the process, she has trained outstanding scientists and thus has contributed to the development of human resources as well."

Spiegel earned her Ph.D. in biochemistry at the Weizmann Institute of Science in Rehovot, Israel, and did postdoctoral work at the National Institute of Neurological Disorders and Stroke. She was named one of Virginia's outstanding scientists and industrialists of 2008.

Wesley Sundquist, University of Utah School of Medicine

Wesley Sundquist is a distinguished professor and the biochemistry department co-chair at the University of Utah School of Medicine. His laboratory originally studied HIV protein structure and assembly, and his work supported the development of a drug candidate that blocks capsid function, which is now in clinical trials. The lab's studies of interactions between the virus and the host endomembrane system have led to a deeper understanding of virus budding and cell biology.

Sundquist is a former member of the ASBMB Council and has served as chair of the Public Affairs Advisory Committee. He also won the 2003 ASBMB–Amgen Award, which was for new investigators who had made significant achievements in the application of biochemistry and molecular biology to the understanding of disease.

Dana Carroll, who nominated Sundquist as an ASBMB fellow, wrote, "It has been my pleasure to have Wes Sundquist as a colleague … and to witness his amazing accomplishments."

Sundquist earned his Ph.D. at the Massachusetts Institute of Technology and conducted postdoctoral research at the Medical Research Laboratory of Molecular Biology in the United Kingdom. He is an elected member of the National Academy of Sciences.

Susan Taylor, University of California, San Diego

Susan Taylor is a distinguished professor at the University of California, San Diego, in the departments of pharmacology and of chemistry and biochemistry. Her lab studies the structure, function and dynamics of cAMP-dependent protein kinase using crystallography, kinetics, fluorescence, hydrogen–deuterium exchange, small-angle X-ray/neutron scattering, cryo-EM and computational tools to define conformational changes, ligand binding sites and sites of protein–protein interaction. She also uses fluorescence imaging to elucidate isoform specificity of PKA signaling in tissues.

Taylor won the ASBMB's 2017 Earl and Thressa Stadtman Distinguished Scientist Award and 2007 William C. Rose Award. She served as the society's president and as a member of the Council, the Nominating Committee, the Publications Committee and the editorial board of the Journal of Biological Chemistry. She planned national meetings and organized workshops including pseudokinase meetings in 2015 and 2018.

She was nominated as a fellow by Alexandra Newton, who wrote, "Susan's service to biochemistry and training the next generation of biochemists is exceptional. … Her leadership has had a far-reaching impact, from UCSD to a global level. … Her infectious enthusiasm for biochemistry is unparalleled."

Taylor earned her Ph.D. from Johns Hopkins University and completed postdoctoral studies at the Medical Research Council Laboratory of Molecular Biology in England and at UCSD. She is an elected member of the National Academy of Sciences, the American Academy of Arts and Sciences, and the National Academy of Inventors.

Herbert Weissbach, Florida Atlantic University

Herbert Weissbach is an emeritus professor at Florida Atlantic University. His lab studies how cells respond to oxidative stress and how oxidative damage can be prevented. At previous stages in his 65-year biochemistry career, Weissbach worked on serotonin and melatonin biosynthesis and metabolism and discovered and investigated the coenzyme form of vitamin B12. After the genetic code was cracked, Weissbach spent years studying the mechanism of protein synthesis. He was a founding member of the Roche Institute of Molecular Biology and a vice president of Hoffmann–La Roche before returning to academia.

Weissbach has been involved with the ASBMB since it was called the American Society of Biological Chemists. He has served as an associate editor for the Journal of Biological Chemistry, treasurer of the society, and member of the Annual Meeting Program Planning, Nominating and Membership committees.

Weissbach earned his Ph.D. from George Washington University while carrying out research at the National Institutes of Health. He did postdoctoral studies at the University of California, Berkeley, and then returned to the NIH before accepting a position at Hoffmann–La Roche. He is an elected member of the National Academy of Sciences.

Adele Wolfson, Wellesley College

Adele Wolfson is a professor emerita of chemistry and natural and physical sciences at Wellesley College. She studied proteases and peptidases with a focus on the enzyme thimet oligopeptidase, which terminates the signal of bioactive peptides. Her recent educational research focuses on concept inventories in biochemistry and on understanding how students connect learning in science and nonscience courses.

Wolfson is a member and former chair of the ASBMB Programmatic Accreditation Committee, and she was nominated as a fellow by 13 current and former members of that committee, who jointly wrote, "Adele is a role model for committee leadership. … She balances a focus on rigor and consistency with the recognition of diversity and promotion of inclusiveness. … She has helped lead this society and helped shape its positions as we move forward into the next decade."

Wolfson earned her Ph.D. at Columbia University and did postdoctoral work at the University of Paris. She is a fellow of the American Association for the Advancement of Science.

Stephen Young, University of California, Los Angeles

Stephen Young is a distinguished professor of medicine and human genetics at UCLA. Working closely with UCLA colleagues, Young has investigated mechanisms by which lipoprotein lipase is transported to the capillary lumen and how the fatty acid products of intravascular triglyceride processing move across endothelial cells and into vital tissues such as the heart.

Young is an associate editor of the Journal of Lipid Research. He is a member of the board that manages the annual ASBMB Deuel Conference on Lipids and has served as that meeting's treasurer. He was the Havel lecturer at the 2009 Deuel Conference.

He was nominated as an ASBMB fellow by Peter Tontonoz, who wrote, "Dr. Young is an international leader in the field of metabolism whose work has transformed decades-old models of lipid physiology. … He has been the force that has kept the Deuel meeting financially viable and scientifically vibrant."

Young attended medical school at Washington University in St. Louis and completed internal medicine training at UC San Francisco and cardiology training at UC San Diego. He did postdoctoral research training in lipid metabolism at UCSD. He is an elected member of the National Academy of Sciences.

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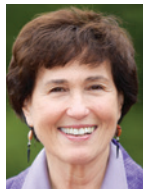


Judith Bond (jsbond13@gmail.com) is an adjunct professor of biochemistry and biophysics at the University of North Carolina at Chapel Hill. She is the chair of the ASBMB Fellows Program Subcommittee.

Edward Eisenstein (eisenste@umd.edu) is an investigator at the Institute of Bioscience and Biotechnology Research and a faculty member of the Fischell Department of Bioengineering at the University of Maryland. He is the chair of the ASBMB Membership Committee.

Ceramides' role in liver disease

By Eleonora Scorletti & Rotonya M. Carr

Alcoholic liver disease, or ALD, is a chronic condition that includes hepatic steatosis, steatohepatitis, fibrosis and cirrhosis. Nonalcoholic fatty liver disease, or NAFLD, is a chronic condition with histological progression similar to ALD, but its pathogenesis is due in large part to diets high in fat and sugar rather than heavy alcohol consumption.

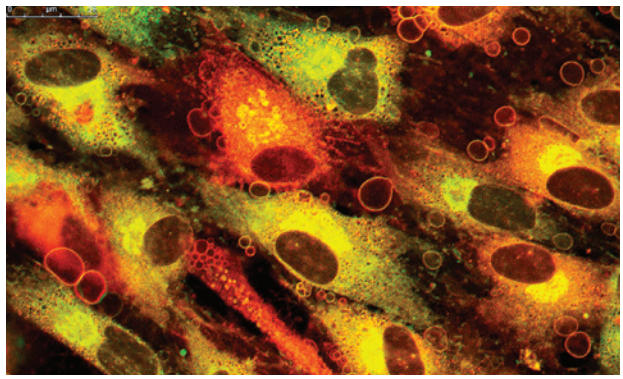
The early stages of both ALD and NAFLD are characterized by excessive accumulation of lipid droplets within hepatocytes. Perilipin 2, or PLIN2, is the most abundant hepatocellular lipid droplet protein. In both ALD and NAFLD, PLIN2 is upregulated and is associated with hepatic accumulation of ceramides.

Ceramides are biologically active sphingolipids that have roles in apoptosis, inflammation and insulin resistance, all critical factors in the pathogenesis of both ALD and NAFLD. Accumulation of ceramides inhibits insulin signaling and promotes insulin resistance. Ceramides can inhibit protein kinase B activity either through the activation of protein phosphatase 2A or protein kinase c isoform zeta. In addition, ceramides impair fatty acid beta-oxidation by promoting mitochondrial fission.

The liver is a key organ for the production of ceramides, the synthesis of which takes place by three pathways: (1) synthesis from simple molecules, which requires several enzymes, including dihydroceramide desaturase 1, or DES1, and ceramide synthase, or CerS, enzymes; (2) sphingomyelin hydrolysis by sphingomyelinases; and (3) lysosomal salvage of complex sphingolipids that requires acid ceramidase, an enzyme that deacylates ceramides into sphingosine and fatty acids and is encoded by the ASAH1 gene.

Recent studies showing that reduction of ceramide synthesis can improve steatosis and insulin resistance have elucidated the critical role of ceramide synthetic pathways in ALD and NAFLD. As our lab reported in the FASEB Journal and Philipp Hammerschmidt and colleagues reported in the journal Cell, reduction of synthesis of ceramide C16:0 using both pharmacologic and genetic models of CerS reduction prevents lipid droplet accumulation and insulin resistance in experimental models of ALD and NAFLD.

Prevention of steatosis and improvement of insulin resistance involve mechanisms that are dependent on



PLIN2 and that prevent mitochondrial fragmentation. Moreover, liver-specific induction of lysosomal acid ceramidase through ASAH1 overexpression improves hepatic insulin sensitivity and ameliorates alcoholic steatosis through very low-density lipoprotein–mediated and lipophagy-mediated mechanisms. Finally, tissue-specific and DES1 null mice fed a high-fat diet have increased levels of dihydroceramides, reduced accumulation of ceramides synthesis (including C16:0 ceramides), reduced steatosis and increased glucose tolerance.

An increasing body of evidence supports the view that reducing hepatic ceramide production improves hepatic lipid accumulation and insulin resistance in ALD and NAFLD. However, little is known about therapies that safely lower ceramides in humans and improve patient health. Further studies are needed to better understand how ceramides affect liver function, with the eventual aim of developing targeted treatments for ALD, NAFLD and insulin resistance.

Eleonora Scorletti
(eleonora.scorletti@pennmedicine.upenn.edu) is a postdoctoral researcher in Rotonya M. Carr's lab in the division of gastroenterology at the University of Pennsylvania. Follow her on Twitter @EScorletti.

Rotonya M. Carr
(rotonya.carr@pennmedicine.upenn.edu) is director of the Liver Metabolism and Fatty Liver Program and an associate professor of medicine in the division of gastroenterology at the University of Pennsylvania. Follow her on Twitter @RotonyaC.

JLR names new junior associate editors

By Angela Hopp

The American Society for Biochemistry and Molecular Biology's Journal of Lipid Research has appointed six junior faculty members to its editorial leadership team.

The journal's junior associate editor program, now in its second year, was created to achieve two chief goals: demystify the peer-review process and train the next generation of journal leaders.

Each junior associate editor will serve a two-year term.

Michael Airola, Stony Brook University

Michael Airola is an assistant professor in the biochemistry and cell biology department at Stony Brook University (also known as the State University of New York at Stony Brook). He runs a lab focused on the structural biology of lipid-modifying enzymes. He earned his Ph.D. at Cornell University in 2010 and completed a postdoctoral research fellowship at the Medical University of South Carolina and Stony Brook Cancer Center. He joined the faculty at Stony Brook in 2017. Airola will partner with JLR Associate Editor George Carman of Rutgers University during his term.

Luke Engelking, University of Texas Southwestern Medical Center at Dallas

Luke Engelking is an associate professor in the internal medicine and molecular genetics departments at the University of Texas Southwestern Medical Center at Dallas. A physician–researcher, Engelking practices adult gastroenterology with a focus on the care of patients with inherited forms of colorectal cancer, such as Lynch and FAP syndromes. His lab focuses on the roles that lipids play in the growth of intestinal cells. He earned his M.D.–Ph.D. at UT Southwestern in 2007, completed his residency at Massachusetts General Hospital in 2010 and then completed a fellowship in gastroenterology and hepatology at UT Southwestern in 2014. He joined the faculty at UTSW after completing his fellowship. Engelking is also an investigator at the UTSW Center for Human Nutrition. During his term at JLR, Engelking will partner with Associate Editor Jay Horton of UT Southwestern and Editor-in-Chief Nicholas Davidson of Washington University in St. Louis.

Scott M. Gordon, University of Kentucky College of Medicine

Scott M. Gordon is an assistant professor in the physiology department at the University of Kentucky College of Medicine, where his lab studies intestinal lipid absorption and atherosclerotic cardiovascular disease. Gordon earned his Ph.D. at the University of Cincinnati College of Medicine in 2012 and completed a postdoctoral research fellowship at the National Heart, Lung, and Blood Institute in 2018. He joined the faculty of UK shortly thereafter. He will partner with Associate Editor W. Sean Davidson of the University of Cincinnati during his term at JLR.

Rebecca Anne Haeusler, Columbia University

Rebecca Anne Haeusler is an assistant professor in the pathology and cell biology department at Columbia University. Her lab studies the mechanisms that link insulin resistance and cardiovascular disease. She earned her Ph.D. at the University of Michigan in 2007 and completed a postdoctoral fellowship at Columbia in 2011. She worked as an associate research scientist at Columbia until 2014, at which time she joined the faculty. During her JLR term, Haeusler will partner with Associ-

ate Editor Paul Dawson of the Emory University School of Medicine.

Renate Schreiber, University of Graz

Renate Schreiber is a senior scientist at the University of Graz Faculty of Science in Austria. Schreiber studies lipid-degrading enzymes and their impact on the generation and degradation of lipid metabolites in health and disease. Schreiber earned her master's degree in 2007 and her Ph.D. in 2011 and then completed a postdoctoral fellowship in 2019 at the University of Graz. She also has held visiting scientist positions at the University of Cambridge, University College London, Umeå University in Sweden and Medical University of Graz. She was named a tenure-track senior scientist at the University of Graz in 2019. Schreiber will partner with JLR Associate Editor Stephen Young of the University of California, Los Angeles.

Judith Simcox, University of Wisconsin–Madison

Judith Simcox is an assistant professor in the biochemistry department at the University of Wisconsin–Madison. Her lab studies the sources of lipids that fuel brown fat thermogenesis using lipidomics, genetics, and cellular and molecular biology techniques. Simcox earned her Ph.D. at the University of Utah in 2014 and completed a postdoctoral fellowship at the University of Utah in 2019. She joined the faculty at Madison soon after. During her term at JLR, Simcox will partner with Associate Editor Alan Attie of Madison.

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

Upcoming ASBMB events and deadlines

MAY		
		Asian American and Pacific Islander Heritage Month
		National Stroke Awareness Month
		Hepatitis Awareness Month
	9	**National Women's Health Week**
	10	**National Lipid Day**
	11, 18 & 25	Protonic bioenergetics and action potential: Latest discoveries and progress in mitochondria, neurons and other biosystems
	15	**Dementia Awareness Week**
	21	Early registration deadline for Teaching science with big data
	23	**World Melanoma Day**
	24	Deadline to apply or submit a nomination for ASBMB annual awards
	27	Abstract deadline for Extracellular vesicle studies: From benchtop to therapeutics
JUNE		
	1	Deadline to apply for Marion B. Sewer Distinguished Scholarship for Undergraduates
	6	**National Higher Education Day**
	14	**World Blood Donor Day**
	16	Regular registration deadline for Teaching science with big data
	19	**World Sickle Cell Day**
	20	**World Refugee Day**
	21	Flux-independent signaling by ionotropic receptors: Unforeseen roles and complexities
	25	Early registration deadline for Extracellular vesicle studies: From benchtop to therapeutics
JULY		
	18	**National Ice Cream Day**
	21–23	Extracellular vesicle studies: From benchtop to therapeutics

Study reveals experimental targets for lymphoma research

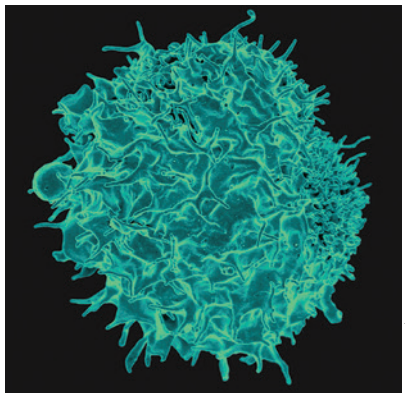
By Caleigh Findley

Lymphocytes, white blood cells made in the bone marrow, are an essential part of the immune system. The two main types of lymphocytes, T cells and B cells, carry out adaptive immune responses. B cells target circulating pathogens in the body, and T cells manage cell response to infection.

Mutations that arise during the production of these immune cells, a process called hematopoiesis, can lead to T-cell or B-cell lymphomas. During hematopoiesis, genes are sometimes said to be turned "on" or "off" through a biological process called DNA methylation. This occurs when a methyl group is added to the DNA power switch that controls the expression of that gene. A family of enzymes called DNA methyltransferases, or Dnmts, carries out this process and is an important part of cellular function.

A new study in the **Journal of Biological Chemistry** reports that one DNA methylation enzyme, Dnmt3, suppresses the development of lymphomas through its catalytic and non-catalytic functions. The authors, researchers at the universities of Florida and Nebraska, also provide evidence for a molecular pathway possibly involved in lymphoma development related to mutated Dnmt3.

Previous research linked lymphoma development with mutations to Dnmt3b — alongside other diseases that impair the immune system. Dnmt3b influences the expression or silencing of genes, an important aspect for cancer research as Dnmt3b suppresses tumor development. Loss of Dnmt3b is linked to human chronic lymphocytic leukemia, leading researchers to wonder if loss of Dnmt3b activity is a major factor in blood cancer.



NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES, NATIONAL INSTITUTES OF HEALTH

T lymphocytes like the one pictured manage cell response to infection, and mutations that arise during their production in the bone marrow can lead to lymphomas.

Katarina Lopusna and colleagues investigated the significance of Dnmt3b in lymphoma by generating mice lacking Dnmt3b's catalytic activity for either one or both of the genetic alleles and comparing them to mice with only one Dnmt3b allele. Knocking out one allele of Dnmt3b decreases all of its functions, including accessory jobs such as recruiting other Dnmts or influencing gene expression (outside of methylation). Taking away the catalytic activity of Dnmt3b, even partially, should hinder DNA methylation specifically, reducing production of blood cells and possibly tumorigenesis.

This study design yielded unexpected results for lymphoma development, according to Eric Fearon, an associate editor for the Journal of Biological Chemistry. "[In] an interesting twist … mice heterozygous for a null (complete loss-of-function) Dnmt3b allele developed T-cell malignancies," Fearon wrote in an email. "In contrast, mice that expressed a Dnmt3b allele encoding a DNMT3b protein that lacked catalytic activity developed B-cell malignancies."

These findings demonstrate that both the catalytic activity and accessory functions of Dnmt3b are important for fighting cancer.

The researchers investigated molecular mechanisms that could explain the link between Dnmt3b and blood cancer. Genome-wide analysis revealed decreased methylation and increased expression of tumor-promoting genes. The results also showed reduced expression of the p53 pathway, known for preventing T-cell transformation.

The researchers' efforts "highlight how careful analysis of mutant alleles in mouse models can yield insights into the potential non-catalytic functions of certain enzymes, such as Dnmt3b," Fearon wrote. The study also puts forth potential molecular targets that may contribute to Dnmt3b-related tumor development for future research.

DOI: 10.1016/j.jbc.2021.100285

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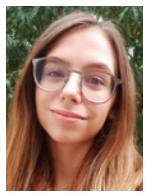


Researchers target cell membrane for cancer research

By Nivedita Uday Hegdekar

Robert Chapkin has spent decades studying the molecular roles components of nutrition play in protein signaling and the prevention of diseases. His lab's recent discoveries about lipids and the cell membrane could revolutionize translational cancer research.

"Cell membranes are the lipid environment in which many proteins function," said Chapkin, a professor of nutrition at Texas A&M University. "It is now appreciated that protein and lipids assemble to form distinct micro- or nanodomains (clusters) that facilitate key signaling events."

Cell membrane composition is altered in diseases such as cancer and obesity. Chapkin believes that membrane therapy — the modulation of cellular membrane lipid composition and organization — might be an effective therapeutic strategy.

"The central idea is that if you alter the composition of the cell membrane, you can potentially alter the functionality of the proteins within the membrane and thus the disease overall," he said.

Chapkin's lab discovered that docosahexaenoic acid, or DHA, a well-known dietary omega-3 fatty acid and chemoprotectant, suppresses the functionality of epidermal growth factor receptor, or EGFR, a protein in the cell membrane that drives the formation of many types of cancer, including colon cancer.

But how does DHA suppress the function of the EGFR protein? Natividad "Robert" Fuentes, a former graduate student in the Chapkin lab and the first author on the lab's recent paper in the **Journal of Lipid Research**, uncovered some groundbreaking molecular insights into this mechanism. Using cell and animal models and a cutting-edge technique called super-resolution microscopy, he studied the changes to the lipid membrane and EGFR after DHA incorporation.

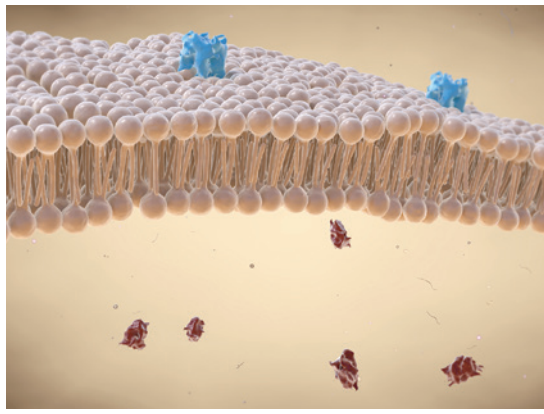
"We found that when DHA is incorporated, it alters the localization of the lipid bilayer with EGFR," Fuentes said. "It alters the spatial orientation of the protein in the lipid bilayer."

It turns out that the architecture of the protein within the lipid bilayer of the cell membrane is one of the factors that drives its function. This might explain why DHA incorporation suppresses EGFR signaling.

Fuentes said he believes such membrane therapy could synergize with other cancer treatments. "The fatty acids that modulate the lipid bilayer are completely innocuous to humans and could potentially be used as adjuvants to suppress the functionality of proteins that drive cancer."

As a postdoc at the University of Texas MD Anderson Cancer Center, Fuentes now uses membrane therapy in translational pancreatic cancer research.

"Pancreatic cancer is resistant to many therapies," he said. "Part of my work is to study how disrupting the pancreatic cell membrane might improve the efficacy of cancer therapeutics."



A lipid bilayer cell membrane with membrane and intracellular receptors.

With membrane therapy still in its infancy, Fuentes believes it will be applicable in other research areas. "Membrane therapy holds promise for any disease states where receptor clustering within the cell membrane is affected," he said. "For instance, it could be used in diabetes research to target the insulin receptor and insulin signaling."

Chapkin is eager to explore the more mechanistic nuances and specificity of membrane therapy and study other potential players.

"We will be researching other preventative components of nutrition and target proteins," he said. "There is so much exciting work to be done in this field."

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Parasitic secretions create microenvironment for survival

By Jaclyn Brennan

Paramphistomes, also known as rumen or stomach fluke, are flatworm parasites that infect sheep and cattle in temperate and tropical regions. In recent years, the incidence and severity of rumen fluke infections (specifically the paramphistome Calicophoron daubneyi) have increased sharply in Western Europe. Heavy infections of immature rumen fluke in the small intestine can lead to hemorrhaging and even death, so early detection and correct diagnosis are imperative. However, researchers still know little about the biology of C. daubneyi and its effects on host animals.

Mark Robinson's lab at Queen's University Belfast focuses on parasitic worms and how they interact with their hosts at the molecular level. He has studied liver fluke for over 20 years. With the recent emergence of the less-studied rumen fluke in Europe (particularly in Northern Ireland, where his lab is based), his latest work shifted to understanding this unusual parasite and its host interactions. His findings, published in the journal **Molecular & Cellular Proteomics**, show how C. daubneyi regulates expression and secretion of certain molecules to establish infection, feed on host tissue and fight off the host immune response in ruminant livestock.

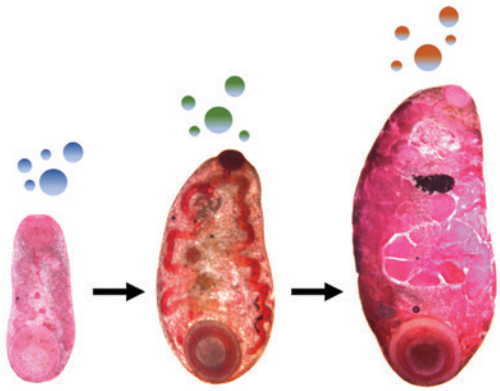
To begin to investigate the molecular biology of rumen fluke, Robinson's group teamed up with other researchers from the United Kingdom. Together, they performed transcriptome analysis of four rumen fluke life-cycle stages and integrated these results with proteomic analysis of secretions from two of these stages. They picked the juvenile flukes and mature adult stages for the proteomics studies, as these are the key stages responsible for acute and chronic disease, respectively.

Juvenile flukes emerge in the small intestine and eventually migrate along the digestive tract to the rumen, where they mature into adults. During each stage, the parasite must adapt to drastic changes in the host microenvironment and counter inevitable attacks by the host immune system. According to Robinson's findings, they do so easily.

"The rumen fluid is like a soup of bacteria and protozoans which the flukes must live amongst and survive," Robinson said.

Rumen flukes appear to secrete certain molecules that help them establish and maintain infection within this challenging host environment. Robinson likens the protective properties of these secreted molecules to those of the garments worn by astronauts: "Imagine stepping onto the surface of the moon without a space suit — you wouldn't last very long. Same goes for flukes within their host environments without their shield of secreted molecules."

Robinson believes the host–parasite interface can be adjusted to fight off infection. "If we can devise ways of blocking the secreted molecules, which are so important for the parasite, we may be able to come up with new treatment options," he said.



ROBINSON LAB / QUEEN'S UNIVERSITY BELFAST

This illustration shows the development of the rumen fluke Calicophoron daubneyi. In a recent study, secretome profiling revealed distinct families of virulence factors and immunomodulators associated with acute and chronic infection.

The lab has developed the first enzyme-linked immunosorbent assay for C. daubneyi, which they hope can be used by veterinarians, animal producers and farmers for disease surveillance and diagnosis. Next, Robinson wants to perform functional studies to validate certain molecules as targets for fluke control. As with all the work done in his lab, these efforts center on improving animal health and welfare, which he says is of benefit to everyone.

DOI: 10.1074/mcp.RA120.002175

Jaclyn Brennan (jabrennan@gwmail.gwu.edu) is a postdoctoral researcher at George Washington University, where her research focuses on electrophysiology of the cardiac conduction system. Follow her on Twitter @jaclynb_phd

From the journals

By Nuala Del Piccolo, Vaishnavi Muralikrishnan, Laurel Oldach & Anand Rao

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

Clathrin-coated endosomes encourage SARS-CoV-2 entry

Severe acute respiratory syndrome coronavirus 2, or SARS-CoV-2, initiates infection by using its spike glycoprotein to engage with the surface of host cells. Previous research in cell cultures and animal models has shown that when the spike glycoprotein engages with host cell receptors, other coronaviruses, such as MERS-CoV and SARS-COV-1, undergo endocytosis. However, researchers don't know yet whether SARS-CoV-2 follows a similar cell entry process and, if so, which mechanism facilitates its entry into the host cell.

Using purified spike glycoprotein and a lentiviral model of SARS-CoV-2 infectivity, Armin Bayati, Rahul Kumar and colleagues at McGill University showed that SARS-CoV-2 undergoes rapid endocytosis when it engages with the host cell surface. The researchers found that upon binding with membrane host cell receptors, SARS-CoV-2 is engulfed by vesicles coated in clathrin, a protein critical for shaping vesicles and sorting their cargo. SARS-CoV-2 infectivity was reduced by blocking clathrin-mediated endocytosis through the knockdown of clathrin heavy chain, a component of clathrin necessary for its function.

These findings, published in a paper in the **Journal of Biological Chemistry**, detail the role of clathrin-mediated endocytosis in viral infectivity and may support the development of new therapies for the treatment of COVID-19.
DOI: 10.1016/j.jbc.2021.100306

How gut bacteria assimilate dietary lipids

The human intestine is home to trillions of microorganisms known collectively as the gut microbiota. The type and amount of fat we eat can have a significant impact on the gut microbiome and thus on our metabolism and immunity. Sphingolipids are a class of bioactive lipids present in foods such as milk and also produced by gut microbes. However, researchers do not understand yet how the gut microbes use sphingolipids.

Recent research by Min-Ting Lee and colleagues at Cornell University published in the **Journal of Lipid Research** used a novel technique called Bioorthogonal labeling-Sort-Seq-Spec, or BOSSS, to study the assimilation of sphingolipids by gut microbes. The first step in BOSSS, bioorthogonal labeling of sphingolipids, involved labeling without interfering with native biochemical processes in the body. The next step was fluorescence-based sorting of microbes containing the labeled sphingolipids. Finally, the sorted microbes were sequenced and analyzed by mass spectrometry to identify products of sphingolipid assimilation.

The researchers found that sphingolipids are assimilated primarily by a type of gut microbe known as Bacteriodes. This improves our understanding of how dietary sphinganine is processed in the body and how it in turn affects the gut microbiome. In addition, the novel BOSSS technique is useful to study the flux of any alkyne-labeled metabolite in diet–microbiome interactions.
DOI:10.1194/jlr.RA120000950

Plasmodium mutant promotes parasite survival

Malaria is a serious and often fatal disease that afflicts over 200 million people worldwide every year, according to a 2020 World Health Organization report. It is spread to humans through mosquitoes carrying Plasmodium parasites. Five species of these parasites cause malaria in humans, and Plasmodium falciparum is responsible for the most common and deadliest form of the disease. Health care providers take a two-pronged approach to combat malaria around the world. One common prevention strategy is the use of drugs that suppress the blood stages of malaria infection, thereby preventing the disease through chemoprophylaxis. However, P. falciparum resistance to antimalarials is a recurring problem, undermining malaria control efforts, so scientists continue to search for new strategies to treat infections.

The drug 4′-deaza-1′-aza-2′-deoxy-1′-(9-methylene)-immucillin-G, or DADMe-ImmG, inhibits the purine nucleoside phosphorylase PfPNP, an enzyme that is essential for P. falciparum growth. Treatment with DADMe-ImmG clears P. falciparum infections in a primate malaria model,

but P. falciparum cultured in the presence of DADMe-ImmG develops resistance to the inhibitor.

In a study published in the **Journal of Biologial Chemistry**, Yacoba Minnow and colleagues at the Albert Einstein College of Medicine describe their efforts to determine how PfPNP develops resistance to DADMe-ImmG. Using covalently linked native and mutant PfPNP monomers, the researchers showed that PfPNP mutants alone are unable to execute the essential function of PfPNP due to a loss in catalytic properties. However, hybrid molecules consisting of mutant and native subunits give rise to DADMe-ImmG resistance while also preserving catalytic function. As a result, these mixed PfPNP molecules can promote parasite survival despite the presence DADMe-ImmG.

DOI: 10.1016/j.jbc.2021.100342

Glycosylation of the SARS-CoV-2 spike protein

Severe acute respiratory syndrome coronavirus 2, or SARS-CoV-2, the virus responsible for the ongoing COVID-19 pandemic, is known to be glycosylated — that is, infected cells attach sugar molecules to viral proteins during replication. In the most common form of glycosylation, known as N-glycosylation, sugars are attached to the amino acid asparagine. The location and composition of these attached sugars can obstruct protein–protein interactions, thereby modulating processes like infectivity of and human immune reaction to a virus.

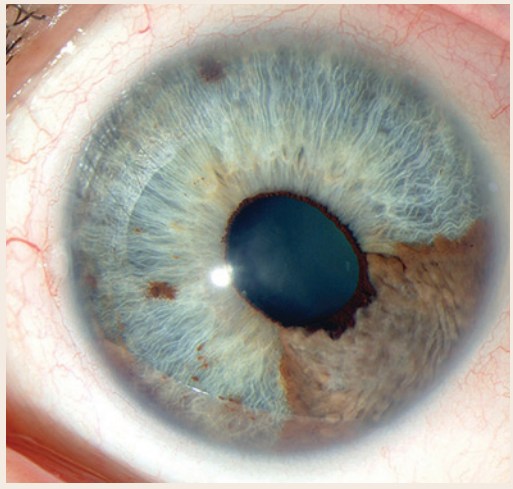
In a recent article in the journal **Molecular & Cellular Proteomics**, Yong Zhang, Wanjun Zhao and colleagues at Sichuan University describe how they characterized N-glycosylation of the SARS-CoV-2 spike protein, which mediates viral

G protein inhibition could help treat uveal melanoma

About 83% of ocular melanoma, a type of eye cancer that develops in cells that produce pigment, arises from the uvea, a layer of the eye beneath the sclera and cornea, according to the American Cancer Society. While rare, uveal melanoma, or UM, is particularly deadly. About 50% of patients with UM develop metastatic disease; with a lack of effective treatment, the long-term prognosis is poor.

Guanine–nucleotide binding proteins, or G proteins, use extracellular signals to initiate intracellular signaling cascades. Activating point mutations in G proteins are causative factors in several human cancers, and recent work suggests that uveal melanoma is driven by G proteins Gq and G11 that have mutated to become constitutively active.

A new paper by Michael Onken and colleagues at Washington University published in the **Journal of Biological Chemistry** explores the therapeutic potential of FR900359, or FR, an extract from the evergreen plant Ardisia crenata that selectively inhibits Gq/11 activity. Using cultured UM cell lines and human UM tissue assays, single-cell RNA-sequencing and animal experiments, the researchers showed that all constitutively active forms of Gq/11 found in UM are sensitive to FR.



JONATHAN TROBE/UNIVERSITY OF MICHIGAN KELLOGG EYE CENTER

Uveal melanomas, like the one show here in the iris of an eye, are driven by G proteins Gq and G11 that have mutated to become constitutively active.

The authors also found that FR arrests UM cell growth but does not kill Gq/11-driven UM cell lines and that it targets UM tumor cells from patient biopsies of primary tumors with both low and high metastatic potential. Lastly, the researchers identified a therapeutic window in which FR strongly arrested tumor growth without causing major effects on heart rate, liver function or behavior.

These findings show new ways that clinicians might be able to use Gq/11 inhibitors such as FR for the treatment of UM patients either alone or in conjunction with current standards of care.

DOI: 10.1016/j.jbc.2021.100403

—Anand Rao

entry into human cells. Using mass spectrometry, the team identified 22 sites of N-glycosylation in the virus' spike protein. The composition of the attached sugars is heterogeneous and depends on the host cell, not the glycosylation site: Insect and human cells preferentially attach high-mannose and complex sugars, respectively. Given the influential role of glycosylation on viral infectivity and immunogenicity, these findings will inform future therapy and vaccine development for COVID-19.

DOI: 10.1074/mcp.RA120.002295

Characterizing the glycan signature of tumor tissue

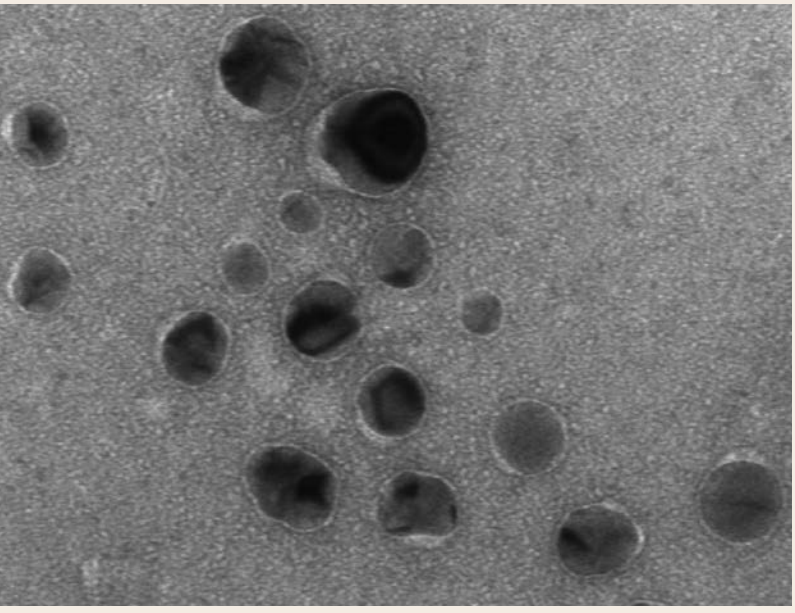
Despite vast improvements in cancer diagnosis and care in recent decades, clinicians still struggle to predict which patients will and will not respond to a specific therapy, which can lead to avoidable disease progression and death. Fanny Boyaval of Leiden University and a team of researchers in the Netherlands hypothesized that the N-glycan signature in tumor tissues can predict patient outcomes. N-glycans, or sugar molecules attached to the surface of membrane-bound and secreted proteins, regulate cancer-related processes including angiogenesis, immunity, metastasis, tumor

Silver nanoparticles target metabolically unadaptive cancer cells

Silver nanoparticles have many applications, including medical uses such as wound dressings and implants, because of their antimicrobial activity: They disrupt cell wall integrity and perforate cell membranes. The particles are considered nontoxic to humans, but researchers have observed that they sometimes cause oxidative stress and programmed cell death by disrupting mitochondrial membranes. These observations raise concern about occupational exposure to silver nanoparticles — but also suggest they might make promising anticancer therapeutics, since cancer cells tend to be more metabolically active than their healthy counterparts.

In a recent article in the journal **Molecular & Cellular Proteomics**, Reetta Holmila and colleagues based at Wake Forest School of Medicine's Center for Redox Biology and Medicine report on an investigation into silver nanoparticles as a cancer treatment. The team used redox proteomics, which detects both the abundance of proteins and their oxidation at cysteine residues, to investigate nanoparticle responses in two cancer cell lines from lung epithelia. Previously, the team had established that one line was sensitive to silver nanoparticle treatment, proliferating more slowly or dying after exposure, while the second was resistant.

A transmission electron microscopy image of the silver nanoparticles studied as a cancer treatment at the Wake Forest School of Medicine.



COURTESY OF CRISTINA M. FURDUI / WAKE FOREST SCHOOL OF MEDICINE

They recently observed that protein oxidation increased in both cell types in the hours after silver nanoparticles were introduced. The resistant cells mounted a robust oxidative stress response through metabolic adaptation, upregulating protein turnover and antioxidant synthesis pathways. As a result, they tended to show less protein oxidation after a long treatment with silver particles than after a short one. The more sensitive cell line failed to ramp up antioxidant metabolism and mitochondrial protection as strongly, and it maintained high oxidation levels, which was ultimately detrimental to cells.

Using microscopy, the researchers observed that the sensitive cell line had started out with mitochondria that were larger and less morphologically defined than their counterparts'. After nanoparticle treatment, mitochondria in sensitive cells swelled and sometimes burst. The findings suggest that preexisting mitochondrial abnormality might predispose some cancer cell lines to respond to nanoparticle treatment by dying, while others manage to adapt.

DOI: 10.1016/j.mcpro.2021.100073

— Laurel Oldach

cell invasion and cell–cell signaling.

Boyaval and her colleagues characterized biopsies from stage II colorectal cancer patients using matrix-assisted laser desorption/ionization mass spectrometry imaging, or MALDI-MSI, a technique that produces a spatially resolved picture of N-glycan distribution and composition in a tissue sample. Writing in the journal **Molecular & Cellular Proteomics**, they report that cancer cells exhibit an increase in sialylated and high-mannose glycans and a decrease in fucosylated and highly branched glycans, but these changes do not correlate with patient survival. However, the N-glycan signature of tumor-adjacent tissue is similar to that of cancer cells and correlates with patient survival. The study shows that MALDI-MSI can characterize primary tissue samples and provides a new technique to classify colorectal cancer patients.

DOI: 10.1074/mcp.RA120.002215

A randomization to measure risk

Variations in certain genes can act as risk factors for some diseases, and these risk associations can be studied using a technique called Mendelian randomization, or MR. This technique measures variations in genes whose functions are known in order to determine whether the variations can cause specific diseases in humans.

In a recent study in the **Journal of Lipid Research**, David G. Thomas and colleagues at Columbia University performed an MR of lipid traits such as levels of low-density lipoprotein, high-density lipoprotein, triglycerides, body mass index, Type 2 diabetes and systolic blood pressure in coronary artery disease, or CAD, in large genomewide association study data sets.

Why high HDL is not always good

Heart diseases are the leading cause of death in the United States. Coronary heart disorder, the most common type of heart disease, is caused by atherosclerosis, or the accumulation of cholesterol in the arterial walls leading to stiffening and lowered blood flow in the arteries.

The two types of cholesterol are low-density lipoprotein, or LDL, and high-density lipoprotein, or HDL. While HDL cholesterol often is referred to as "good cholesterol" because of the inverse correlation between HDL levels and heart disorders, the presence of excess HDL in plasma may be due to reduced plasma clearance of cholesterol. The primary receptor for HDL is scavenger receptor class B type I, or SR-BI, which promotes clearance of excess cholesterol from the plasma, thus reducing the risk for atherosclerosis.

In a recent study in the **Journal of Lipid Research**, Sarah May and colleagues at the Medical College of Wisconsin characterized a rare heterozygous variant of the gene encoding SR-BI that results in the substitution of arginine-174 with cysteine, or R174C, in a patient with high HDL cholesterol levels. They demonstrated that the R174C mutation leads to diminished cholesterol transport, suggesting this variant does not clear cholesterol from circulation as intended.

The researchers write that the reduced function of this variant could be due to disruptions in surface electrostatic charges of SR-BI leading to a decrease in the net-positive charge, which in turn could affect the ability of SR-BI to bind HDL and transport cholesterol from HDL particles.

This study provides insight into the structure and function of SR-BI and emphasizes that measurement of HDL-cholesterol levels may not be a sufficient indicator to predict the risk of cardiovascular diseases accurately.

DOI: 10.1016/j.jlr.2021.100045

—Vaishnavi Muralikrishnan

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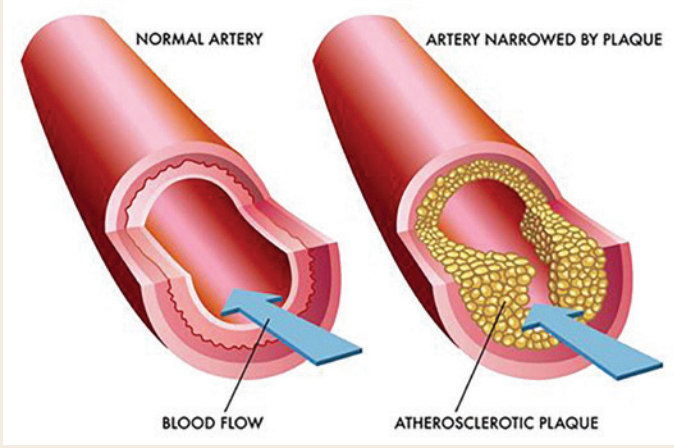

A normal artery is shown on the left, and narrowing of the artery due to deposit of cholesterol plaque, which represents atherosclerosis, is on the right.

A challenging aspect of determining the effect of risk factors is that some of these lipid trait variants may be pleiotropic, meaning that a single gene can influence two or more seemingly unrelated phenotypic traits. This study used multivariate MR analysis to evaluate the pleiotropic effects of lipid trait genetic variants and to adjust for these effects in evaluating the risk for CAD. The researchers reported that the lipid traits they studied all are associated independently with CAD even after adjusting for their pleiotropic effects.
DOI: 10.1194/jlr.P120001000

Rab11 reorganizes sialyltransferases

Sialylation, or the addition of sialic acid to glycoproteins, is a modification involved in embryonic development, neurodevelopment, oncogenesis and immune responses. The enzymes responsible for catalyzing this modification, known as sialyltransferases, primarily reside and function in the endoplasmic reticulum, and it is unclear how their localization to this region and trafficking to other regions are regulated.

In previous work, Masato Kitano at Osaka University and colleagues identified a connection between N-glycosylation and Rab11, a small GTPase that is a key player in the post-Golgi transport that connects recycling endosomes and other compartments. The authors recently elaborated on Rab11's role in glycan modification. By knocking down Rab11 protein levels in HeLa cells and using liquid chromatography–mass spectrometry, they discovered that a reduction in Rab11 selectively enhanced the sialyation of glycoproteins. They found that the major alpha-2,3-sialyltransferase ST3GAL4 was confined tightly to the trans-Golgi network in the absence of Rab11 versus its more diffuse localization when Rab11 is present.

These findings, published in a recent article in the **Journal of Biological Chemistry**, present a new mechanism for the regulation of glycosylation modification.
DOI: 10.1016/j.jbc.2021.100354

Macrophage mannose receptors rely on sugars

The human mannose receptor is expressed on macrophages and plays a critical role in innate and adaptive immunity as well as reducing damage after tissue injury. The receptor's function depends on its C-type carbohydrate-recognition domain 4, or CRD4, which contains a site for Ca^{2+}-dependent interaction with sugars. However, researchers do not yet know the details surrounding CRD4–ligand interactions.

In an article published in the **Journal of Biological Chemistry**, Hadar Feinberg and colleagues at Stanford University School of Medicine used glycan array screening to identify mannose-containing ligands that are likely to interact strongly with CRD4. The authors then explored mechanisms of ligand–CRD4 binding by generating and examining crystal structures of CRD4, and their structural analyses highlighted several distinctive aspects of ligand binding by the mannose receptor to additional classes of ligands.

The authors state that the details revealed in this work could help to explain differences in the way pathogens interact with host receptors.
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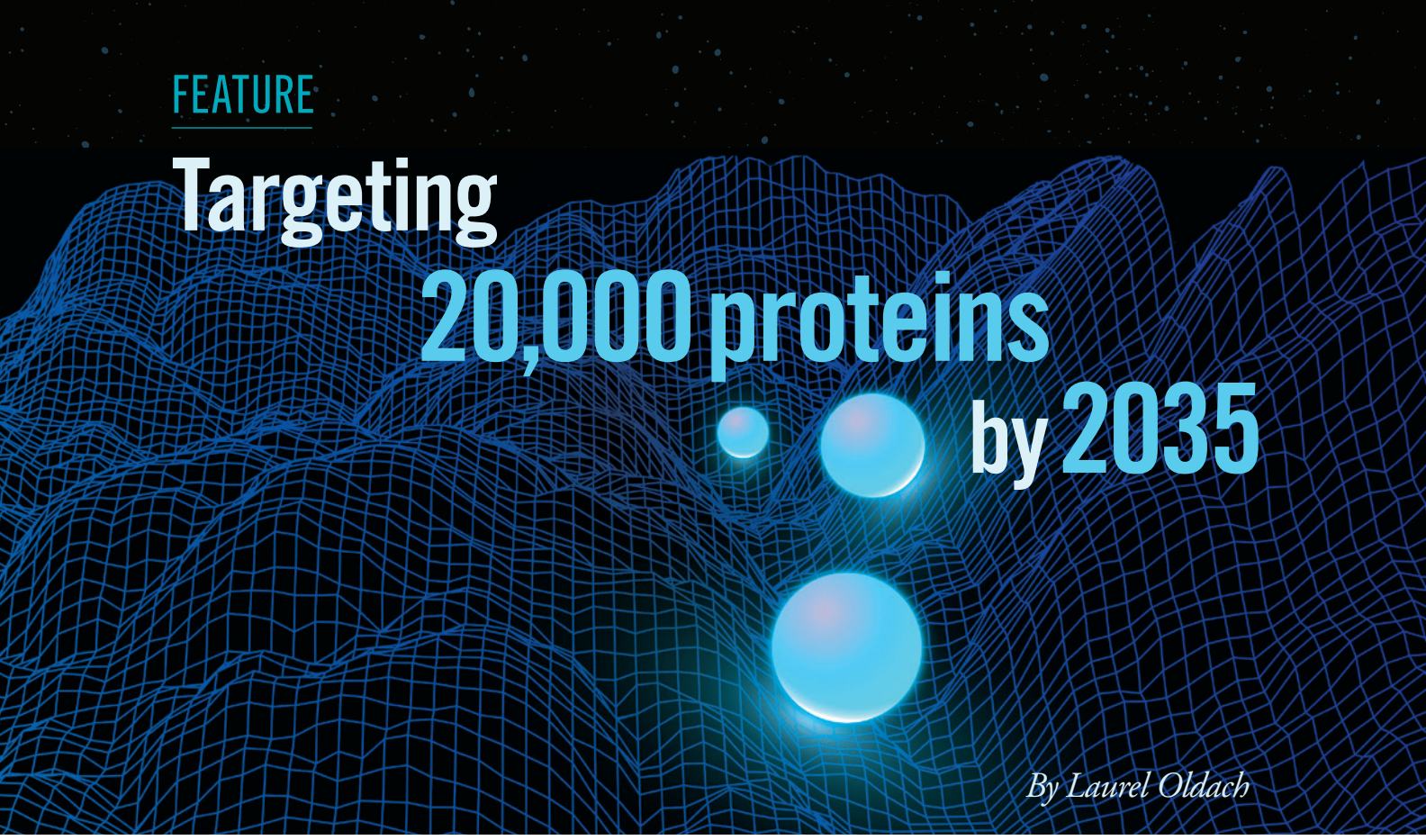
FEATURE

Targeting 20,000 proteins by 2035



By Laurel Oldach

When you run a web search for "Target 2035," most of the results are investment options. Aled Edwards and Cheryl Arrowsmith are hoping that by the time Generation X has begun to retire, a second meaning will be as common — at least in the chemical biology community.

Target 2035 is the name of their effort to inspire the community to develop a probe, or a specific small-molecule modulator, for each of humanity's 20,000 proteins.

The two Canadian structural biologists, among the leaders of the international Structural Genomics Consortium, are the driving force behind Target 2035, which launched in November.

"It's an ambitious project," said pharmacologist Bryan Roth, who is not part of the consortium but has advised for it, a role he compares to reviewing for a journal. "It'd be great if we had real, useful chemical tools for all the targets in the genome."

Assessing the Human Genome Project

Edwards began to consider the whole proteome about a decade after the Human Genome Project was completed in 2001. That project had identified 20,000 protein-coding genes, many of them for the first time.

After some fellow researchers in the Structural Genomics Consortium in 2010 urged the cancer research community to explore as-yet-undrugged kinases instead of revisiting ones that already had been chemically validated, Edwards and collaborators conducted a literature review to see how research into other protein families, such as ion channels and nuclear receptors, had progressed. They found that most research had continued to circle historical targets.

"This makes no bloody sense!" he said. "If you were a logician and not a scientist, you'd say, 'Well, that's kind of dumb.'"

But science funding agencies and journal editors tend to reward a more conservative approach. Arrowsmith saw that while serving on a Canadian study section recently. "Everybody else on the panel said, 'Why (is the applicant) studying this protein? Nobody works on this protein; it doesn't do anything important that we know of.' I was disappointed, but it was kind of hard to argue."

During a recent seminar, Edwards said, "It's so much easier to work where people know about stuff. It's really hard to develop hypotheses about something that is unknown."

During their literature review, Edwards and his team also noticed a few proteins that had bucked the trend. Over the 10-period they examined, those molecules had gone from obscurity to popularity. In those cases, Edwards said, almost without fail there was a potent and specific inhibitor available for the protein. Having a pharmacological approach to perturb a protein's activity made it much easier to study.

"We thought, OK, then why don't we start to proactively make research tools for proteins that no one currently gives a shit about?"

The SGC

The "we" was the Structural Genomics Consortium.

Founded by the Wellcome Trust, several Canadian research organizations and GlaxoSmithKline in 2004, the SGC is a nonprofit public–private partnership that aims to coordinate and accelerate protein structure discovery.

"Al was recruited to be the CEO of SGC, and the first person he asked to join him was me," Arrowsmith said. She became the chief scientific officer of the consortium's Toronto location.

Edwards and Arrowsmith, who met as structural biology trainees at Stanford University, already had collaborated on large-scale approaches to find protein structures as professors at the University of Toronto before getting involved in the nascent project.

Both said that their working styles complement each other: Edwards, an energetic speaker whose tangents sometimes eclipse his original point, appreciated Arrowsmith's focus and follow-through. She appreciated his big ideas.

"We kind of feed off each other in terms of what can be done and what should be done," Arrowsmith said.

The SGC now supports university-affiliated scientific teams in six countries and is funded by eight multinational pharmaceutical companies, Wellcome and Genome Canada.

"Initially it was purely a structure-determination organization," said Susanne Müller–Knapp, a molecular biologist who co-authored the initial kinase study and today coordinates activities at the Frankfurt arm of the consortium.

Structures and inhibitors can be mutually beneficial; knowing a protein's structure can help in the rational design of a small molecule to bind to it, while having a small molecule that binds to the protein can sometimes stabilize it, making crystallization and structural studies easier.

Over time, the group collected inhibitors of proteins they were studying and noticed when inhibitors were lacking. Müller–Knapp said, "At some point, we were wondering, 'We have these freezers full of proteins; what else can we do with them?'"

COURTESY OF ALED EDWARDS

Aled Edwards is the CEO of the Structural Genomics Consortium.

COURTESY OF CHERYL ARROWSMITH

Cheryl Arrowsmith is the chief scientific officer of the Structural Genomics Consortium in Toronto.

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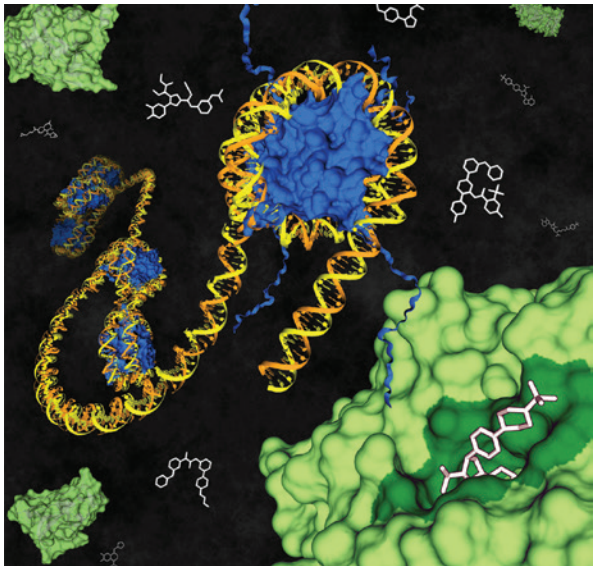
Susanne Müller–Knapp is a molecular biologist who coordinates activities at the Frankfurt arm of the Structural Genomics Consortium.



D. IVANOCHKO AND S. ACKLOO

A scientific illustration shows a chemical probe that SGC scientists designed to bind the histone methyltransferase KMT4 (green), which modifies DNA-binding histone complexes (blue).

That was when the team started to work on developing small-molecule tools to bind to those proteins and block their activity, with a tight focus on epigenetic modulators, enzymes that modify DNA or histones or detect these modifications, to alter gene expression patterns.

Rigorously defining a probe

Although genetic techniques to manipulate protein expression are well developed, the SGC team is not interested in generating 20,000 knockout mice or cell lines. They argue that removal of a protein through genome editing may have wider-reaching effects than blocking its function with a small molecule and is harder to translate into potential drug development.

Instead, the team focuses on small-molecule and biological tools, or probes, to block protein activity.

"Probe is a word that anyone can apply to their molecule," Edwards said during a webinar. But the SGC team applies a stringent definition: A probe is a molecular tool that acts selectively, by a known mechanism, to modulate protein activity.

Unlike a drug, a probe doesn't need to make its way through an organism to its target. Unlike an inhibitor, a probe doesn't need to block enzymatic activity; it might act, for example, by inducing protein degradation or binding to an allosteric site.

In some cases, a bad chemical tool could be worse than no tool at all. Arrowsmith cited a compound called DZNEP, often reported as an inhibitor of the widely studied histone methyltransferase EZH2. However, the compound actually was developed to disrupt the synthesis of S-adenosylmethionine, the cell's universal methyl group donor, wreaking havoc on every methyltransferase.

The original report on DZNEP was not strictly wrong, Arrowsmith said. "It does inhibit EZH2. It inhibits everything." However, interpreting experimental results after DZNEP treatment as specific to EZH2-mediated methylation would be a mistake. Unfortunately, Arrowsmith added, although this molecule's drawbacks have been known for some years, many reagent supply companies still offer it as a specific inhibitor of EZH2. "Even now, I still see papers where people use this DZNEP, which is a sloppy compound."

DZNEP is similar to other molecules known in the chemical biology community as pan-assay interference compounds, or PAINs. They act by a variety of mechanisms, but the uniting feature is that they are not specific to individual proteins. They tend to show up in the literature again and again, particularly after high-throughput screens, frustrating experienced medicinal chemists and leading less experienced ones astray in interpreting their data.

To be sure that each probe the SGC develops or distributes is selective for the target it was designed to block, the team collects a standardized set of assays. They look for data that demonstrate a probe binds to its target protein and blocks its activity in test tubes and in cells — and ideally can be cocrystallized, giving structural proof that it binds. They consider a molecule's selectivity between closely related proteins and its stability in solution to make sure it will not degrade

into inactive compounds. Ideally, along with each probe, the SGC also hopes to distribute control compound that is chemically related but does not affect the same protein target. Two expert panels, one from within the SGC and one of external academics, review each probe to certify it before publishing.

Although the team has been successful in developing probes for epigenetics, the rigorous development process takes time. To achieve their genome-scale ambitions, the SGC team will need reinforcements. Edwards said, "We've spent considerable time and effort making 100 probes — and obviously, that won't scale."

Pharmaceutical partners

The largest developers of protein inhibitors are pharmaceutical and biotech companies, which routinely bombard protein targets with potential inhibitors and fine-tune the results one functional group at a time on the hunt for future drugs.

"Discovering new medicines is extremely difficult and also increasingly expensive," said Adrian Carter, the head of discovery research coordination at pharmaceutical company Boehringer Ingleheim, at a recent Target 2035 webinar. "Much of that high cost is driven by failure, unfortunately."

The SGC hopes that molecules that don't make it as drug candidates still might be useful as chemical probes — and that companies will make them freely available to researchers. This historically has been a difficult sell for companies whose business model depends on proprietary molecules. However, Arrowsmith said that thanks to a culture shift in the pharmaceutical industry, companies are now more willing to release molecules from "both past and failed drug-discovery programs where there are good modulatory molecules. Normally they'd just go sit on the shelf and wouldn't be used anymore. Now many companies are making these available to the community."

GlaxoSmithKline was one of the first companies to make samples and annotation about its probes openly available. In 2014, inspired by SGC scientists' work, the company made 367 previously published kinase inhibitors available to researchers.

In an article in the journal SLAS Discovery, a team of medicinal chemists originally from GlaxoSmithKline but now affiliated with the SGC described the process of publicizing those probes, which they called "extreme open science." First, the chemists collected the hundreds of inhibitors and screened each molecule for effects on more than 260 human kinases (see "Chemogenomics" box on this page). Next, an equally daunting task, they worked out a process with the company's legal team to distribute molecules for research use under a simplified materials transfer agreement.

The kinase inhibitor set broke a trail for other companies to make

Chemogenomics: Putting imperfect probes to use

Finding a selective modulator of a protein can be difficult, according to Cheryl Arrowsmith, a structural biologist and co-founder of Target 2035. "Often, one has to make a compromise with saying, 'OK, this compound is good enough; let's publish it and see what we can do with it, warts and all, if you will,'" she said. "The issue is, everybody should know what the warts are."

Some approaches take the warts into account and work around them. For example, adenosine triphosphate mimics tend to block numerous kinases. An approach developed by chemists at the Structural Genomics Consortium and numerous pharmaceutical companies involves applying many kinase inhibitors, each of which targets a relatively small number of kinases, and using the overlap in results to determine exactly which kinase target is responsible for an assay result. The approach is called chemogenomics.

> "If academics use compounds that are not characterized, they will always ascribe the phenotype to the so-called 'specific target' that the inhibitor was made for. And so the whole literature is polluted."
>
> SUSANNE MÜLLER–KNAPP

Machine learning and the future of probe design

In November, the protein folding program AlphaFold made headlines by correctly predicting the structures of some two dozen proteins that had been solved by researchers but were unpublished.

"Bingo! Miracle result," Canadian structural biologist Aled Edwards said. "Only 50 years in the making."

The folding program evolved from a structural biology competition called CASP, or Critical Assessment of Structure Prediction, which organizers always had envisioned as a training ground for new structure prediction tools. Using sequence–structure relationships made public in the Protein Data Bank as a training set, the competition has challenged participants to extrapolate from a known sequence to a new structure.

A success like AlphaFold's "was exactly the plan of structural biologists," Edwards said. "They've spent literally billions and billions of dollars creating the foundation so that this could happen."

Just as the Protein Data Bank collected and organized knowledge about protein structure, becoming an integral resource for machine learning, Edwards said that the Structural Genomics Consortium, which he co-founded, means to organize knowledge about chemical probes and their activities that may be used for data mining in the future.

Researchers already are beginning to use computational tools to develop new probes. For example, in a Nature paper in 2020, labs at the University of North Carolina at Chapel Hill and University of California, San Francisco, used computational tools to dock 150 million hypothetical compounds to a melatonin receptor, synthesizing and screening only the most promising.

The approach dramatically expands the speed of screening, said Bryan Roth, who led the UNC team. "It's now possible, once you have a structure of a protein, to dock billions of small molecules that don't actually exist in the physical universe … then to get them synthesized, and to develop probes that way."

their probes publicly available as well. Müller–Knapp led a team that recruited about 90 more selective molecules from numerous companies in a collection called the donated chemical probes panel, which they announced in a paper in eLife in 2018. Each compound had taken medicinal chemists years to develop, at a cost of up to 2 million euros apiece.

According to Müller–Knapp, companies are motivated to release the right to use their compounds in part to make the literature they rely on more reliable and reproducible. "If academics use compounds that are not characterized, they will always ascribe the phenotype to the so-called 'specific target' that the inhibitor was made for," she said. "And so the whole literature is polluted."

By enabling academic researchers to make more discoveries, these probes (which, after all, already had been rejected as drug candidates) could contribute to the pool of reliable knowledge about biology that industry researchers draw from regularly.

Besides, Arrowsmith said, making a small molecule available for research use is not the same as giving up the exclusive right to sell it. "If they let one of the molecules out there, they still may be covered by a patent, but they're making it available to the world to use."

But it's not without effort for companies. In industry, the discovery process is aimed at bringing molecules to market. If a probe does not have a reasonable path forward, researchers often stop experimentation. This leaves some molecules incompletely characterized by SGC standards. According to Müller–Knapp, companies that have committed to donating a set number of probes have occasionally dropped one and proffered another if the original candidate needed too much additional wet lab characterization.

Target 2035

The SGC has sent out thousands of samples of the epigenetic probe collection its scientists developed, the Published Kinase Inhibitor Set and the donated chemical probes set, according to Arrowsmith.

Phil Cole, a pharmacologist at Harvard University who studies epigenetic modulators and has used some of the epigenetic probes, said, "SGC has had enormous impact in producing important protein structures and

small-molecule probes and is one of the great success stories in big science applied in chemical biology."

SGC organizers say they're not sure whether the consortium will continue to function as a warehouse for the chemical probes they certify. To do so might institutionalize the SGC alongside nonprofits like Addgene, Jackson Labs and the American Type Culture Collection, or ATCC. On the other hand, Arrowsmith said, most SGC investigators are also active researchers and want to focus on using the probes they've worked so hard to develop to study biological questions.

Target 2035 kicked off with a series of webinars in November, and organizers have continued to hold monthly webinars on topics in drug development.

In the project's first phase, set to last until 2024, organizers aim to solicit donations of existing small molecules and develop processes for validating the molecules and sharing characterization data. In later phases they will try to use those data mining and biochemical profiling tools to coordinate and speed up probe development assays.

Like the improvements in sequencing during the Human Genome Project, Arrowsmith said, she expects the available tools for drug design to improve during the project, accelerating discovery.

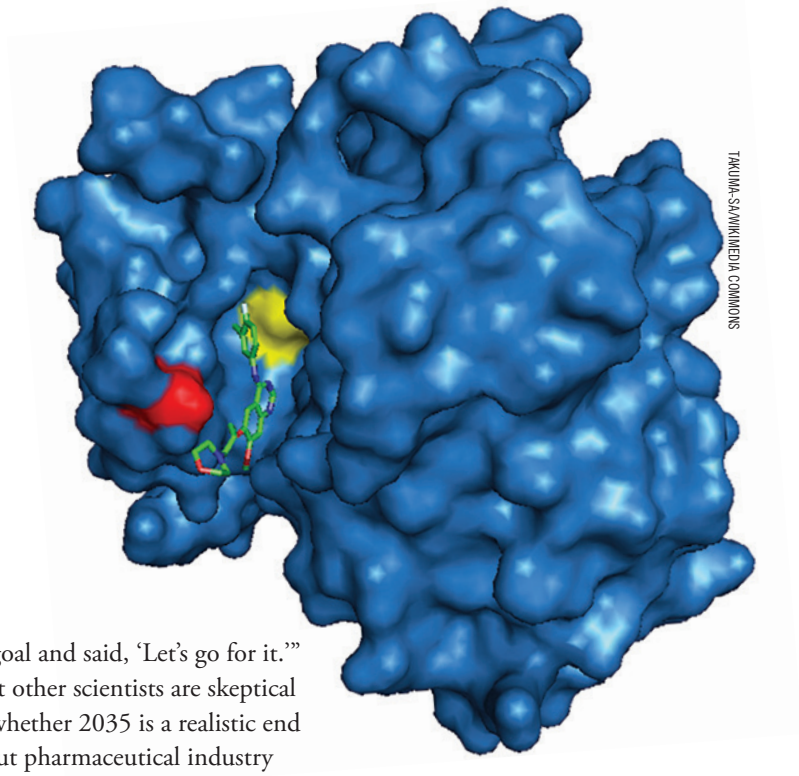
How did they settle on the 15-year target date? "That was Aled," Arrowsmith said with a chuckle. "He pulled that out of a hat somewhere."

To achieve the goal of disrupting every protein in the proteome, Edwards explained, "You need to improve the technologies … You need to get better at chemistry, faster and more effective. But it doesn't break any laws of physics, right? So it should happen. It's just a matter of when. We chose 15 years as an aspirational goal and said, 'Let's go for it.'"

Most other scientists are skeptical about whether 2035 is a realistic end date. But pharmaceutical industry commentator Derek Lowe wrote, "The good news is that this isn't one of those efforts that has to make it to the end to be really valuable."

Target 2035 overlaps with a major National Institutes of Health initiative called Illuminating the Druggable Genome, which targets kinases, ion channels and receptors, and a more recent European effort called EUb Open that takes aim at 1,000 proteins. SGC adviser Roth said that because of differences in funding streams, "They're all separate projects, sadly. It'd be great if we could all be part of one gigantic project."

According to Edwards, bringing major international projects, industry groups and individual academic labs into alignment is precisely the goal of Target 2035. "I'm talking about a science project," he said. "But my No. 1 and 2 projects are culture."



TAKUMA-SA/WIKIMEDIA COMMONS

A crystal structure drawing shows the epidermal growth factor receptor, or EGFR, which is frequently mutated in cancer, in complex with the cancer drug gefitinib.

"It doesn't break any laws of physics, right? So it should happen. It's just a matter of when. We chose 15 years as an aspirational goal and said, 'Let's go for it.'"

ALED EDWARDS

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

Exploring underappreciated molecules and new cities

Meet Journal of Lipid Research associate editor Xianlin Han

By Laurel Oldach

COURTESY OF XIANLIN HAN

Xianlin Han presented at the International Symposium on Metabolomics in Shanghai in 2019.

Maybe you've never heard of sulfatides, sphingolipids that contain a sulfate moiety in the head group. That won't offend Xianlin Han. The genial neurochemist, a professor at the University of Texas Health Science Center at San Antonio, is accustomed to explaining his work to people who are unfamiliar with most of his favorite molecules. His lab studies how changes in sulfatides and other lipids may contribute to Alzheimer's disease, along with other brain lipidomics research.

Among his many professional service activities, Han has been an associate editor for the Journal of Lipid Research since 2019. In a wide-ranging conversation with ASBMB Today, Han explained how his interest in instrumentation led him to a lifelong study of lipids and to his penchant for exploration both in his research and in his travels. This interview has been condensed and edited.

Q. How has the pandemic affected your work life? You have a lot of collaborators in China — did you have a sense of the risks of COVID-19 very early on?

A. I was in Hong Kong, Guangzhou and Macau in January 2020. At that time, people over there were saying, "Something is going on in Wuhan, it seems very strange."

Then Wuhan started to lock down, and I thought, "It seems like it's not easy to get this virus totally controlled; seems like it's going to be a global problem." And gradually, it was.

I knew it would become a problem, but I didn't foresee how severe it would be here. I asked our lab

manager to order PPE — at that time it was still available. On March 5, 2020, we had a JLR editorial meeting at La Jolla, in San Diego. I was the only one wearing a face mask in the entire plane. People probably thought, "He's so strange." Three weeks later, there was no PPE available anywhere, and we donated some face masks to the hospital.

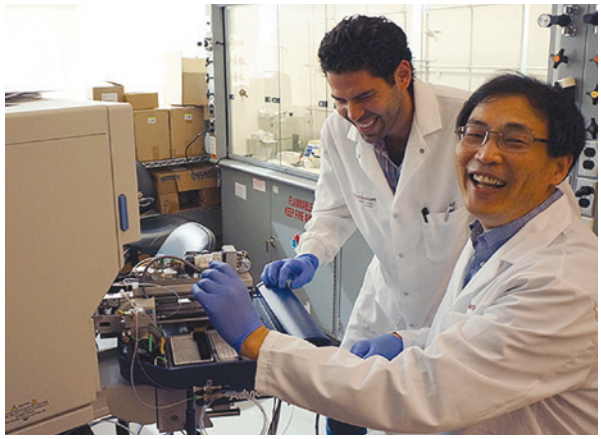
Our lab actually remained open. We are in the medical center, so all the different lab heads could make their own decision. Our lab has a lot of animals that we needed to keep working on. We remained open to keep an eye on them; otherwise, we would have lost at least three years' work.

Q. Tell me about your research.

A. My lab is lipidomics based; most of our projects are related to how brain lipids connect to some kind of disease. We use lipidomics to discover lipid changes, then try to identify the molecular mechanisms that contribute to the lipid changes and find the consequences of these altered lipids in context of the disease or physiological change. The three keys are discovery, identification and determining the consequences. Our whole lab's research is based in these strategies, which has a fancy name, "functional lipidomics."

We've been studying Alzheimer's disease for almost 20 years now. A long time ago, when I was at Washington University School of Medicine, we used a lipidomics platform and found that three classes of lipids changed very significantly in the earliest clinically recognizable stages of Alzheimer's disease. One kind was called the plasmalogens, the second was ceramides and the third was sulfatides.

The plasmalogen change is a



COURTESY OF XIANLIN HAN

Xianlin Han (right) and postdoc Juan Pablo Palavicini enjoy a light moment while working on the lab's mass spectrometer.

reduction people had already reported and linked with oxidative stress. I thought, "That seems like it's not very novel, although it's interesting." Ceramides were linked to neuroinflammation, which was also well connected to Alzheimer's disease. So I picked the last class of lipids, sulfatides, and for the last 20 years, we have kept working on this area. Not too many people study sulfatides, so we can gradually understand many different areas. The bad thing is that not very many people are interested. Some have never heard of them.

The sulfatide reduction turned out to be very interesting. Using transgenic and knockout animal models obtained from our collaborators, we found that the mechanism is a lipid change connected with apolipoprotein E. You probably know that ApoE4 is the strongest genetic risk factor for Alzheimer's. In the early 2000s, we found that the ApoE4 particle carries a much higher content of sulfatide than other ApoE isoforms. When ApoE4 is transported, that leads to the brain having much less sulfatide.

Later on, we studied the consequences. If the sulfatides are lost, what symptoms does that cause in the brain? We found that loss of sulfatide

> "(T)hat's what we study — the connection of sulfatide loss with diabetes, traumatic brain injury, anesthetic toxicity, etc."
>
> XIANLIN HAN

causes A-beta toxicity and hyperphosporylation of tau, the hallmarks of Alzheimer's disease.

Loss of brain sulfatides can cause other consequences: ventricular enlargement, bladder enlargement, glial cell activation, and neurotoxicity and neuroinflammation. When the conditional knockout animals are about 12 months old, we already see cognitive decline.

People are always thinking Alzheimer's is a multifactorial disease. We thought, What if many factors could cause sulfatide loss, and once the sulfatides are lost then the consequences are the different hallmarks? So that's what we study — the connection of sulfatide loss with diabetes, traumatic brain injury, anesthetic toxicity, etc.

We also try to understand the mechanisms of diabetic neuropathy. And traumatic brain injuries can also cause sulfatide loss, so we're trying to understand the mechanism there. Then there are other areas, including end-stage diabetic neurotoxicity and other metabolic diseases.

Q. So your trainees have a lot of projects to choose from?

A. Yeah, we have too many projects — too many meats on our plate. They can try whatever: pork, beef, chicken.

Q. Now must be a good time to be an Alzheimer's researcher who doesn't study amyloid beta. Have you noticed a change in other researchers' interest in your work?

A. When I say we are studying lipids, most people's first reaction is to think we are trying to develop biomarkers for Alzheimer's disease. Second they think that our study is based on lipid metabolism. Everybody thinks you're working on cholesterol, because ApoE is connected to cholesterol metabolism. So usually I need to take a while to explain what we are studying.

People think that lipids are only a readout reflecting some kind of protein activity or gene expression, or maybe affecting the membrane integrity. But actually, the sulfatide appears to behave as a signaling compound. It senses the environmental changes and interacts with cell receptors. That kind of action turns out to be very important.

Q. What got you interested in lipids?

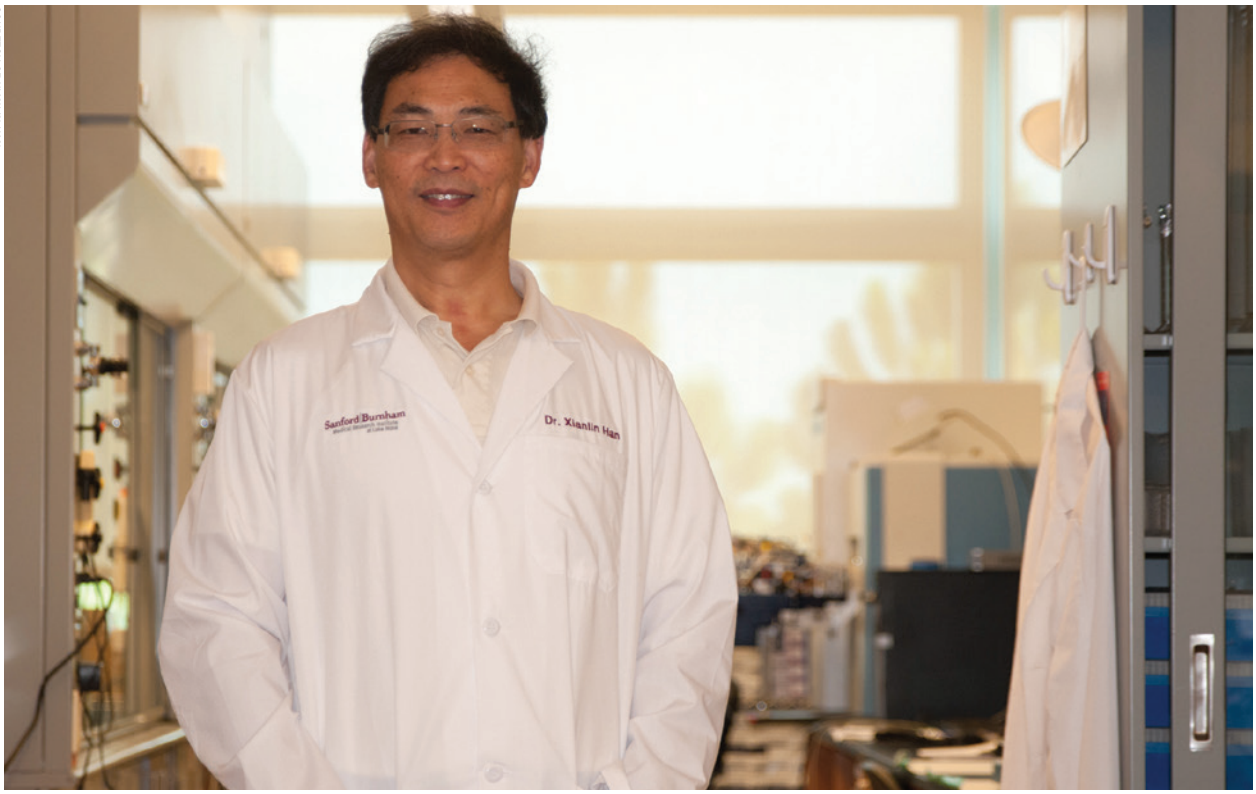
A. That takes us back 30 years. I came to the United States in 1985 and went to Washington University to do my Ph.D. in chemistry. I really liked using instruments; my goal was to learn all kinds of instrumental technologies to study biology.

My mentor, Richard Gross, was studying the calcium-independent phospholipase A2 and chemical biology of membranes in health and disease, using a variety of techniques such as high-performance liquid chromatography, fluorescence spectroscopy and nuclear magnetic resonance. I thought that was cool. When I talked with him, he said, "Whatever you want to use we can make available." That's how I initially moved into studying lipids.

At the time, we were trying to understand how lipids travel on the membrane and interact with different regulatory proteins. How are they transported from the outer leaflet to the inner leaflet? How do they affect ion channel function?

We used HPLC to purify mem-

COURTESY OF XIANLIN HAN



Xianlin Han in his lab space at Sanford Burnham Prebys Institute, where he was a professor for several years before moving to Texas in 2018.

brane components and to quantify lipids. I had so many headaches. I really hated all of this HPLC purification. You don't know how much time I spent late at night, doing months of work to get one data point, not knowing whether it's a good one or a bad one.

After I graduated, Dr. Gross asked me whether I would like to stay in the lab, so I stayed and became a postdoc. At this period, I had the opportunity to apply mass spectrometry to study lipids when Dr. Gross brought an electrospray ionization mass spectrometer to the lab.

Q. Why did you move on?

A. I got a little bit bored after 25 years in St Louis. I was at the same university from Ph.D. to postdoc and as faculty. I thought I'd make some change. Also, in St. Louis the weather is terrible, and when I hit middle age, my joints started to get poor. I grew up in the southern area of China. So I moved south, first to Sanford Burnham Research Institute in Florida, then to the UT Health Science Center at San Antonio three years ago.

UT Health Science Center at San Antonio is relatively small compared to other centers in the UT system. But it has faculty with broad interests, from cancer to neurodegeneration to metabolic diseases. I can collaborate on all my projects in such an environment. That's why it's the right place for me.

Q. Besides research and teaching, you also do community service. What organizations are you involved in?

A. I'm on the editorial board for a number of journals, mostly related to lipids. Besides lipids, I have

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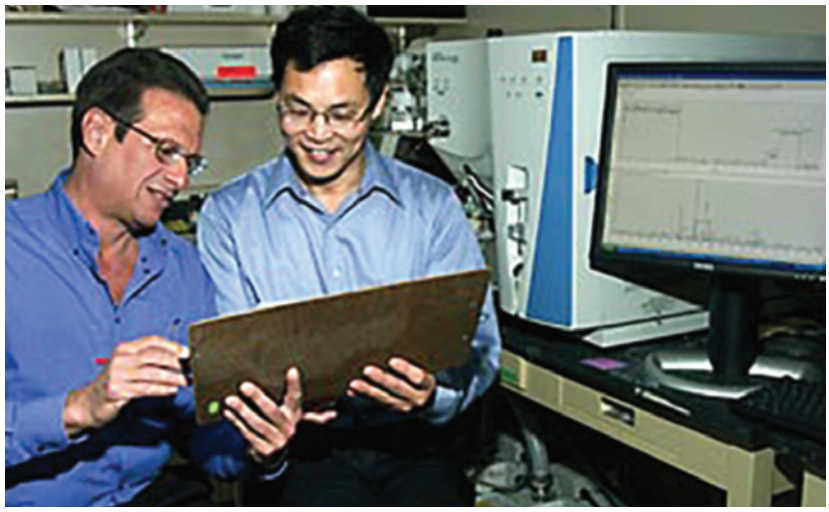
COURTESY OF XIANLIN HAN



Xianlin Han (right) and doctoral mentor Richard Gross look at data in 2009.

done mass spectrometry, so I am involved in the Chinese American Society for Mass Spectrometry; I served as president for two years, and I've basically been a board member forever. I also serve as secretary for the International Lipidomics Society. Since I study the brain, I'm also involved in the neurochemistry community.

Q. Where do you find the time?

A. I'm usually in the office six days a week, from 9 to 7 every day. Still, there are so many things I almost cannot finish. I agree to review so many papers because I know the editor, or I know the author or I think the research is interesting. Having a big network is good and bad. Good is that I've made lots of friends. Bad is that I always have something to do — it's so busy.

Q. Do you have any time for hobbies?

A. I like hiking. San Antonio has a really good hiking system called the Greenway, which goes around the entire city. Usually my wife and I go hiking once a week, for about 10 miles. The next week we go from there to the next stop, seeing the city and exploring.

Whatever city I'm staying in, whether at home or traveling to a conference, I like to take time to walk around and see what's there.

And I like to travel. People ask, "Hey, Han, maybe you could come join our meeting and give a talk?" I say, "Sure, I'll come!" Travel not only exchanges science and advertises your work but also makes new friends. You explore areas you've never visited. That's what's so exciting. People sometimes say, "Why do you take so much time and expense to travel?" I say, "It's fun."

My third hobby is stamp collecting. I've learned a lot through stamp collecting: geography, language, cultures. I used to go fishing at stamp shows. Now I do not have time anymore; I had to hide all my albums.

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

Winners of the 'aha moments' essay contest

To celebrate our three journals going open access, we invited readers to share their moments of discovery in science.

Here are our top 10 essays.

FIRST PLACE

Finding a common ancestor

By Richard F. Ludueña

As a child, I loved science fiction. I always have liked history, and I especially was drawn to stories about time travel, because I loved to imagine looking far back into the past.

My aha moment came in 1972 when I was a graduate student in Dow Woodward's laboratory at Stanford determining the first 25 amino acids in the sequences of alpha- and beta-tubulin from chickens and sea urchins. At that time, very little was known about tubulin sequences.

The results came off the sequencer around Christmas Day. I realized that chicken and sea urchin α-tubulin were about 95% identical and that the same was true of the β-tubulins.

This meant that I had just learned something very intimate about the common ancestor of vertebrates and echinoderms, an organism whose appearance and morphology were unknown and only could be guessed at. I felt like I was looking perhaps 700 million years into the past. I had no idea what that animal looked like, but I knew something about its tubulin.

I also observed that α- and β-tubulin were themselves about 40% to 45% identical, so I now perhaps was seeing more than 2 billion years into the past to the time of the first eukaryotes, one-celled organisms that lived on a planet that would be unrecognizable to us.

This was one of the most exciting moments of my career as a biochemist and the closest I ever came to realizing my childish fantasy of time travel. I think a child lives inside every scientist, a child whose curiosity is challenged by mysteries, who wants to make visible the invisible and to magnify the microscopic and who wants to look back into time as far as the origins of everything — of cells, life, the earth and the universe.

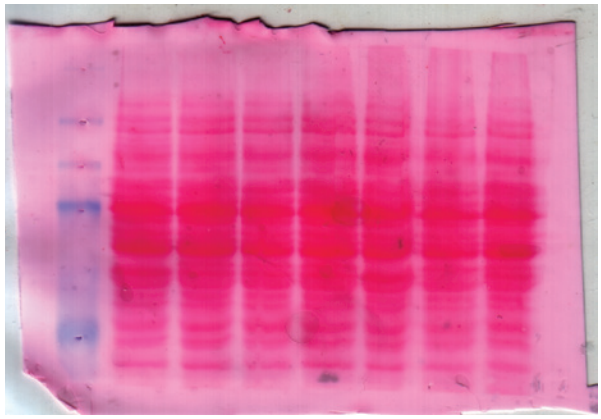
Richard F. Ludueña (luduena@uthscsa.edu) is a professor emeritus of biochemistry at the University of Texas Health Science Center at San Antonio. He received his Ph.D. in biological sciences from Stanford University in 1973. He spent his professional career investigating tubulin–drug interactions and the functions and expression of tubulin isotypes.

SECOND PLACE

Dreaming of Western blots

By Mindy Engevik

It was a cold night; the wind was blowing, and the branches of a nearby tree were scratching against the roof of my apartment. I was in bed huddled under a big down comforter, which enveloped my whole body like an amoeba. I was deep in REM sleep, dreaming of Western blots. Horrible Western blots … the bane of my existence.



ARGYMEG/WIKIMEDIA COMMONS

A nitrocellulose membrane stained for protein detection during Western blotting.

As a graduate student, I was fascinated by the beautifully orchestrated events of ion transport of the intestine. I gloried over ion transporter mRNA, enjoyed functional assays in tissue cultures, reveled in measuring fecal ion concentrations by flame photometry — but then I encountered the dreaded Western blot.

I needed to measure the protein levels of the sodium–hydrogen exchanger isoform 3 and the colonic HK-ATPase in mouse colon by Western blot. Day after day, I had been troubleshooting these Western blots. I had tried optimizing the denaturing steps, removed the denaturing step, changed the blocking buffer, modified the run times … I had tried everything I could think of and everything my helpful colleagues had recommended. But to no avail — the Western blot had won.

But that night, in my dreams, I went over the Excel sheet provided by my PI that provided a handy plug-in for calculating the amount of protein to add to the Western blots. I dutifully added my dream concentrations and realized … the math was wrong.

I bolted awake, ran to my laptop, checked the Excel sheet and voila — the Excel sheet math equation was incorrect!

That morning, I went to the lab, added the correct amount of protein, and this time, the Western blot worked. I felt like a conquering hero. I guess dreams really do come true.

Mindy Engevik (engvik@musc.edu) is an assistant professor at the Medical University of South Carolina. She earned her Ph.D. in systems biology and physiology at the University of Cincinnati and did her postdoctoral fellowship at Baylor College of Medicine. She loves mucus, microbes and all things science. Follow her on Twitter at @micromindy.

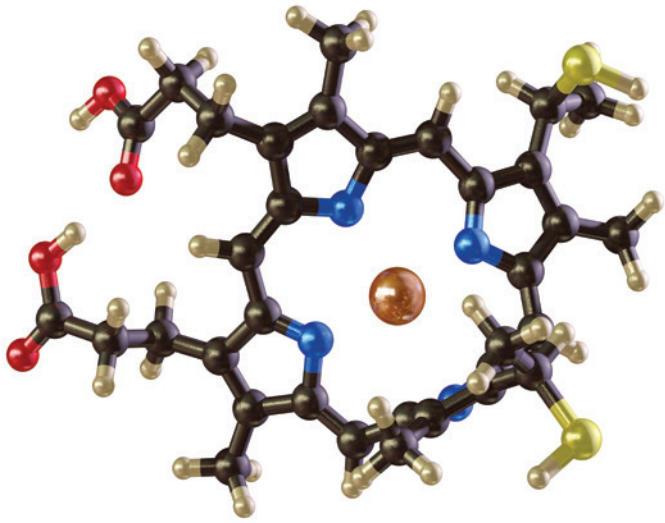
THIRD PLACE

Beauty in brown

By Kazuhiko Igarashi

The laboratory where I started as a new faculty member, led by Norio Hayashi and Masayuki Yamamoto, focused on erythroid cells: Colleagues were working on the regulation of heme synthesis during erythropoiesis, and I was trying to identify transcription factors that would regulate globin genes by binding to their superenhancers, the locus control region, together with two graduate students.

One student, Ken Itoh, got two promising candidate cDNA clones in two hybrid screenings using MafK, one of the subunits of nuclear factor erythroid 2, as a bait. The other student, Tatsuya Oyake, expressed one clone in E. coli for purification. When he came out of the cold room, he was disappointed, thinking that his purification was a total failure. The protein solutions looked brown.



We were troubleshooting in front of the cold room, with the tubes in his ice box. Then our lab head, Norio Hayashi, who has a long track record in enzymes of heme synthesis, happened to walk by. It did not take a second before he saw the tubes and suggested carefully, "This may be a heme protein."

A beauty emerged: Heme, which is massively synthesized during erythropoiesis, would regulate the activity of this transcription factor, BACH1, coordinating heme synthesis and globin gene expression.

As so many scientists know, the simplicity of a model does not guarantee a simple way forward. For us, it took another two decades to come to a reasonably correct answer on the function of the heme–BACH1 axis in erythropoiesis. Various functions of BACH1 and the other clone, BACH2, which also is regulated by heme, have emerged in not only erythropoiesis but also iron and heme metabolism, immune response and cancer progression.

If Tatsuya had discarded the tubes out of disappointment or Professor Hayashi had not seen those tubes, what would we be doing today?

Kazuhiko Igarashi (igarashi@med.tohoku.ac.jp) is a professor of biochemistry studying regulation of cell responses and differentiation by transcription factors at Tohoku University in Japan and a member of Science Council of Japan. Follow him on Twitter @kazuigarashi.

HONORABLE MENTIONS

Fringe inspiration

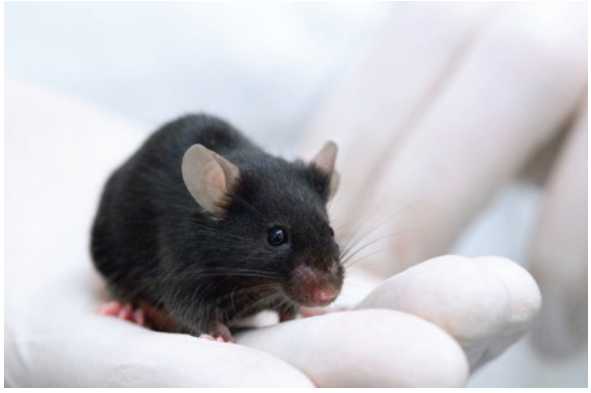
By Miguel A. Contreras Hidalgo

When I was a junior faculty member, my only break from research was to have dinner with my family and, from time to time, enjoy a science fiction TV show and then get back to the lab.

Back in September 2008, I sat down to enjoy the second episode of a new show called "Fringe." The show follows the adventures of FBI agent Olivia Dunham (assigned to the bureau's Fringe Division); junior FBI agent and sidekick Astrid Farnsworth; fringe science researcher Dr. Walter Bishop; and his son, Peter.

In this particular episode, a pregnant woman delivers a newborn that ages rapidly in minutes and soon dies, having aged into an 80-year-old man. Olivia and her associates are called to investigate. Eventually, Dr. Bishop makes a connection to the pituitary gland, which controls growth in humans.

I literally jumped from the couch. For the past three years, I had been using the twitcher mouse model to study the molecular mechanism of Krabbe disease, an inherited lysosomal disorder in which galactosylsphingosine (psychosine) accumulates mainly in the central nervous system. The mouse recapitulates genetic and enzymatic aspects of the disease and is characterized by its small size. It has been a valuable tool to advance our understanding of the development/progression of the disease's inflammatory process in the CNS.



It never had occurred to me before to investigate the molecular mechanism by which the toxic accumulation of psychosine in peripheral organs was responsible for the inhibition of the postnatal somatic growth of the mouse until this moment — my aha moment — and to understand the pathobiological and translational consequences of psychosine accumulation outside the CNS.

(In memory of Maria Leticia Sanchez Ortiz, a teacher and a mentor.)

Miguel A. Contreras Hidalgo (miguel.contreras@nih.gov) is a program officer at the National Institutes of Health. He earned his Ph.D. in molecular and cellular biology and pathobiology at the Medical University of South Carolina. This essay was prepared by the author in their personal capacity and does not reflect the view of the NIH.

A life filled with aha moments

By Danielle Guarracino

A life dedicated to science is filled with aha moments. For me, a few noteworthy ones define my trajectory.

In seventh grade, I had an inspirational female teacher who delved into biology with a memorable gusto. We did dissections, talked to marine biologists via satellite and had many hands-on activities. I remember one night, when studying, I realized that science offers an answer to every "why." My first aha.

Later, in high school, when I lost a close friend to what seemed like a medical mystery, I was empowered to want answers: in science, in medicine, in life.

Fast-forward through my doctoral program, where late-night incremental gains celebrated over a few hours of sleep and the whir of the laboratory instruments were punctuated with the aha of innovation.

Now I have been a professor for 10 years at a small college and am lucky to see aha moments for a living. Recently, a student, camera not on, stayed after our remote class in need of validation. When I assured her she understood a concept, she switched her camera on, doing a dance in excitement — the aha moment of a connection made.

As I bridge teaching remotely while caring for my toddler, I love introducing my daughter to science. One day we stabbed pencils through Ziploc bags filled with water, amazed they did not leak. When I asked her later

HONORABLE MENTIONS

DANIELLE GUARRACINO

Danielle Guarracino's daughter enjoys an aha moment, discovering principles of science first-hand.

about "science time," her face lit up as she remembered the pencils — her aha became mine, setting no age limits on science engagement.

Perhaps one of the most poignant aha moments in my career came to me unexpectedly this past summer. After muddling through several months of isolating at home, navigating issues with work and home life, I received an email from a former student who was about to start medical school after years in the service, including several tours in Afghanistan. He wrote to thank me for recommendation letters and for the materials from my class, which he was using to prepare for this new phase of life. I was humbled and proud to know I had played a small part in his path.

Some of us are heroes, but others get the unique opportunity to educate them. For me, that was the aha moment that speaks to me most and that I return to whenever I am in doubt about what I do and who I am.

Danielle Guarracino (guarracd@tcnj.edu) is a biochemistry professor at the College of New Jersey, studying the folding of short peptides into secondary structures and peptides as inhibitors to protein–protein interactions implicated in disease. She earned her Ph.D. in bioorganic chemistry and chemical biology at Yale University. Follow her on Facebook or Instagram @daguarracino.

The first to know

By Guy Hervé

At 3 o'clock in the morning, locked into the small black room in the basement of the biology building of the deserted Saclay Nuclear Research Centre in Paris, lighted only by a small red lamp, I was waiting for the development of an autoradiograph that was going to tell me if a modified aminoacyl–tRNA that I had deaminated was able to initiate protein biosynthesis by a bacterial ribosomal system, thus indicating that the initiation of protein biosynthesis does not involve the N terminus.

In the darkness and solitude of this peculiar environment and atmosphere, I was suddenly assaulted by the strange feeling that, although the result I was expecting was a very small piece of knowledge, I was going to be the first one to know it in the history of the universe.

COURTESY OF GUY HERVÉ

Guy Hervé gets out of a small submarine during the French–American expedition HOT 96; he dove 2,600 meters to the bottom of the Pacific Ocean to collect tube worms, Riftia pachyptila, which he was studying in the lab when he had his aha moment.

Guy Hervé (guy.herve@sorbonne-universite.fr) is director of research at the French National Centre for Scientific Research and at Sorbonne University in Paris and vice president of the Biophysical Committee of the French Academy of Science. He earned his doctorate in 1965 at the University of Paris and was a postdoc at Stanford University. His research concerns molecular and cellular enzymology, aspartate transcarbamylase, allosteric regulation, extremophile and deep-sea-vent organisms, and high-pressure studies.

The right experiment

By Iris Lindberg

There are only very few moments in experimental science when one realizes that all of the parts to the puzzle have fallen neatly into place. One tests hypothesis after hypothesis — but nothing clicks. It is as if

phenomena occur by magic rather than by any orderly process.

I knew that overexpression of the enzyme precursor proPC1/3 in CHO cells resulted in the robust secretion of active enzyme, but expression of the related enzyme precursor proPC2 resulted only in the secretion of catalytically dead enzyme — even at the pH known to cause intramolecular autoactivation.

I did know that proPC2 had a binding protein, 7B2, and bound cofactor proteins can be key to activating enzyme precursors. But time after time, no matter how many conditions were tried, adding recombinant 7B2 to secreted dead proPC2 did nothing to generate active enzyme.

The only way we could obtain any active PC2 at all was to immunoprecipitate it from the conditioned medium of a pancreatic cell line.

Finally, I decided to look at the problem as the cell would: by co-expressing 7B2 in our proPC2-overexpressing cell line. The next day, a short enzyme assay resulted in the rare eureka: I saw abundant PC2 enzyme activity in medium from proPC2 cells co-expressing 7B2!

The aha moment: I suddenly realized that proPC2, while still being efficiently secreted, must undergo a denaturing event during transport through the cell. It turned out that binding 7B2 blocks the deadly aggregation of proPC2 and permits it to retain an activatable form.

Finally, I realized that instead of facilitating a positive process, such as enzyme activation, 7B2 blocked a negative event: spontaneous misfolding. This is very unusual within the secretory pathway, where misfolded proteins generally are degraded rather than efficiently secreted. But once the right experiment was done, the pieces fell into place.

Iris Lindberg (ilindberg@som.umaryland.edu) is a professor of anatomy and neurobiology whose lab at the University of Maryland–Baltimore studies both proprotein convertase cell biology and neuronally expressed chaperones in neurodegenerative disease. Follow them on Twitter @lindberglab or visit thelindberglab.com.

Prepared mind leads to life-saving medical advice

By Rona R. Ramsay

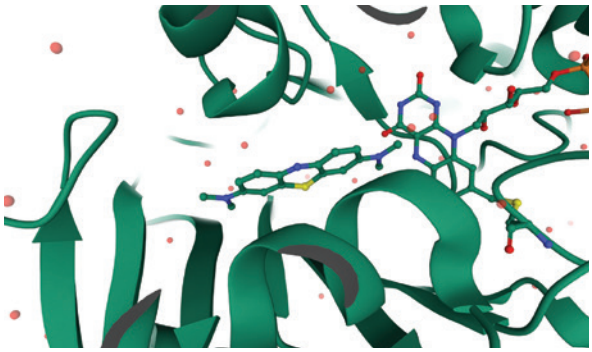
The neural activity ahead of an aha moment was evident in a hypothesis from the psychiatrist Ken Gillman regarding the nature of the potentially fatal drug interaction called serotonin toxicity, which had caused unexplained deaths over the previous decades.

His understanding of pharmacology and intellectual curiosity about serotonin toxicity mechanisms prepared his mind with an understanding of how drugs affecting the monoamine system of the brain interacted. This included the interactions and effects, both clinical and experimental, of monoamine oxidase, or MAO, inhibitors on serotonin levels in the brain. An anomalous report of serotonin toxicity after surgery where methylene blue, or MB, was used led him to suppose that MB had unrecognised monoamine oxidase inhibitory properties.

To substantiate a biochemical cause–effect relationship, Ken contacted me in November 2006 and made a case for testing his theory. I found literature indicating a Ki value of 5 millimolar for MB against the MAO-B found in glial cells and serotonin neurons, but nothing on the serotonin-metabolizing enzyme MAO-A found

HONORABLE MENTIONS

PROTEIN DATA BANK



Methylene blue (center) in the active site of monoamine oxidase close to the flavin–adenine dinucleotide (right).

in all the other neurons as well as glial cells.

My student tested it and quickly found that MB was indeed a tight-binding inhibitor of MAO-A with a Ki value of 27 nanomolar. Furthermore, spectral experiments showed that MB could both donate and accept electrons from MAO-A, indicating a close active-site association.

Subsequent drug discovery work by others found that many common compounds sharing the structure had additional influences in the brain.

After our joint publication in 2007 and Ken's efforts to spread the word via publications, website and networking, medical advice on the use of MB was changed to avoid its use in patients on antidepressants to prevent the elevation of brain serotonin to toxic levels.

Rona R. Ramsay (rrr@st-andrews.ac.uk) is a biochemist who studied mitochondrial enzymes over 45 years at the University of Cambridge, University of California, San Francisco, and University of St. Andrews. Highlights include the carnitine carrier, neurotoxins and electron transport, and monoamine oxidase and drug design.

Superhero science

By Mona Al–Mogotir

Normally, life throws things at us, leading to some aha moments. In my case, my kids were doing the throwing part on behalf of life.

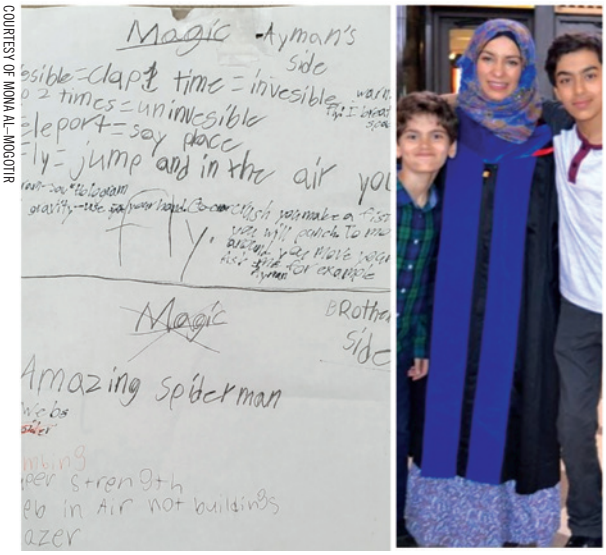
I started my Ph.D. with two superhero-aspiring boys, ages 6 and 3. One day, as I was reading and dodging flying toys and shoes generated by superheroic excitement, a moment of silence followed that storm instead of the other way around. Two amused faces were looking over my shoulder at a figure on my laptop screen.

"You are making a Hulk, right, Mom?" one asked.

I looked to check how serious they were and then looked back at the figure to connect some dots. It was a microscopic image of green fluorescent cells. I realized the connection with the green pulsing cells in the opening sequence of the 2003 Hulk movie. A moment of desperation led me to say "Yes!" and continue explaining that this was indeed my thesis project.

In the years that followed, I enjoyed support most student parents can only dream of. My only worry was to be sure my boys didn't perceive me as David Banner's evil scientist character. And I had to give routine updates of my progress over the dinner table, probably more often than I did with my Ph.D. committee members.

COURTESY OF MONA AL–MOGOTIR



LEFT: The author's sons gave her these original specific aims for the superheroes project during her first year in graduate school. The older one, Ayman, wrote on behalf of his little brother, Ibraheem, as noted in the bottom "brother side." Ayman's payback for doing the writing was the freedom to allocate more powers to himself. He even crossed out the request for magic for his brother. This sheet went through one edit by Ayman several months later as shown by the different pen colors and addition and omission of certain powers.
RIGHT: Mona Al–Mogotir, Ayman and Ibraheem five years later, after her graduation ceremony in May 2018.

Eventually, I was handed a paper with a list of superpowers to work on, which looked very much like a specific aim page. With time, speculations were raised, and I had just the right response to obliterate them, a green EGFP-tagged protein in solution.

At the end of my defense presentation in April 2018, I decided to come clean about my real project during my acknowledgments. My two superheroes-in-waiting were among the audience. Since then, the story lives as a joyous memory at home and work.

Mona Al–Mogotir (mona.x.almugotir@gsk.com) is an analytical chemist at GlaxoSmithKline. She earned her doctorate in biochemistry and molecular biology from the University of Nebraska Medical Center and continued her postdoctoral training in Gloria Borgstahl's lab for three years before moving into her current position.

Not quite out of the box

By Najla Arshad

It was way back during my master's program that I had this epiphany of sorts.

One of our laboratory classes seemed on the verge of being canceled due to the absence of clean glass measuring cylinders. Or was it pipettes? I don't remember that detail now. The bottom line was that we needed to measure a specific volume of a liquid reagent and didn't have the necessary apparatus.

While the prospect of a free afternoon lit up my classmates' faces, something in the back of my mind lit up as well. An abstract idea, a definition memorized and an equation used to answer quiz questions suddenly made perfect practical sense.

"But we don't need to measure the volume," I piped up.

While some wondered where I was going with this, I added, "We know the density. We can calculate the weight for the volume we need and just weigh it out."

I looked around for a response.

"Well done!"

"What an idea!"

"Let's do it!"

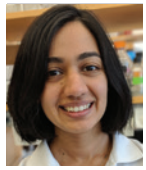
That was just in my head. In reality, we were given

the afternoon off, and I took the time to reflect on this with two of my friends. They thought it was a pretty smart idea. They even thought that the professors were impressed.

Then why didn't we do it? Because, when an out-of-the-box idea meets the set ways of human nature, the latter often wins.

Recognizing this was an aha moment reminded me to be open to taking risks and creative suggestions, trying new things, and applying old ideas in new ways. How well has that worked out for me so far? That's a different story!

Najla Arshad (najla.arshad@yale.edu) is an associate research scientist in the laboratory of Peter Cresswell at Yale University, where she studies how ER chaperones regulate immune responses. She received her Ph.D. from the Indian Institute of Science. Follow her on Twitter @arshad_najla.



"I could be happy doing other things"

By Laurel Oldach

When Alanna Mitsopoulos decided that her aspiration to become a forensic scientist was not practical for financial reasons, it spurred a lot of exploration — and she found that there were many jobs to consider.

Mitsopoulos told ASBMB Today about her career path and her current role at the nonprofit AddGene, which catalogues and distributes plasmids for research. This interview has been condensed and edited.

1 Tell me about your scientific training?

I've been interested in science since middle school, when I did a women in science and engineering program. In college I earned a biochemistry degree with a forensic science concentration. My senior year, I did an internship with the Boston Police Department crime lab, right at the time of all the scandals with the Massachusetts state labs. (Editor's note: In 2011 and 2013, two state forensic scientists were accused and later convicted of falsifying evidence in criminal cases and stealing confiscated drugs, respectively.) They actually just made a Netflix documentary on it. I'm watching it and thinking, "I remember this conversation happening!"

2 Wow. So what was your role?

The crime lab was considering switching to a different preliminary test to look for semen for sexual assault cases. They had a lot more to do because the state labs had shut down; with the backlog of evidence, they were trying to reduce false positives and avoid sending something out for secondary analysis that would come back without any DNA. There wasn't a lot of (comparative) research, so I dug really deep to find information on how the tests work so that after I left they could decide whether to switch.

3 First job after college?

To pursue forensic science, I would have needed to go to grad school, and I didn't have the money to do that right away. In exploring other careers, I realized that I could be happy doing other things; that's when I found embryology. I spent four years in an in vitro fertilization clinic, doing everything from egg retrieval to inseminating, assessing the embryos, and freezing or transferring them.

4 Now you're at Addgene. What do you do there?

I'm part of the viral vector team; we produce readymade virus aliquots to make it easier for researchers. My average day involves culturing cells — those are always being taken care of — and following my virus prep through till the end: harvesting, purifying and concentrating the virus. Our team takes turns to do quality control checks; we're very proud of the way we handle quality control to confirm that we're sending the customer exactly what we say we are.

Alanna Mitsopoulos

CURRENT POSITION
Viral vector senior technician, Addgene

CAREER PATH
Bachelor's degree, biochemistry and forensic science

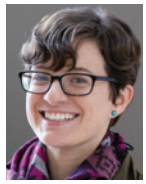
FIRST JOB OUTSIDE OF ACADEMIA
Embryologist

FAVORITE MOLECULE OR PROTEIN
p30, a prostate-specific antigen used to detect semen at crime scenes

5 Advice for younger scientists?

Internships are the best way to get experience. But when that's not possible — because internships are hard to get, especially now — make yourself stand out in some way. Have your professors review your resume and your cover letter. And always look into the company that you're hoping to be a part of.

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



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