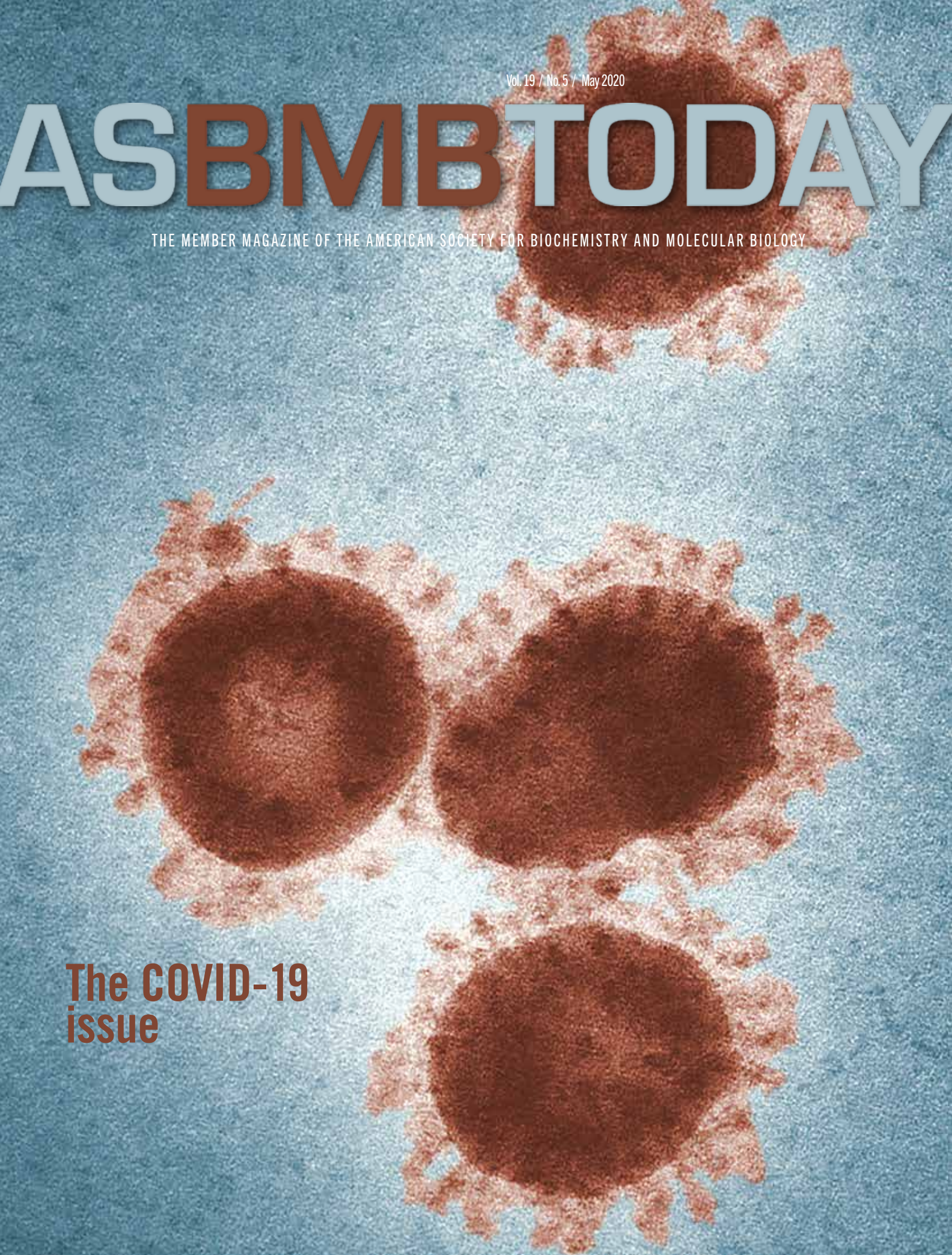


Vol. 19 / No. 5 / May 2020

# ASBMB TODAY

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

**The COVID-19  
issue**



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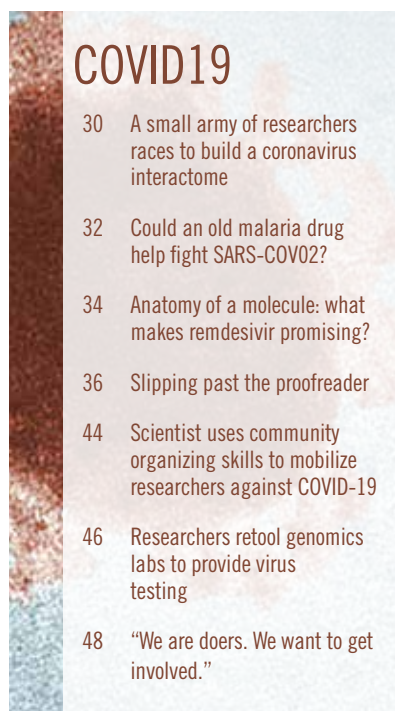
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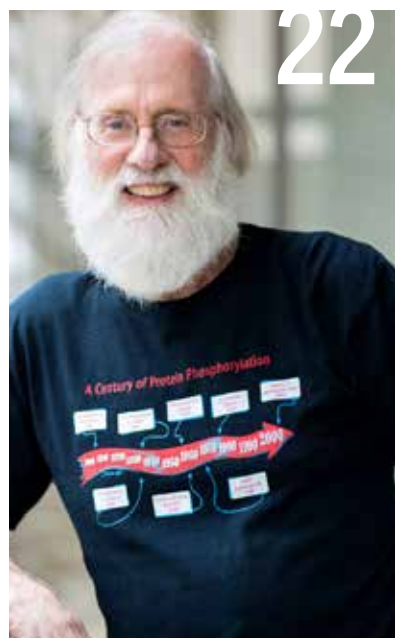
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## EDITOR'S NOTE

# Breaking the news

*By Comfort Dorn*



PHOTO BY MIKA BAUMEISTER ON UNSPLASH

Protective masks, normally used for surgery, are now in use to fight the coronavirus, SARS-CoV-19.

This month marks my third anniversary as managing editor of ASBMB Today. If COVID-19 restrictions continue, I'll probably celebrate privately with an extra cup of coffee at my kitchen table/desk. Maybe even a doughnut.

As I've mentioned in this space before, I worked for about 20 years at daily and weekly newspapers before I came to the ASBMB to edit a monthly magazine. The change was stark, mostly in terms of pacing. I spent much of my career hounding reporters to turn around daily stories in a matter of hours. Here, I found that we had the luxury of working for weeks, even months, on articles and essays to get them exactly right for this magazine. Very little was urgent. We moved at a stately and thoughtful pace, rather like an ocean liner or a dowager countess.

That changed this year. And it changed fast.

First, we moved to daily publishing on our website in January, meaning we were posting fresh stories every morning — often several a day. This had been a longtime goal of the ASBMB Today staff, and we were delighted with our fresh new website, even though it meant major pivots in our workflow.

Later that month, we became

aware of an insidious new disease that was sickening people in China. We posted our first article about research related to chloroquine and “the new coronavirus” on Feb. 6, covering a paper published two days earlier.

Since then, this job and my old jobs have felt increasingly similar as we race to share news of COVID-19 research and how our members are helping and coping. Our staff writers, contributors and members have churned out articles and essays at what, for us, is an astonishing pace.

Why am I telling you this?

This issue of ASBMB Today reflects these recent changes. Here we have collected the best of the COVID-19 writing that we've posted on our website since February. We tried to update articles wherever possible, but the story is evolving quickly. This is a snapshot, from the viewpoint of this magazine and this society, of a moment that comes once in a century.

Stay well and stay safe.

### Comfort Dorn

([cdorn@asmb.org](mailto:cdorn@asmb.org)) is the managing editor of ASBMB Today. Follow her on Twitter @cdorn56.



[www.asmb.org/asmbtoday](http://www.asmb.org/asmbtoday)

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### Three ASBMB members win Protein Society awards



Pictured, from left, are Protein Society award winners Catherine Drennan, Stephen Sligar and Karen Fleming.

The Protein Society has honored three members of the American Society for Biochemistry and Molecular Biology with 2020 awards. **Karen Fleming** of Johns Hopkins University, **Stephen Sligar** of the University of Illinois at Urbana–Champaign and **Catherine Drennan** of the Massachusetts Institute of Technology were set to receive their awards at the World Conference on Protein Science in June, which was canceled in response to the COVID-19 pandemic.

Karen Fleming, a professor of biophysics at Hopkins and a pioneer in the study of membrane-protein folding, won the Carl Brändén Award, which honors a protein scientist who has contributed significantly to science, education and/or service.

Fleming is an associate editor for the *Journal of Biological Chemistry*, served on the ASBMB Council from 2014 through 2017 and co-founded the Gordon Research Conference on Membrane Protein Folding. She recently received the Society of General Physiologists' inaugural Sharona Gordon Award.

The Brändén award is sponsored by Rigaku Corp. ASBMB members who have won it in past years include Billy Hudson, Vanderbilt (2017); C. Robert Matthews, University of Massachusetts (2015); Stephen White, University of California, Irvine (2014); Sheena Radford, University of Leeds (2013); Helen Berman, Rutgers University (2012); Michael Summers, University of Maryland, Baltimore County (2011); and Bruce Alberts, University of California, San Francisco (2010).

Stephen Sligar, who chairs the biochemistry department at UIUC, won the Christian Anfinsen Award for methodological advances in the field of protein sciences.

Anfinsen received the Nobel Prize in chemistry in 1972 for his work on enzyme structure. His namesake award recognizes “a technological achievement or significant methodological advances in the field of protein sciences.”

Sligar discovered and developed nanodiscs,

lipid-membrane patches stabilized by a belt of membrane-scaffolding proteins. For that work, he also won the ASBMB's 2016 Herbert A. Sober Lectureship, recognizing outstanding biochemical and molecular biology research, with a special emphasis on the development of methods and research techniques.

The Anfinsen award is sponsored by the Protein Society. ASBMB members who have won it in the past include Anthony Kossiakoff, University of Chicago (2019); Sachdev Sidhu, University of Toronto (2015); and Barry Honig, Columbia University (2012).

Catherine Drennan, a professor at MIT and a Howard Hughes Medical Institute investigator, won the Dorothy Crowfoot Hodgkin Award for solving high-resolution structures of proteins and protein complexes that enhance understanding of the biology of metalloproteins.

Hodgkin used X-ray crystallography to determine the structure of vitamin B12 and won the 1964 Nobel Prize in chemistry.

The Protein Society, in its announcement, pointed to Drennan's determination of the first structure of cobalamin-dependent ribonucleotide reductase, one of the three enzymes that catalyze the final step in production of deoxyribonucleotides in all organisms.

Drennan is a former member of the ASBMB Education and Professional Development Committee, a past ASBMB annual meeting session organizer, and a past winner of the ASBMB–Schering–Plough Research Institute Award.

The Hodgkin award is sponsored by Genentech. ASBMB members who have won it include Hao Wu, Harvard Medical School (2019); Susan Marqusee, University of California, Berkeley (2018); Manajit Hayer–Hartl, Max Planck Institute of Biochemistry (2017); Rachel Kleivit, University of Washington (2016); Judith Frydman, Stanford University (2014).

## University of Vermont names Parise as dean



Parise

**Leslie Parise**, a biochemist who is currently chair of the department of biochemistry and biophysics at the University of North Carolina, Chapel Hill, and until recently was chair of the faculty at that university, will soon join the faculty of the University of Vermont. There, she will serve as the dean of the College of Agriculture and Life Sciences.

Parise's lab focuses on the molecular mechanisms of cancer and blood clot formation. One line of inquiry focuses on the protein calcium and integrin-binding protein 1, or CIB1, which may be a drug target in triple-negative breast cancer cells; a second research program has to do with the role of a lipid deacetylase in platelet aggregation.

In addition to her service at UNC Chapel Hill, Parise was an associate editor for the journal *Blood*. She has served as president of the Association of Medical and Graduate Departments of Biochemistry and on the American Society for Biochemistry and Molecular Biology's public affairs advisory committee. She is scheduled to start at UVM in May.

## Eichman wins award from Biochemical Society



Eichman

Eichman's lab uses structural biology techniques including X-ray crystallography to

Vanderbilt University biochemistry professor **Brandt Eichman** has won the Biochemical Society's 2021 International Award.

Eichman's lab uses structural biology techniques including X-ray crystallography to

interrogate the protein machines involved in repairing DNA and maintaining genome integrity.

The International Award — one of 10 awards given each year by the United Kingdom-based Biochemical Society — recognizes research that illustrates the importance of the molecular biosciences in the advancement of life sciences and is given to early-career scientists of any nationality who are located outside the UK and Ireland.

"This certainly would not have been possible without the hard work and creativity of the members of my laboratory," Eichman said of the award in a statement. "I thank my colleagues who made and endorsed the nomination and who have guided me over the years, and my family for their support and encouragement. This award will help maintain momentum within my research team, so that we may continue to approach what we feel are important and interesting questions related to genome maintenance."

## Pagliarini to move from Madison to Missouri



Pagliarini

**Dave Pagliarini**, an associate professor of biochemistry at the University of Wisconsin–Madison best known for his work on defining and functionalizing mitochondrial proteins, has been named a BJC investigator and will join the faculty at Washington University in St Louis in May.

Pagliarini received the Earl and Thresa Stadman award from the American Society for Biochemistry and Molecular Biology this year and has previously landed young investigator awards from the Protein Society

and a Presidential Early Career for Scientists and Engineers for his metabolism research. In one line of inquiry, his lab uses novel systematic screening to glean functional insights into orphan mitochondrial proteins. Other lines of inquiry concern the synthesis of coenzyme Q and the role of phosphatases in regulating mitochondrial activities.

Since 2015, in addition to running his lab, Pagliarini has also directed the metabolism branch of the independent Morgridge Institute for Research, a nonprofit institute affiliated with UW-Madison and located on its campus.

BJC Investigators are funded by the St. Louis-based hospital and physician organization BJC (originally Barnes–Jewish/Christian) Health-Care. They are selected by a search committee of 42 professors at Washington University School of Medicine. Pagliarini is the fifth of 10 professors the program is projected to recruit.

## Olzmann wins presidential award



Olzmann

University of California, Berkeley faculty member **James Olzmann** was among the 315 recipients of the 2019 Presidential Early Career Award for Scientists and Engineers.

Olzmann, an associate professor in the department of nutritional studies and toxicology and an investigator at the Chan Zuckerberg Biohub, investigates the regulation of lipid droplets and the role that they play in maintaining lipid homeostasis in conditions such as obesity and fatty liver disease. He joined the faculty at UC Berkeley in 2013 after earning

his Ph.D. from Emory University and doing postdoctoral work at Stanford University.

Established in 1996, the PECASE honors the contributions scientists and engineers have made to the advancement of science, technology, education, and mathematics education and to community service as demonstrated through scientific leadership, public education and community outreach.

### Outstanding investigator award for UW's Bornfeldt



Bornfeldt

**Karin Bornfeldt**, a professor of medicine and pathology at the University of Washington and an associate editor of the *Journal of Lipid Research* and several other journals, has received an Outstanding Investigator Award from the National Heart, Lung and Blood Institute.

Diabetes can accelerate the process of atherosclerosis, wherein cholesterol-rich lesions form in arterial walls. This puts people with diabetes at heightened risk of heart attack and stroke. Bornfeldt's lab studies the role of lipids, lipoproteins and immune cells in this process. In addition to running a research lab, she directs the Diabetes Complications Program and serves as associate director for research of the UW Medicine Diabetes Institute and as deputy director of the UW's Diabetes Research Center.

The Outstanding Investigator Award mechanism provides substantial flexible funding for a research program, rather than supporting specific projects. Bornfeldt and her team will receive \$7.2 million over up to seven years to pursue strategies for preventing cardiovascular complications of diabetes.

### Fuchs and Bissell win 2020 Gairdner awards



Mina Bissell and Elaine Fuchs

**Elaine Fuchs** and **Mina Bissell** are among the five scientists to receive a 2020 Canada Gairdner International Award.

The award honors Fuchs, a pioneering cell biologist, for revealing the mechanism by which skin cells make and repair tissues. Much of what we know about human skin's capacity to heal and regenerate — and, in cases of mutation, to succumb to diseases like epidermolysis bullosa — has been made possible by Fuchs' work, from her first lab at the University of Chicago to her current position as the Rebecca C. Lancefield investigator at the Rockefeller University.

The award honors Bissell, a distinguished senior scientist at the Department of Energy's Lawrence Berkeley National Laboratory, for her paradigm-shifting work in modeling the two-way interactions between normal and malignant cells in tumor microenvironments. This behavior, called "dynamic reciprocity," revealed that tumor cells behave differently in lab environments than in patients, led to 3D understanding of tumor behavior and has had significant impacts on cancer therapies.

The Gairdner Foundation was established by Canadian businessman and philanthropist James A. Gairdner in 1957 with the goal of recognizing and rewarding international excellence in fundamental research that impacts human health. The foundation has bestowed 395 awards on laureates from 35 countries, 92 of whom have gone on to receive Nobel prizes. This year's International award winners also include Roel Nusse, Rolf Kemler and Masatoshi Takeichi.



### Marion B. Sewer Distinguished Scholarship for Undergraduates

Deadline: June 1

[asbmb.org/diversity/undergraduate-scholarship](http://asbmb.org/diversity/undergraduate-scholarship)



## Student chapter members land Goldwater scholarships

The recipients of this year's Goldwater scholarships were announced in late March.

The scholarships, named in honor of Senator Barry Goldwater, offer \$7,500 per remaining academic year to sophomore and junior students pursuing bachelor's degrees in the natural sciences, math or engineering.

Many of this year's recipients in the life sciences are American Society for Biochemistry and Molecular Biology Student Chapter members. The ASBMB congratulates these promising sophomores and juniors:

- **Furyal Ahmed**, Agnes Scott College
- **Chris Bragança**, Villanova University
- **Daniel Cheong**, University of Oklahoma
- **Landon Clark**, University of Georgia
- **Madeline Farringer**, Iowa State University
- **Shellaina Gordon**, Northeastern University
- **Edena Khoshaba**, Chapman University
- **Stella Ma**, University of Wisconsin–Madison
- **Eran Maina**, The College of Wooster
- **Emily Mahoney**, Rochester Institute of Technology
- **Rishi Mehta**, University of Cincinnati
- **Mlana Lore**, Eckerd College
- **Jessica Pierce**, Salisbury University
- **Cynthia Schofield**, University of Massachusetts Boston
- **Ramiz Somjee**, Rhodes College
- **Daniel Wieland**, University of Arizona
- **Karen Zhang**, University of Washington

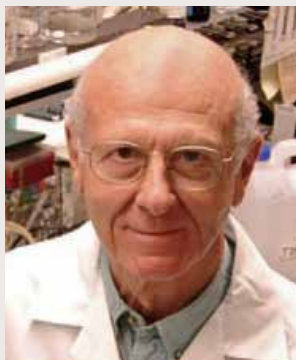
As part of the application, students write an essay about their experience with their research mentors. ASBMB salutes the many mentors of this year's 287 Goldwater scholars in the life sciences, who helped ignite their students' excitement about biology. Among the ASBMB members who mentored a Goldwater scholarship recipient are:

- **Jeanine Amacher**, an assistant professor at Western Washington University, working with Min Gao
- **Pascale Charest**, an associate professor at the University of Arizona, working with Jamison Takashima
- **Mark Hargrove**, a professor at Iowa State University, working with Behnia Rezazadeh Shirazi
- **Matthew Francis** and **Jennifer Doudna**, professors at the University of California, Berkeley, working with Casey Mogilevsky
- **Leslie Hicks**, an associate professor at the University of North Carolina at Chapel Hill, working with Lauren Lim
- **Terry Hill**, a professor at Rhodes College, working with Ramiz Somjee
- **Vincent Hilser**, a professor at Johns Hopkins University, working with Andrew Munoz
- **Michael Jewett**, a professor at Northwestern University, working with Alexandra Wooldredge
- **Henrik Kibak**, a professor at California State University, Monterey Bay, working with Samantha Miller
- **Daniel Kraut**, an associate professor at Villanova University, working with Chris Bragança
- **C. Martin Lawrence**, a professor at Montana State University, working with Sheridan Brown
- **Teresita Padilla-Benavides**, a professor at the University of Massachusetts Medical School, working with Shellaina Gordon
- **Tanya Paull**, a professor at the University of Texas at Austin, working with Cassandra Bishop
- **Subbiah Pugazhenti**, an associate professor at the University of Colorado Anschutz Medical Campus, working with Anit Tyagi
- **Jacob Schwartz**, an assistant professor at the University of Arizona, working with Daniel Wieland
- **Vincent Tagliabracchi**, an assistant professor at the University of Texas Southwestern Medical Center, working with Patrick Nnoromele
- **Timothy Wenczewicz**, an associate professor at Washington University in St. Louis, working with Michael Moore
- **James West**, an assistant professor at The College of Wooster, working with Eran Maina
- **Crystal Young-Erdos**, an assistant professor at Eckerd College, working with Mlana Lore



## Jerry Lingrel

Jerry Lingrel, a longtime associate editor of the *Journal of Biological Chemistry* and a University of Cincinnati College of Medicine faculty member for almost 60 years, died Feb. 22. He was 84.



In a 2007 autobiographical paper, Lingrel wrote that as a child he “spent a lot of time watching things grow and being fascinated by the complexity of the structure of different flowers, trying to understand how engines worked . . . I had a real curiosity about science, but had no idea what real experimental science involved.” Encouraged by an enthusiastic biology teacher, he went to Otterbein College where he majored in biology and chemistry, then earned a Ph.D. in biochemistry from The Ohio State University followed by a postdoc at the California Institute of Technology.

Lingrel joined the faculty of the University of Cincinnati in 1962 and became a professor of biochemistry and molecular biology in 1972. He served for 27 years as chair of the department of molecular genetics, biochemistry and microbiology. After stepping down in 2008, he returned to serve as the department’s interim chair from 2014 to 2017.

Lingrel was known for taking a biochemical approach to physiological problems. Recently, his research had focused on a zinc finger transcription factor called Kruppel-like factor 2, or KLF2, that is required for vascular integrity and might play a protective role against atherosclerosis. In years past, his lab cloned the Na,K-ATPase, a major transport protein, and identified specific amino acids involved in binding sodium and potassium as well as those necessary for binding the cardiac stimulant molecule ouabain.

Lingrel’s career spanned disciplines, he wrote, and “while biochemistry has been a very important aspect of this work, I think my research has always had as a focus the use of chemical principles to understand physiological function.” He also stressed the impact of working with others, writing, “we probably have more influence on the individuals we train than we anticipate and clearly mentoring should be taken very seriously.”

## Bruce S. McEwen

Neuroscientist Bruce S. McEwen, who made important discoveries about the effects of stress and sex hormones on the brain, died Jan. 2. He was 81.



McEwen, the Alfred E. Mirsky professor and head of the Harold and Margaret Millikin

Hatch Laboratory of Neuroendocrinology at The Rockefeller University, worked at the intersection of neurobiology, endocrinology and behavioral science. His research changed the way scientists conceived of the brain.

“When he began his career in the 1960s, most scientists believed that the brain ceases to change when it becomes fully developed, at which point its basic architecture becomes stable,” explained Rockefeller writer Katherine Fenz. “Research of the day focused largely on ion movements and the transmission of chemical signals across synapses. But McEwen, along with a few other scientists, recognized that the brain is in fact malleable and can be modified by circulating hormones.”

McEwen discovered adrenal steroid-binding sites in the brain, showed that brain regions not previously linked to hormone or stress regulation, including the hippocampus and prefrontal cortex, selectively bind radiolabeled corticosterone, and studied glucocorticoid influences on neuroplasticity.

McEwen was born in Fort Collins, Colorado, on Jan. 17, 1938. He grew up in Ann Arbor, Michigan, where his father was a professor at the University of Michigan.

He earned his bachelor’s degree in chemistry at Oberlin College in Ohio and then his Ph.D. in cell biology from Rockefeller University in 1964. He did postdoctoral work in Sweden and took a faculty position for a short time at the University of Minnesota.

He returned to Rockefeller as a faculty member in 1966. He was promoted to professor in 1981 and served as associate dean and then dean of the graduate training program between 1985 and 1993. He was named the Mirsky professor in 1999.

McEwen won many awards and honors during his career. He was elected to the National Academy of Sciences, the National Academy of Medicine and the American Society of Arts and Sciences.

He is survived by his wife, neuroimmunologist Karen Bulloch, with whom he collaborated; his former wife, Nancy, and their two daughters, Carolyn and Sarah; stepchildren, Kimberly McGrath and Scott Murasz; and eight grandchildren.

## Michael Wakelam

Michael Wakelam, a professor at Cambridge University and an associate editor for the ASBMB's *Journal of Lipid Research*, died March 31 of respiratory failure, likely from COVID-19 infection. He was 64.



Wakelam studied lipids' structural, metabolic and signaling roles and pioneered the use of high-sensitivity liquid chromatography–mass spectrometry to measure lipid levels in various cell and tissue types.

He had been director of the Babraham Institute, a life science research center near Cambridge, since 2007 and a JLR associate editor since 2013.

In a joint statement, JLR's editors-in-chief, Kerry-Anne Rye and Nicholas O. Davidson, said this about Wakelam's personal qualities and work for the journal: "Those who had the privilege of knowing him enjoyed his generous spirit as well as his passion for science. Michael maintained the highest standards of objectivity in his role as an (associate editor) and was an exceptional judge of scientific merit."

Wakelam was born in 1955. He earned his undergraduate and doctoral degrees at Birmingham University in 1977 and 1980, respectively. He went on to complete postdoctoral training at Glasgow University and worked in Germany and London before joining Glasgow as a lecturer in 1985. In 1993, he returned to Birmingham as a professor of molecular pharmacology.

The director position lured him to Babraham in 2007. There, he oversaw a team of researchers engaged in preclinical and clinical studies of the cellular and molecular details of aging.

He is survived by his wife, Jane, and their two grown children.

*Editor's note:* In May 2019, ASBMB Today science writer Laurel Oldach wrote a cover story about efforts to harmonize lipidomics. For that story, she interviewed Wakelam and others involved with the Lipid Metabolites and Pathways Strategy, known more commonly as LIPID MAPS. Read the story.

## James C. Hu

James C. Hu, a longtime professor in the Texas A&M University department of biochemistry and biophysics, died in his home in College Station, Texas, on Jan. 23 from complications of liver disease. He was 66.



Born April 3, 1953 in Berkeley, California, Hu grew up in Palo Alto. He earned a B.S. in biology at Stanford University and a Ph.D. in molecular biology from the University of Wisconsin. He worked as a postdoctoral fellow at the Massachusetts Institute of Technology before establishing his lab at Texas A&M.

In his research, Hu worked to develop biological ontologies, sets of standardized controlled vocabularies for annotation. Most recently, his lab worked with other groups on the Ontology for Microbial Phenotypes, a resource for reuse and analysis of microbial genetics data. His group worked with the Gene Ontology Consortium on annotation of gene functions and developed systems for integrating annotation with education in the Community Assessment of Community Annotation with Ontologies. They also worked on systems for building model organism databases for community annotation, including EcoliWiki, which uses and modifies the open-source software built for Wikipedia to provide specialized scientific data resources.

Along with his work in microbial genomics and community annotation, Hu was known as a supportive colleague who was generous with his time and energy. He loved teaching and interacting with students. He mentored undergraduate and graduate students in the lab, at meetings and in collaborative projects.

Hu is survived by his wife, Deborah Siegele, a professor in the biology department at Texas A&M. Generations of students and colleagues have known them as the rare couple who collaborated at work and at home, in symbiosis yet with fierce independence.

## Manford K. “Bud” Patterson Jr.

Manford K. “Bud” Patterson Jr., a former officer of the Samuel Roberts Noble Foundation and former president of the Oklahoma Academy of Science, died Jan. 22 in Edmond, Oklahoma. He was 93.



Born Aug. 20, 1926 in Muskogee, Oklahoma, Patterson served in the U.S. Navy Air Corps after high school, then earned a B.S. in chemistry and an M.S. in biochemistry from the University of Oklahoma. He worked for several years in the soils lab of the Noble Foundation, an agricultural research institution, before earning a Ph.D. in biochemistry from Vanderbilt University. He served as a consulting biochemist for the Interdepartmental Committee on Nutrition for National Defense before returning to the Noble Foundation in 1973 as vice president and director of the biomedical division. Following his retirement from the foundation, he joined IMTEC Corporation as a senior vice president of research and development.

Patterson played a role in developing L-asparaginase, a drug used to treat acute lymphocytic leukemia in children. He developed a quality control system that enabled IMTEC to market in the U.S. He co-edited a book, “Tissue Culture: Methods and Applications,” contributed chapters to other scientific books, published more than 60 articles in scientific journals and held three patents. He was an adjunct professor at Oklahoma University and served the American Tissue Culture Association as an officer and editor-in-chief of its journals. He played an active role in many scientific and civic organizations and served as a judge at numerous international science and engineering fairs.

Patterson is survived by his wife of 66 years, Beverly; a daughter, Shelley Goetz, and her husband, Dan; and a grandson, Manford Goetz, and his wife, Julie.

## Paul Starr Sypherd

Paul Starr Sypherd, a microbiologist who held leadership roles at the University of California, Irvine and the University of Arizona, died Jan. 18. He was 83.



Born Nov. 16, 1936, in Akron, Ohio, Sypherd moved to Arizona at age 6. He earned

a B.S. in microbiology at Arizona State (College) University, an M.S. in microbiology at the University of Arizona and a Ph.D. at Yale University. He was a postdoctoral fellow at the University of California, San Diego and later said he believed his training and experiences at UCSD set him on his academic trajectory.

Sypherd began his career at the University of Illinois; he had a fully funded research laboratory and obtained tenure there before he was recruited to the University of California, Irvine where he served as chairman of the department of microbiology and molecular genetics for more than a decade, director of the medical scientist program, vice chancellor for research and dean of graduate studies. He returned to the University of Arizona in 1993 as executive vice president and provost, leading development of an integrated learning center. As provost, he focused on improving staff and faculty working conditions. One of his lasting contributions was closing the campus between Christmas and New Year’s, so employees could spend time with their families. He retired in 2002 and was designated provost emeritus and professor emeritus of molecular and cellular biology at the UA.

Over the course of his 35-year research career, Sypherd and his students published more than 150 articles in peer-reviewed journals, many on protein synthesis and nucleic acid metabolism in bacteria and fungi. He was also a pioneer in ribosome research. He was a founding editor of the *Journal of Molecular and Cellular Biology* and editor for the *Journal of Bacteriology*, and he served on the National Institutes of Health study section for microbial chemistry for two terms and on the National Research Council committee on medical education.

Sypherd is survived by his wife, Linda; his daughter, Denise; sons David, Sean and Scott; his grandchildren; and many other relatives.

# Yeast as a detective's assistant

## Susan Henry's work on inositol-containing phospholipids

By Martin J. Spiering

**M**acromolecules such as proteins, lipids and carbohydrates often have complex structures that underpin their cellular functions. The sugar alcohol myo-inositol is a notable exception — its simple six-carbon structure looks unremarkable but is used in countless cellular processes in all domains of life.

According to Susan Henry, a professor of molecular biology and genetics at Cornell University, inositol is absolutely essential in cells. “It’s a major phospholipid precursor as well as a signaling molecule,” she said.

Henry has studied inositol metabolism in the yeast *Saccharomyces cerevisiae* since the 1970s. “I focused on the phospholipids and the metabolites that regulate their formation,” she said. “Inositol turned out to be the strongest regulatory metabolite of these pathways.”

Early in her career, Henry chose to work with *S. cerevisiae*, she said, because it is easier to study inositol and phospholipids in this organism than in more complex eukaryotes.

### Making a mutant resource

Yeast species have been a workhorse for scientists since the dawn of modern research. Their widespread use in fermentations led to the coinage of the term “enzyme” (Greek for “in yeast”). *S. cerevisiae* grows rapidly in culture as single cells, a boon for investigating eukaryotic biochemistry. The species can be maintained stably in the haploid state, and its genes can be manipulated easily.

“Yeast is almost like the *Escherichia coli* of the eukaryotic world,” Henry said, adding that yeast helped researchers “to figure out exactly where the metabolic components are coming from.”

The fully sequenced *S. cerevisiae* genome did not become available until 1996, so earlier studies of the genetics and biochemistry of even this simple organism required skilled detective work to find all the players involved in a molecular pathway.

At Albert Einstein College of Medicine in the mid-1970s, Henry and Ph.D. student Michael Culbertson used the mutagenic agent ethyl methanesulfonate to generate more than 50 *S. cerevisiae* mutants defective in inositol biosynthesis. This mutant strain collection provided a resource to launch investigations into the genes involved in inositol and phospholipid metabolism.

In a 1981 JBC paper, Henry and co-author Thomas Donahue reported the first purification and characterization of yeast myo-inositol-1-phosphate synthase, or Ino1, an enzyme that catalyzes a reaction that yields inositol 1-phosphate, an immediate precursor to free inositol.

The two scientists also mapped its gene to a locus called INO1 in the yeast genome and developed antibodies for specific detection of Ino1, laying the groundwork for more detailed biochemical and genetic studies.

### The first classic

In three JBC papers published in



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**Susan Henry's work on the regulation of inositol and phospholipids in yeast enabled numerous studies of the same pathways in humans and other eukaryotes.**

the late 1980s and early 1990s and now recognized as Classics, Henry and colleagues at Albert Einstein College and at Carnegie Mellon University reported the sequence and genetic analysis of the INO1 gene along with its regulation by a transcriptional repressor and two transcriptional activators.

In the first of these papers, Henry and Margaret Dean-Johnson sequenced the cloned INO1 gene and also determined the amino acid sequence of the purified protein. This analysis uncovered an open reading frame, or ORF, as a prime candidate for encoding the entire enzyme.

When they disrupted the predicted INO1 ORF in yeast cells, the researchers found that the cells did not express the Ino1 protein and grew only when supplied with inositol from the growth medium.

Their findings showed that the INO1 gene encodes myo-inositol-1-phosphate synthase in yeast and made available the full-length nucleotide and amino acid sequences of this pivotal phospholipid enzyme.

In keeping with earlier findings of the Henry lab that expression of the Ino1 enzyme is transcriptionally regulated, their work revealed several conserved short DNA motifs in the 5' promoter region of the INO1 gene that likely were bound by transcriptional regulators.

Henry next set her sights on deciphering the regulation of INO1 expression by inositol and another phospholipid precursor, choline. Using various INO1 promoter constructs fused to the *E. coli* lacZ gene to measure the promoters' activities, her team pinpointed the main regulatory regions in the INO1 promoter.

In particular, the team found a region that appeared to be bound by a transcriptional repressor, Opi1, they had previously identified.

### The regulatory circuit

In the second Classics paper, Henry and colleagues mapped the

OPI gene in the yeast genome, cloned and sequenced it, and identified several features of the predicted Opi protein sequence, including a leucine repeat and polyglutamine stretches present in many other regulatory proteins.

The paper defined an important regulatory mechanism controlling INO1 expression. It also provided critical momentum for identifying an important regulatory DNA element, the inositol-sensitive upstream activation sequence. This element is present in the promoters of genes for biosynthesis of phospholipids and the lipid triacylglycerol.

The third Classics paper further elucidated the regulatory circuit that controls phospholipid biosynthesis in yeast. Henry and colleagues demonstrated that the yeast proteins Ino2 and Ino4 form a heterodimeric complex that binds and activates the INO1 promoter and delineated the binding sites of the Ino2–Ino4 complex on this promoter.

The paper was the first to describe a basic helix-loop-helix, or bHLH, heterodimeric transcription factor in yeast and represented a milestone in

uncovering how phospholipid synthesis is regulated in eukaryotes.

### A ladder for research

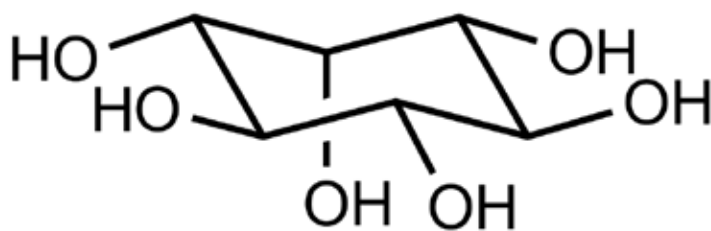
Looking back, Henry says that mentorship by Seymour Fogel and Alec Keith laid the foundation for her career. Besides sharing their expertise in genetics and biochemistry, they gave Henry critical material support to get her work off the ground.

“I was really lucky that they were not the kind of people who wanted me to (work exclusively) on their hot project,” she said. “They were willing to let me come into the laboratory and use their materials to do the things that I wanted to do.”

Moreover, although she was working with yeast, she secured funding through agencies that typically support mainly medical research. “I didn't have any trouble getting support from the National Institutes of Health, because of the connection with lipid metabolism in other eukaryotic organisms,” she said.

This investment paid off. “Many of the genes that I worked on were homologous to those in other eukaryotes, providing a ladder for other people to find the (corresponding) genes in other organisms,” Henry said.

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The sugar alcohol myo-inositol is a signaling compound and a ubiquitous precursor to phospholipids and many other important structural and signaling metabolites.

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# Cow born in Japan after removal, replacement of placental cells

By John Arnst

**R**esearchers at Hokkaido University have found that cow embryos from which placenta-forming cells had been removed can regrow those cells, form a placenta and successfully gestate. The scientists recently published their results, which provide insight into the regenerative capacity of mammalian embryos, in the **Journal of Biological Chemistry**.

All mammalian embryos follow the same blueprint in the first week of development: After being fertilized, a zygote divides into two cells, which quickly become four, eight, then 16 cells that specialize into an inner cell mass and outer cells that are known individually as trophoblasts and collectively as the trophoderm.

Nanami Kohri, the lead author on the paper, was intrigued by the fact that mouse embryos in which the trophoblasts — which differentiate to form the placenta — had been removed were much less successful in regenerating a placenta than bovine embryos that also had trophoblasts removed.

“Although isolated inner cell masses in both mice and cattle underwent trophoderm regeneration, they were significantly different in terms of regeneration efficiency, marker protein distribution and expression status of key genes,” he said. “Surprisingly, a calf was successfully delivered after the transfer of the reformed inner cell mass to the surrogate mother, but no descendants were obtained from reformed inner cell masses in mice.”

Kohri and his colleagues at the



Scientists in Japan removed placenta-forming cells from a bovine embryo, but it was able to regrow those cells, form a placenta and successfully gestate. It is now this healthy 23-month-old cow. The researchers named the cow Matoryona because as an embryo it resembled a Russian matryoshka nesting doll.

Laboratory of Animal Breeding and Reproduction previously had isolated bovine inner cell masses from embryos at the early blastocyst stage to find where the genes that give rise to the trophoderm were being expressed. Other groups had shown that cells positioned at the outer margin of the inner cell mass could be transformed into trophoderm in mouse embryos.

To understand why the bovine embryos had more success regenerating placental cells than the murine embryos, the researchers at Hokkaido University investigated the expression of the gene SOX17, which creates a protein that regulates cell specialization in development. They found that the expression of SOX17 varied significantly between the two species and was localized to the trophoderm cells that had been originally absent in murine embryos, which might explain

the weaker regenerative capacity.

Kohri and colleagues plan to investigate what drives the differences in embryonic protein expression among mammals as they continue to monitor their calf, which is now 23 months old and healthy.

“It has been suggested that the molecular basis of determining cellular divisions and localization in development differs among species,” Kohri said. “In the future, we will have to use our experimental system to evaluate trophoderm regeneration from the reformed inner cell masses in mice and cattle.”

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COURTESY OF NANAMI KOHRI/ HOKKAIDO UNIVERSITY

# How is myelin made?

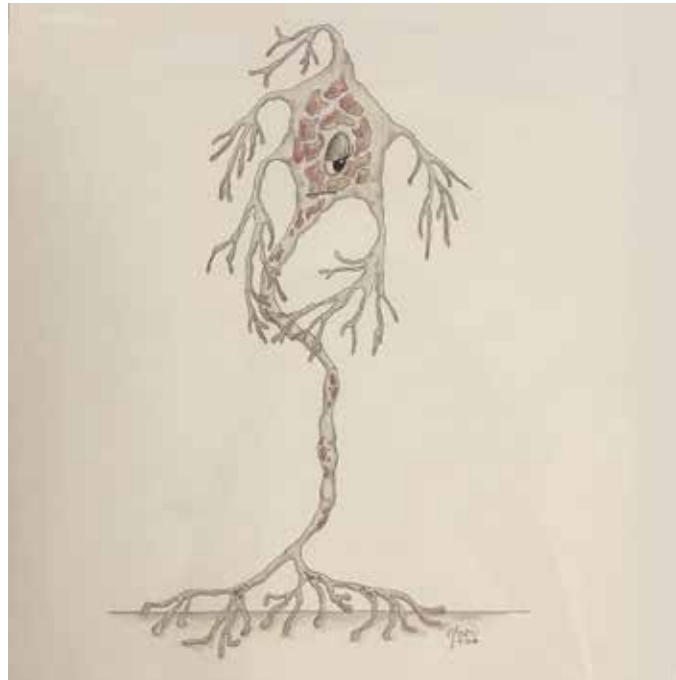
Understanding the protective coating on neurons may inform future therapies

By Nuala Del Piccolo

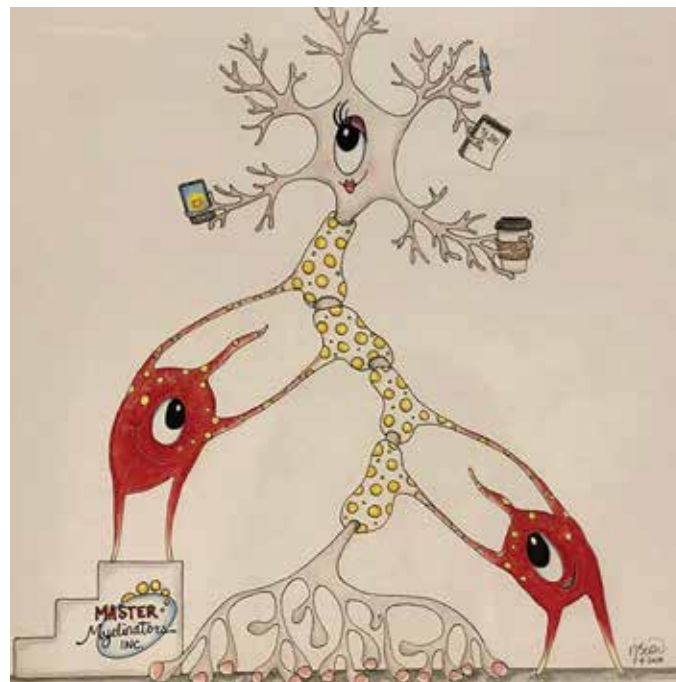
**M**yelin is the protective lipid sheath wrapped around a nerve. It functions as an insulator, akin to the protective coating on a wire, speeding up electrical transmission of signals along a neuron. Myelin also plays a role in maintaining the health of neurons. Myelin function is dysregulated in many neurological disorders, including multiple sclerosis.

Oligodendrocytes are the myelin-producing cells of the central nervous system. The myelin sheath around a neuron is part of an oligodendrocyte's plasma membrane, and a single oligodendrocyte can myelinate as many as 50 neurons. During myelination, an oligodendrocyte stretches out tubes of membrane in search of a neuron. When it finds one, it sends the necessary building materials down the tubes and, still operating from a distance, assembles a myelin sheet around the neuron. Composition, number of wraps and total coverage all matter. A myelinated neuron that loses its coating cannot transmit electrical signals properly, leading to loss of muscle control and other neurological problems.

The myelin sheath is mostly made of lipids, including sphingolipids, which are critical to myelin's structure and function. The enzyme serine palmitoyltransferase, or SPT, produces the backbone of all sphingolipids, and the membrane-bound protein ORMDL monitors sphingolipid levels and regulates SPT activity. ORMDL's activity must be precise:



JENNIFER SIOW



This artist's rendition shows neurons with (bottom) and without (top) a myelin sheath. The neuron with a myelin sheath functions at full capacity, while a neuron without myelin is unhealthy. Oligodendrocytes are depicted in red.

Too little sphingolipid production impedes myelination, and too much can be toxic.

Binks Wattenberg, a professor of biochemistry and molecular biology at Virginia Commonwealth University, studies membrane biogenesis and now focuses on lipid biogenesis. “I am very curious about how the cell knows when to make sphingolipid and when to stop,” Wattenberg said. “I think ORMDL might be the key to answering that question.”

Wattenberg’s next-door lab neighbor, Carmen Sato–Bigbee, a professor in the same department, studies myelination, with a focus on oligodendrocytes. The two joined forces to study the role of sphingolipid biosynthesis in myelination in developing brains. They report their recent results in the **Journal of Lipid Research**.

To uncover the dynamics of sphingolipid content and synthesis

during myelination, Wattenberg and Sato–Bigbee’s team worked with newborn rat brains, because peak myelination occurs directly after birth. Only one in five cells in the brain is an oligodendrocyte, so the team isolated these myelin-producing cells for their experiments.

The researchers found that a large portion of the sphingolipids present in oligodendrocytes during myelination have an atypically long backbone — an 18-carbon chain instead of a 16-carbon chain. “The 18-carbon chain backbone points to a change in lipid composition during myelination, which might explain the insulating properties of myelin,” Wattenberg said. “In future work, we want to look at the role of each type of sphingolipid in myelination.”

The study also found that SPT activity increases for the first few days of myelination and then begins to decrease. ORMDL activity is not

measurable, but the team deduced that ORMDL isoform expression varies over time. These findings pave the way for future experiments.

“The control of sphingolipid biosynthesis is key to myelination, and understanding how this process works will enable us to alter it in future treatments,” Wattenberg said. “Our pie-in-the-sky goal is to understand sphingolipid biosynthesis so well that we can reprogram oligodendrocytes and reverse demyelination in degenerative myelination diseases like MS.”

DOI: 10.1194/jlr.RA120000627

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



## Upcoming ASBMB events and deadlines

### MAY

- 12–18 **National Women’s Health Week**
- 20 World Autoimmune Inflammatory Arthritis Day
- 27 Virtual event: Enzyme regulation by filamentation and other alternate and emerging mechanisms
- 28 Virtual event: Shape shifting in the control of protein function

### JUNE

- 1 Deadline for Marion B. Sewer Distinguished Scholarship for Undergraduates

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# Review delves into proximity proteomics

By Laurel Oldach

In a recent review article in **Molecular & Cellular Proteomics**, Payman Samavarchi–Tehrani and colleagues in the Gingras lab at Sinai Health Systems and the University of Toronto offer an introduction to proximity-dependent biotinylation, a key first step in proximity proteomics. The authors give researchers who are new to the field information about the natural history of biotinylation enzymes. They also offer insights into the mechanisms of these enzymes and new perspectives on future proximity

nearby proteins with a chemical tag that then can be purified. After purification, mass spectrometry identifies the tagged proteins.

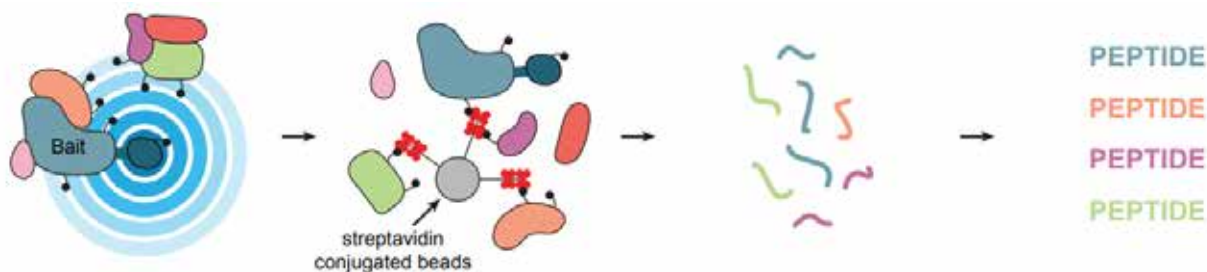
Most often, the chemical tag is biotin, a cofactor that is key to carboxylase enzyme activity in several metabolic pathways. Two types of enzyme are used for proximity-dependent biotinylation: peroxidases, used for methods such as APEX, and biotin ligases, used for methods such as BioID.

Ordinarily, biotin ligases append biotin to the carboxylases that need

The second enzyme family, the peroxidases, evolved to convert hydrogen peroxide to water by redox chemistry. In the presence of a biotin–phenol substrate and hydrogen peroxide, they can make a short-lived free radical that reacts with certain amino acid side chains, once again tagging nearby proteins for later identification.

As proximity proteomics has grown in popularity, both types of enzyme have been the targets of extensive engineering and molecu-

SAMAVARCHI–TEHRANI ET AL./MCP



A schematic diagram shows the proximity proteomics workflow. A bait protein is tagged with a biotinylation enzyme (center of concentric circles), which allows for covalent labeling of proteins in its vicinity with a reactive biotin intermediate. Then the researcher lyses the cells and uses streptavidin to extract biotin-tagged proteins, digests those proteins and uses mass spectrometry to determine their identity.

proteomics experiments.

Traditional proteomics can provide information about the quantitative contents of a cell or tissue, but it sacrifices much information on the spatial organization of proteins within cells. Since protein activity often depends on location and interactions with other proteins, researchers have developed approaches such as proximity proteomics to obtain information about the environs of a protein of interest. Proximity proteomics methods developed in the past 10 years depend on fusing the protein of interest to an enzyme that will label

it as a cofactor. Biotin ligases found in cells have high specificity for their substrate proteins, but certain mutations reduce that specificity by decreasing the ligase enzyme’s affinity for a reactive intermediate. Such mutants lose their grip on the cofactor and can release a reactive biotin that can bind the next amine group it encounters — often on a nearby protein. When researchers pull down biotin after this reaction occurs, they can determine what proteins were localized in the neighborhood of the biotin ligase and, by extension, the protein it was tethered to.

lar evolution to coax them toward the activity profiles users want. The authors review the available enzymes and discuss experimental design considerations, such as choice of control conditions and how to get rid of what they call “frequent flyer” proteins that often are isolated nonspecifically.  
DOI: 10.1074/mcp.R120.001941

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# From the journals

By *Latavia Hill, Kian Kamgar-Parsi & Anand Rao*

We summarize a selection of recent papers from the **Journal of Biological Chemistry**, the **Journal of Lipid Research** and **Molecular & Cellular Proteomics**.

## How a pathogen adapts to survive

*Pseudomonas aeruginosa*, a Gram-negative opportunistic pathogen, causes burn wound infections and pneumonia. It produces siderophores to acquire iron for survival and can express various iron-uptake pathways with specific TonB-dependent transporters, or TBDTs, which allows it to use exosiderophores produced by other bacterial species.

Quentin Perraud of the University of Strasbourg and a team of researchers in France recently published work in the journal **Molecular & Cellular Proteomics** focused on understanding how *P. aeruginosa* selects, regulates and adapts its expression levels of iron-uptake pathways in response to environmental stimuli. In this study, the researchers showed that *P. aeruginosa* uses different siderophores at different chelating efficiencies, with catechol siderophores being the most powerful. They also showed that expression of the TBDTs varied when *P. aeruginosa* was grown in three different media, which suggests that different phenotypic patterns exist. This work also shows that *P. aeruginosa* can detect the presence of epithelial cells and adjust gene expression accordingly. These findings show that *P. aeruginosa* senses changes in its environment and alters the expression of its

various iron pathways to acquire iron and effectively compete with other bacterial species.

DOI: [10.1074/mcp.RA119.001829](https://doi.org/10.1074/mcp.RA119.001829)

## A new therapeutic target for inflammatory CRMO

The autoinflammatory bone disease chronic recurrent multifocal osteomyelitis, or CRMO, is mediated by the inflammatory cytokine interleukin 1 beta, or IL-1beta, a known driver of bone lesions in CRMO. To develop effective therapies for the treatment of CRMO, researchers need to better understand the signaling events that result in high levels of IL-1beta. Tejasvi Dasari and colleagues at St. Jude Children's Research Hospital used mutant mouse strains, immunoblotting and microcomputed tomography to reveal a role for the nonreceptor spleen tyrosine kinase, or SYK, in the signaling cascade, resulting in elevated IL-1beta levels.

Their work, published in the **Journal of Biological Chemistry**, suggests that SYK may be a therapeutic target for the treatment of CRMO.

DOI: [10.1074/jbc.RA119.010623](https://doi.org/10.1074/jbc.RA119.010623)

## Good cholesterol gone bad in coronary heart disease

High-density lipoprotein, commonly called HDL, often is referred to as “good cholesterol” for the beneficial role it plays in maintaining cholesterol balance in the body. HDL also has been shown to mediate coronary heart disease, or CHD, but so far clinical trials of drugs that target

HDL have failed. According to Katrina Niisuke and a joint team from Tufts University and the Centers for Disease Control and Prevention, our limited knowledge of the composition–function relationship in HDL particles could be a reason for those failures. In new research published in the **Journal of Lipid Research**, the researchers sought to elucidate better the role of lipid composition in HDL function.

Using samples from CHD patients and healthy controls, Niisuke and colleagues were able to separate out large and small HDL particles and characterize their lipid compositions. Compositional differences were found between the large and small particles in all patient groups, but differences in both lipid composition and the function of apoA-1 between healthy subjects and CHD patients were primarily in the large particles. These large particles influence cholesterol control through the scavenger receptor class B type 1 pathway; thus, this research not only provides a deeper understanding of the composition–function relationship of HDL but also could inform development of treatments for CHD.

DOI: [10.1194/jlr.RA119000258](https://doi.org/10.1194/jlr.RA119000258)

## A new drug's role in cholesterol trafficking

Niemann–Pick type C disease, or NPC, is a fatal genetic disorder that results in the accumulation of excess cholesterol in lysosomes, a key waste disposer in cells. While there are no approved drugs to treat NPC,

## Shedding light on lipid raft formation

A major recent advance in our understanding of cellular membranes is the discovery of so-called lipid rafts or nanodomains. These domains are membrane regions enriched for certain lipids and proteins and are predicted to be important for a range of biological processes. With many questions outstanding on their function, structure and formation, nanodomains are the subject of significant research in the field of lipid membranes.

Attempts to study these nanodomains, however, have been hampered by difficulties in detection, leading many studies to use model membranes called giant plasma membrane vesicles, or GPMVs, at low temperatures (0°C to 20°C). These conditions induce larger-scale membrane ordering that can be detected by basic light microscopy techniques. While such studies have been valuable, researchers remain concerned that low temperature studies on these large-scale phase separations do not represent accurately the behavior of smaller nanodomains in human cells under physiological conditions.

In a recent paper published in the *Journal of Lipid Research*, a

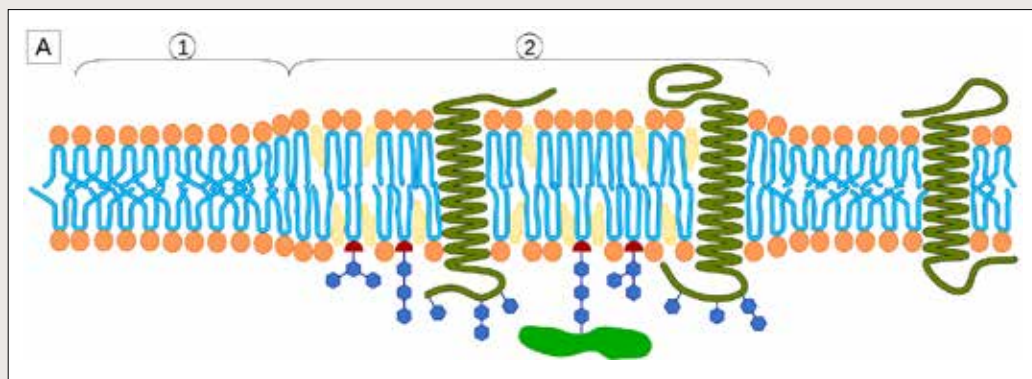
team from Stony Brook University led by Guangtao Li write that they were able to circumvent this common shortcoming. The researchers used a technique called Förster resonance energy transfer, which sensitively can detect low nanometer distances between labeled lipids otherwise undetectable by normal microscopy. With this technique, the researchers detected nanodomain formation in GPMVs at temperatures at least as high as 38 degrees, where larger-scale separations disappear, confirming that nanodomains occur at physiological temperatures. Li and colleagues also were able to modulate the lipid and cholesterol compositions of their GPMVs, confirming that differing membrane compositions could influence domain formation.

With the importance of nanodomains in normal cellular function, the ability to study these domains under more biologically relevant conditions is invaluable. Future research not only could expand our scientific knowledge of nanodomain behavior but potentially allow scientists to target and manipulate these domains for new drugs and treatments.

DOI: 10.1194/jlr.RA119000565

— Kian Kamgar–Parsi

ARTUR JAN FLIAKOWSKI/WIKIMEDIA COMMONS



Lipid bilayers often are separated into disordered regions (1) and ordered nanodomains (2), with these relatively poorly understood nanodomains serving important biological functions.

2-hydroxypropyl-beta-cyclodextrin, or CD, is a promising molecule currently in human trials. However, researchers know little about the details of CD's mechanism of action. Previous studies have shown CD to decrease lysosomal cholesterol accumulation but also have shown no effect on total cellular cholesterol. To reconcile these seemingly disparate findings, McKenna Feltes and a team from Washington University labeled cholesterol and tracked its movement through model NPC cells treated

with CD.

In a paper published in the *Journal of Lipid Research*, Feltes and her colleagues were able to confirm CD-dependent decrease in lysosomal cholesterol levels. Rather than removing this cholesterol from the cell, however, CD promoted transfer of lysosomal cholesterol to the plasma membrane. From there, cholesterol either would exchange with lipoprotein-bound cholesterol or be routed to the endoplasmic reticulum for processing if excess accumulation

occurred. These findings provide a more complete picture of CD's role in mediating cholesterol homeostasis in NPC and could prove useful in CD's continued development as a drug for this disease.

## Using a fusion protein to make fat levels fall

Lipoprotein lipase, or LPL, is an enzyme that metabolizes circulating triglycerides. When LPL activity is compromised — as is the case in familial chylomicronemia syndrome,

## Identification of another risk factor for AITDs

Autoimmune thyroid diseases, or AITDs, are caused by a self-mediated attack on thyroid cells and ultimately affect thyroid gland function. Two common AITDs are Hashimoto's thyroiditis, or HT, and Graves' disease. Before clinical symptoms appear, the human body produces autoantibodies against the thyroid cells, which allows clinicians to detect these illnesses. Researchers hypothesize that thyroid peroxidase antibody, or TPOAb, a commonly used diagnostic marker, has a role in autoimmunity by modulating IgG glycosylation.

Recently, Tiphaine C. Martin of King's College and an international team published a paper in the journal **Molecular & Cellular Proteomics** that focused on determining whether immunoglobulin G, or IgG, glycosylation is associated with TPOAb that is positive for AITD and whether AITD and glycan structures share any genetic, heritable factors.

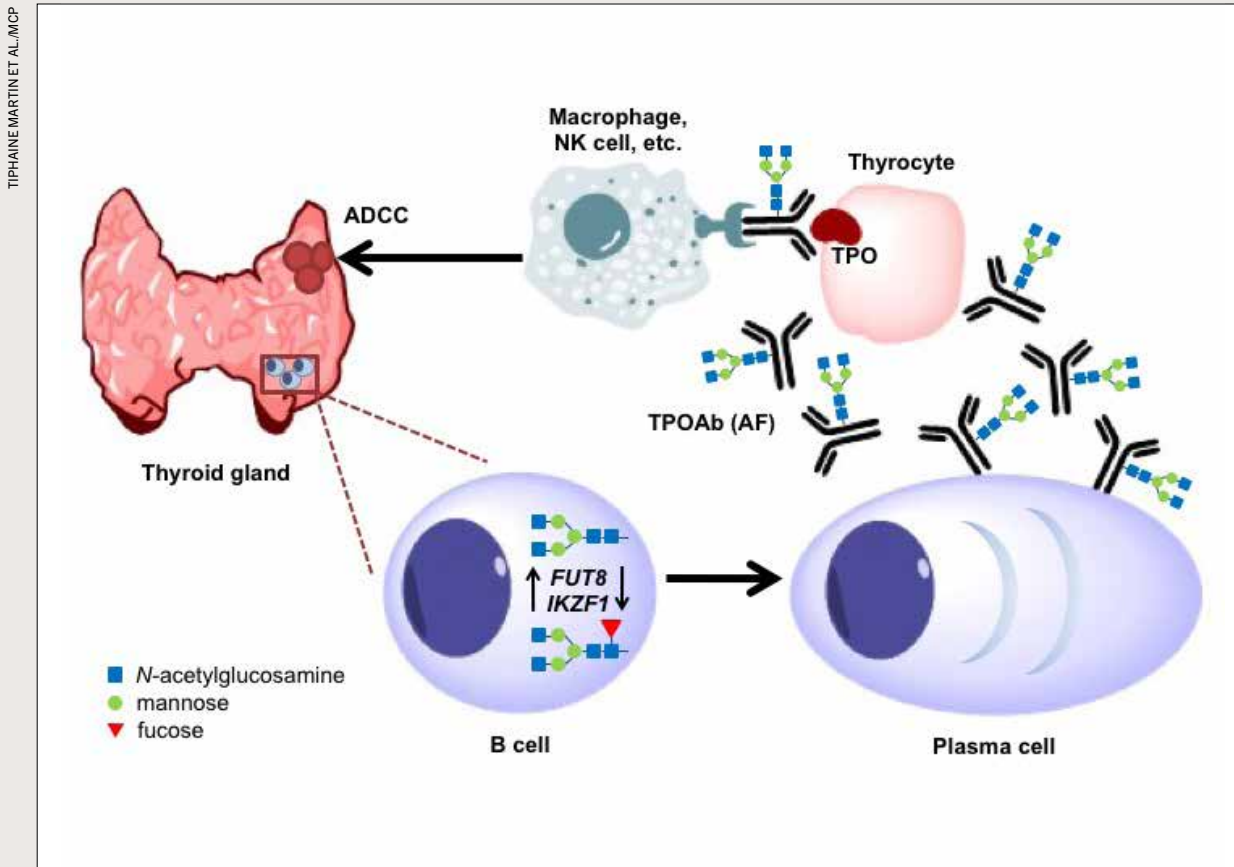
In this study, the researchers found that TPOAb level and AITD are associated with decreased IgG core fucosylation. Additionally, they

showed that HT is linked to a decrease of antennary alpha1,2 fucose and that enrichment of IgG N-glycan traits is associated with genes FUT8 and IKZF1, which are essential for IgG core fucose formation. The researchers could not determine genetic variances between AITD and IgG N-glycan traits; however, they showed that decreased core fucosylation and antennary alpha1,2 fucose are not associated with gene expression alteration in peripheral blood mononuclear cells.

In conclusion, the researchers propose a model in which FUT8 and IKZF1 have an aberrant expression in a tissue-specific manner instead of in the blood. They think this model will show that the altered expression causes antibody-dependent cell-mediated cytotoxicity directed against the thyrocyte due to afucosylated TPOAb antibodies. In turn, they propose that this cytotoxicity leads to AITD development.

DOI: 10.1074/mcp.RA119.001860

— Latavia Hill



This proposed model illustrates the role of FUT8 and IKZF1 in the development of autoimmune thyroid diseases.

## Knocking out Nogo to rouse regeneration

The nervous system has the remarkable ability to adapt and respond to a variety of environmental signals. Its two components are the central nervous system and peripheral nervous system, or CNS and PNS, respectively. The peripheral nervous system, which consists of the nerves and ganglia outside of the brain and spinal cord, can heal after a traumatic injury through spontaneous axonal regeneration. Curiously, this same type of self-repair does not occur after CNS injury such as stroke or spinal cord injury. In 2012, Feras Akbik of the Yale School of Medicine and a team of researchers explored this disparity and identified Nogo-A, a protein expressed by neurons and nonneuronal cells called oligodendrocytes, as a molecule that hinders nerve cell regeneration. However, how Nogo-A might disrupt axonal regeneration after spinal cord injury remained a mystery. In a recent paper published in the *Journal of Biological Chemistry*, researchers describe how they helped to solve this mystery by identifying Nogo-A in a different location: exosomes.

Exosomes are small cellular storage compartments that can traffick select cargoes throughout cells, and their contents can mediate

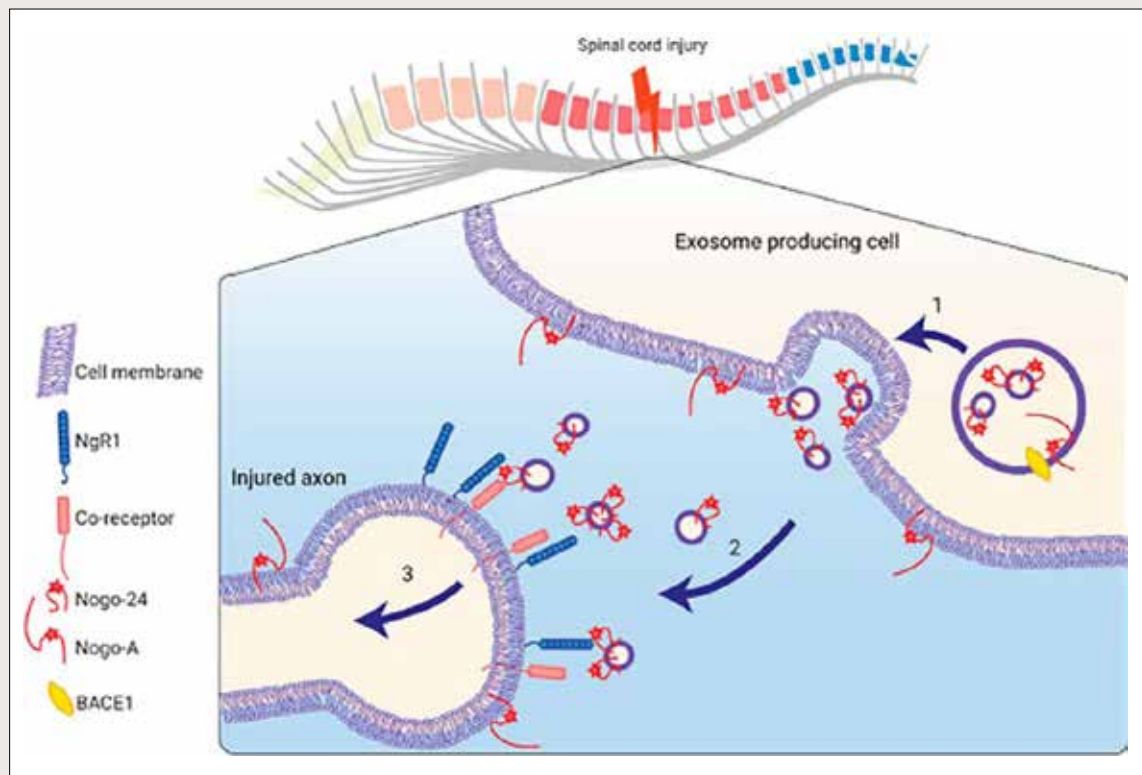
cellular communication, exerting effects on other cells. So, could exosomes be suppressing axon regeneration after traumatic injury? Yuichi Sekine and colleagues at Yale University School of Medicine tested this hypothesis by first expressing Nogo-A in a human cell line. They found that the enzyme beta-secretase 1 created a fragment of Nogo-A, called Nogo-24, that escapes from cells into the surrounding fluid on the outer surface of exosomes. Then, to confirm that Nogo-24 inhibits axon regeneration when presented to cells on the surface of exosomes, the authors cultured neurons and observed that injured axons regrow in the absence of exosomes with the Nogo-24 fragment. Finally, the researchers found that the Nogo-24 was present in an exosomal fraction of mouse spinal cord tissue that was injured but not in tissue from uninjured animals.

Their findings suggest a new pathway by which disruptive signals may be presented to prevent axon regeneration after injury.

DOI: 10.1074/jbc.RA119.009896

—Anand Rao

SIENNA DRAKE AND ALYSON FOURNIER



This illustration shows how exosomal Nogo-24 may be released after spinal cord injury and signal through NgR1 to inhibit neuron regeneration.

or FCS — plasma triglyceride levels are elevated dangerously, and few clinical options are available to correct them.

In a recent paper published in the **Journal of Biological Chemistry**, Amitabh Nimonkar and colleagues at Novartis Institutes for BioMedical Research showed that a fusion complex between LPL and the LPL transporter glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1, or GPIHBP1, demonstrates high enzymatic activity and is resistant to inhibitors of LPL. Moreover, injection of the LPL–GPIHBP1 fusion protein lowered triglyceride levels in several mouse strains, indicating its therapeutic potential for the treatment of FCS and other triglyceride-related diseases.

DOI: 10.1074/jbc.RA119.011079

## Amino acids activate mTORC

The mammalian target for rapamycin 1, or mTORC1, senses amino acids in the cellular environment and regulates cell growth and metabolism to match nutrient availability. Disruption in this sensing mechanism can result in metabolic disease and cell growth disorders.

Using cultured cells, immunoblotting, immunofluorescence and pharmacological approaches, Delong Meng of the University of Texas Southwestern Medical Center and colleagues demonstrated that some

amino acids, such as leucine and methionine, signal mTORC1 through the well-characterized Rag guanosine triphosphatase signaling pathway, while others, such as glutamine and asparagine, signal through Rag-independent pathways. Their work was published recently in the **Journal of Biological Chemistry** and shows that mTORC1 is differentially regulated by amino acids and may be useful in furthering treatments for metabolic disease.

DOI: 10.1074/jbc.AC119.011578

## Enzyme regulates ubiquitin's role in cells

The post-translational modification ubiquitination plays an important role in many cellular processes, including cellular immunity, transcriptional regulation and membrane protein maintenance. Deubiquitinases, or DUBs, such as Cezanne — an enzyme that cleaves ubiquitin from protein substrates — are crucial for the regulation of ubiquitin signaling. In a recent paper published in the **Journal of Biological Chemistry**, Julia Mader and colleagues at Goethe University in Frankfurt, Germany, discovered that adding hydroxyl groups to asparagine regulates Cezanne's interaction with ubiquitin in an oxygen-dependent manner.

These findings demonstrate that Cezanne-mediated removal of ubiquitin and the related physiological processes affected by the removal of ubiquitin are regulated in an oxy-

gen-dependent manner.

DOI: 10.1074/jbc.RA119.010315

## An essential protein in the cell cycle

Each day, millions of cells undergo cell division to make daughter cells. This extensively studied cell cycle consists of four phases: a gap phase, synthesis, a second gap and mitosis. Each checkpoint in this cycle is crucial, because any irregularities can lead to uncontrollable cell growth, also known as cancer.

A recent paper by Patrick Herr of Karolinska Institutet and a team in Sweden, published in the journal **Molecular & Cellular Proteomics**, focused on dissecting cell cycle dynamics at the protein level in asynchronous cells, using methods other than chemical synchronization. The researchers characterized protein oscillation patterns over the course of the cell cycle and found that many vital processes are affected. The team detected differences in mRNA abundance and phosphorylation patterns among cell cycle phase groups. They characterized predicted cell cycle-dependent proteins, including S-adenosylmethionine synthase, or MAT2A. They found that MAT2A nuclear localization was enriched in synthesis and in the second gap and mitosis, and they speculate that this protein is essential for epigenetic histone methylation during DNA replication.

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# A LEGACY OF TYROSINE

Tony Hunter, the Salk Institute biochemist who discovered this amino acid's phosphorylation, was scheduled to speak about his work at EB 2020.

*By John Arnst*

**T**ony Hunter hasn't had a clean shave in more than 40 years. "On one of his trips to the Grand Canyon, he stopped shaving, and he hasn't shaved since," said Walter Eckhart, Hunter's former postdoctoral advisor and longtime colleague at the Salk Institute for Biological Studies. "Well, he's trimmed his beard."

A member of the National Academy of Science since 1998, Hunter has received many awards and honors throughout his career, including the 2018 Tang Prize in biopharmaceutical science; he was scheduled to deliver the 2020 Tang Prize Award Lecture in April at Experimental Biology in San Diego before the meeting was cancelled due to the COVID-19 pandemic. His discovery that the activity of tyrosine kinases drives the growth of cancerous cells ultimately led to the development of tyrosine kinase inhibitors and the groundbreaking leukemia therapy Gleevec, as well as an entire subfield of biochemical regulation.

## **An English upbringing**

Born in 1943, Anthony Rex Hunter grew up in the southeast of England near Canterbury. He attended the venerable Felsted School in Essex, which celebrated its 450th anniversary in 2007. During his time there, he gravitated toward biology

and biochemistry, which he went on to study as an undergraduate at Christ's College at the University of Cambridge.

"We had a great set of teachers, including Nobel Prize winners like Fred Sanger and Max Perutz," Hunter said of his time at Christ's. "I didn't really know that I wanted to go into research as a career, but they were a major influence."

After Hunter graduated, he stayed at Cambridge and began graduate studies with the molecular biologist Asher Korner in the department of biochemistry, obtaining his Ph.D. in 1969.

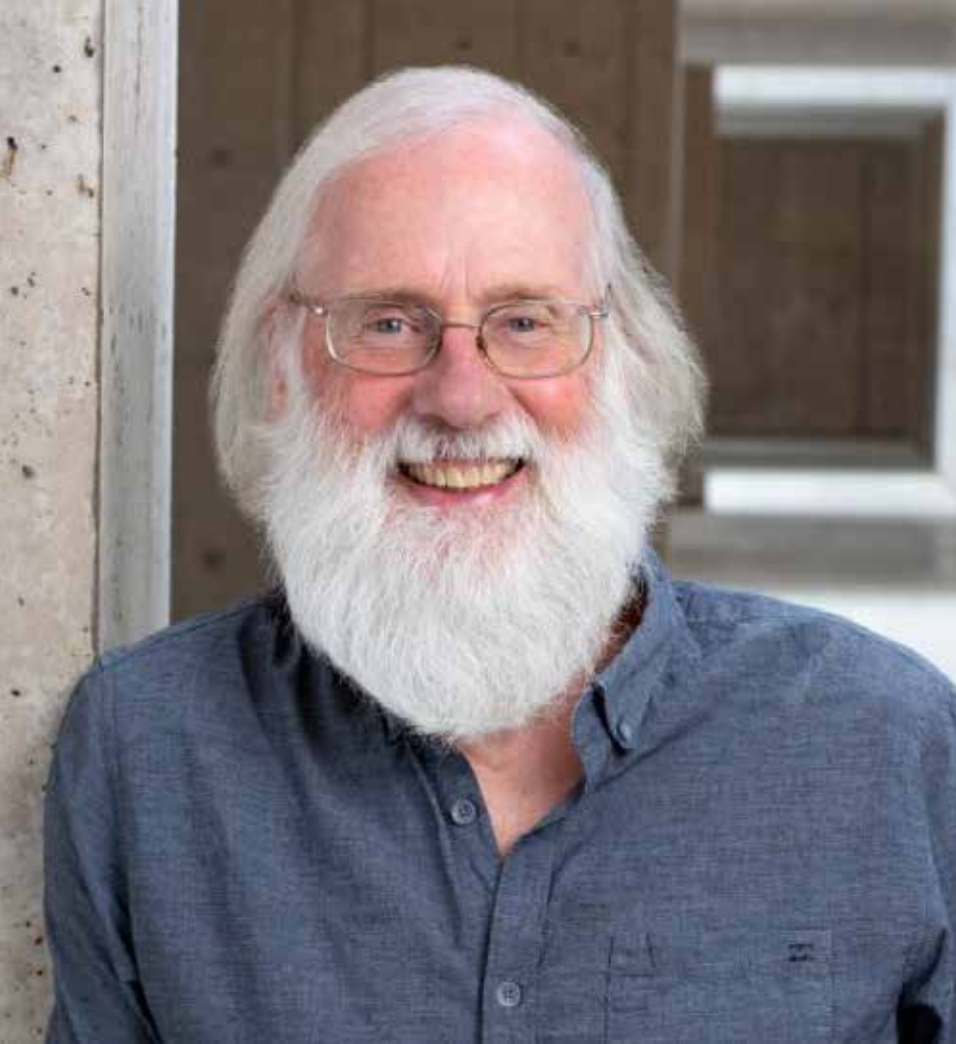
After a brief fellowship at Christ's, Hunter followed his first wife, Philippa "Pippa" Marrack, whom he had met while they were both graduate students, to California for her postdoctoral fellowship at the University of California, San Diego.

"I tagged along and ended up with the Salk because her advisor, Alan Munro, had done a short sabbatical here to learn immunology, so he suggested that I come."

There, for the first time, he encountered tumor viruses — and an abundance of sunshine.

"I thought when I left to do my postdoc, that I'd be here two years, find out about California and then go back to Cambridge to the rest of my career, but it didn't work out that way," he said. "It was a huge culture





**Tony Hunter, who discovered tyrosine phosphorylation in 1979, served as the director of the Salk Institute Cancer Center from 2008 to 2016.**

shock, obviously.”

After a brief return to Cambridge, Hunter settled at the Salk Institute in 1975. Four years later, he made his crucial discovery that unchecked tyrosine phosphorylation in cancerous cells was behind their aberrant growth.

### **Tyrosine and tumors**

By Hunter’s recollection, he and his colleagues stumbled on tyrosine phosphorylation through their work on the polyoma DNA tumor virus. In a 1979 paper in the journal *Cell*, they described their findings that phosphate in cell culture was associated with one of the three proteins the virus encodes to transform normal cells into tumor cells. They quickly followed it with another paper in the *Proceedings of the National Academy of Sciences* wherein they reported finding that v-SRC, the transforming

protein of a second oncovirus, has kinase activity. According to Hunter, this provided an immediate hint that human cells might also have tyrosine kinases.

“We found, in short order, that a Rous sarcoma virus encodes a similar tyrosine kinase activity,” Hunter said. “And since that gene was derived from the cellular SRC gene by viral capture, we already knew that cells must have at least one enzyme with this type of activity. We realized that having two viruses using a similar mechanism could mean that it was a common mechanism of viral transformation, but we didn’t know at the time it would be important in cancer in the way that we now know.”

Not long afterward, a group led by Stanley Cohen at Vanderbilt University reported that the transmembrane epidermal growth receptor protein, or EGFR, was also a tyrosine

kinase. This led Hunter to generate sequence alignments of the viral tyrosine kinase proteins, as well as protein kinases that phosphorylate serine and threonine, which revealed that the catalytic domain of tyrosine kinase has a series of conserved short sequence motifs that are essential for transferring phosphate.

He and various colleagues then used PCR amplification and degenerate oligonucleotide probes that recognize the short sequence motifs to identify new tyrosine and serine kinase genes. When those genes were combined with analysis of the human genome sequence, the researchers ultimately wound up discovering nearly 500 human kinases, about 90 of which are tyrosine kinases.

According to Hunter, the first major hints that tyrosine phosphorylation played an important role in growth of cancer cells came when

scientists at the National Cancer Institute and Erasmus University found that chronic myeloid leukemia, or CML, was caused by a chromosomal translocation between chromosomes 9 and 22 that fuses together the kinase-producing ABL gene with the BCR gene. They reported their findings in three papers that appeared in 1982 and 1983 in the journal *Nature* and in 1984 in the journal *Cell*.

“The fusion gene encodes a chimeric BCR-ABL protein that is constitutively activated as a tyrosine kinase,” Hunter said. “Within a few years, several other tyrosine kinase genes were shown to be mutationally activated or overexpressed in human cancer.”

Work by David Baltimore and by Owen Witte’s group at the University of California at Los Angeles had laid the groundwork for the hypothesis that inhibiting the activity of the BCR-ABL kinase made by the gene fusion created by the Philadelphia

translocation, which occurs in 95% of CML cases, would shut down cancerous CML cells. In the early 1990s, Brian Druker, a physician scientist at Oregon Health and Science University who had been working with CML patients, reached out to scientists led by Nicholas Lyndon at the Swiss pharmaceutical company Ciba-Geigy, which later became Novartis, who were developing tyrosine kinase-blocking compounds. After homing in on the kinase inhibitor STI-571, they found both that it caused a 92% to 98% decrease in the number of cells exhibiting the BCR-ABL fusion in human bone marrow cells predisposed to develop into leukemia cells and that it kept the cancerous cells from returning. Within short order, the drug, which was renamed imatinib and later marketed as Gleevec, entered human trials.

“It proved to be a very effective treatment for early-stage CML,”

Hunter said. “So much so that some of the patients who went on the drug experimentally in 1999 and 2000 when it was in trials are still on the drug 20 years later because it’s well-tolerated and is keeping their disease in check.”

Today, 40 tyrosine kinase inhibitors have been approved by the Food and Drug Administration as cancer therapies.

“And kinase inhibitors as a class are now up over 65,” Hunter said. “That’s pretty impressive, considering this all started only about 20 years ago in a huge effort in this area, and there are many, many more in clinical trials. I’m sure the number will continue to increase.”

## Knowledge and notes

While the Salk Institute was founded in 1960 as a place where scientists could devote themselves to research free of teaching obligations, mentoring remains a significant part of each Salk scientist’s career.

Ruth Palmer, a biochemist at the University of Gothenburg in Sweden who was a postdoctoral fellow in Hunter’s lab from 1996 to 2000, recalled the latitude Hunter gave his postdocs and his openness to their ownership of projects.

“He’s very generous in terms of whatever you generate in his lab; he supports it and then you can take it with you completely,” Palmer said. “For me, that was incredibly important. When I started my own lab after that, which I did here, I felt it was actually quite easy because I had already become very independent in his lab.”

Jonathon Pines, now head of the Division of Cancer Biology at the Institute for Cancer Research in

COURTESY OF RUTH PALMER



An avid traveler, Hunter attends many conferences each year. In 2017, he met up with his former postdoctoral researchers Clare Isacke (left) and Ruth Palmer (right) at the European Molecular Biology Organization’s annual meeting, during which the two were inducted into the organization.



Tony Hunter has rafted the Grand Canyon several times, most recently in 2010. Top left: Marble Falls Canyon, a launching point on the Colorado River north of the Grand Canyon, in 1981. Top right: Lava Falls Rapid in 1987. Bottom: Hermit Rapid in 2010.

London, was a postdoc of Hunter’s from 1988 to 1992.

“Tony was incredibly generous,” Pines said. “When I arrived, there wasn’t anybody working on the cell cycle in his lab, but he was interested in cell cycle regulation.” During his doctoral work at Cambridge with Tim Hunt, who had worked alongside Hunter when they were both graduate students, Pines had cloned cyclin B, a protein critical for regulating mitosis in animal cells.

“So he just said, ‘Why don’t you go ahead and continue to work on the cell cycle,’” Pines said. “And

within a very short period of time, he knew as much about the cycle as I did. He has this extraordinary capacity to absorb and remember information.”

During his time in Hunter’s lab, Pines cloned the first human cyclins, A and B1, and mapped their interactions with proteins involved in promoting cancer and regulating the cell cycle.

“I learnt a huge amount from him in terms of how to design research that was productive, particularly how to interpret data,” Pines said. “His encyclopedic knowledge

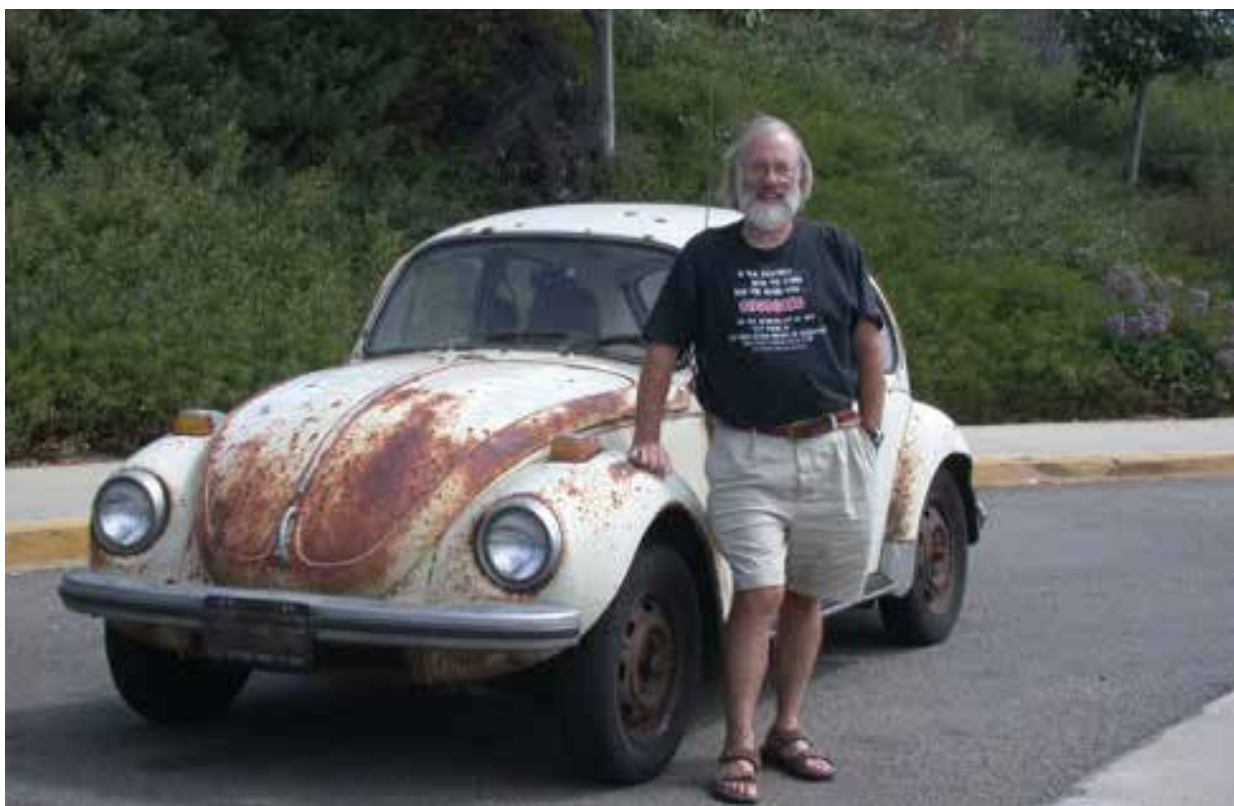
of the literature meant that he’s also able to make connections that might not be apparent to other people. He’s always been able not only to master a particular subfield, but also make connections between fields.”

According to Pines, and every other scientist interviewed for this feature, this knowledge takes a physical manifestation in decades of voluminous, detailed notes.

“Tony’s notes are famous in the lab,” Pines said. “He listens to every talk and writes everything down in pencil, because it’s fireproof.”

During Hunter’s second stint at

IMAGE COURTESY OF TONY HUNTER



When Tony Hunter returned to La Jolla in 1975, he bought a Volkswagen Beetle, which many Salk faculty members have borrowed over the years. In 2003, the Beetle hit 240,000 miles, the equivalent of a one-way trip to the moon.

Cambridge as a postdoc, a fire that started on a Friday night destroyed the lab he was working in and burned much of the adjoining room where the scientist kept their notes. Despite being burned and blackened, however, Hunter's notebooks remained legible and salvageable.

"It turns out you can see pencil writing even if the pages are totally black because it's a slightly different color," Hunter said. Although investigators could not determine the origin of the fire, Hunter believes it was caused by ether, which is extremely flammable.

Moreover, according to Hunter's longtime colleague Eckhart, the bearded biochemist can recall his notes on a whim.

"We had a job candidate at the Salk last year, and it turns out that

Tony remembered that this person's father had also been a job candidate some years before," Eckhart said. "So he took great pleasure in showing this guy the notes from his father's seminar."

### Beyond the lab

During his time in southern California, Hunter has taken an adventurer's spirit to the western states, hiking in the deserts, camping on deserted beaches, off-roading on the Baja peninsula and rafting rivers with all manner of rapids.

"I've enjoyed all the outdoor activities that are possible in California that are not available so easily in Europe," he said. "I still enjoy doing some of those things, although physically they're not quite that easy to do anymore."

Since 1972, Hunter has gone on 35 rafting trips in 10 rivers in Idaho, Washington, Oregon, California, Utah and Arizona, with many early members of his lab tagging along at least once.

"We went down a river called the Selway, and Tony had one of those big inflatable rafts that take about six people," Pines said. "He navigated the class IV and V rapids with aplomb." (Rapids are graded on a scale of I, which are swimmable, to VI, which are off limits and can be life-threatening even to expert rafters.)

Many of Hunter's trips have been on the Colorado River, through the Grand Canyon.

"I think the ultimate trip is rafting through the Grand Canyon," Hunter said. "It's a 230-mile

trip, and the maximum amount of time you can take, according to the permit, is 18 days. In the days before they instituted that limit, our longest trip was 28 days. I calculated that I have spent nearly six months at the bottom of the Grand Canyon over the years.”

**Pancreatic cancer and histidine horizons**

Though his laboratory, along with all others at the institute, is closed during California’s COVID-19 shelter-in-place order, Hunter continues

to analyze what he can from home, and he hosts journal club meetings with Salk cancer researchers on Zoom every Friday morning.

Hunter and his wife, Jennifer Price, have two sons; the younger, James, born in 1996, recently graduated from Virginia Tech with a degree in mechanical engineering and their older son Sean, born in 1990, recently defended his thesis at Stanford University. His project was to engineer a fragment of the leukemia inhibitory factor receptor to act as a ligand trap for the LIF cytokine,

which could then be used as a new therapeutic approach for pancreatic cancer, a topic Hunter has been pursuing in his own lab in recent years.

Hunter remains optimistic about the future of his research, which in recent years has begun to focus on both pancreatic cancer and histidine kinases.

“Right now, we think it’s still a little unclear what histidine phosphorylation does,” he said. “In some cases, it’s an enzyme intermediate, but in the other cases, it has regulatory effects ... like any new phosphorylation, you have to prioritize what to study, because it takes a lot of effort just to analyze one site. So we are trying to do that.

“I just got a seven-year outstanding investigator award from the NIH to study the role of histidine phosphorylation in cancer. So, I’ll be busy for a while longer.”

*Author’s note: Geoff Wahl and Ron Evans contributed information about Tony Hunter for this article.*

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IMAGE COURTESY OF TONY HUNTER

**In October 2018, Hunter dyed his beard purple for the Purple Stride San Diego walk, which raises funds for the Pancreatic Cancer Action Network.**



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A large, detailed electron micrograph of a coronavirus particle, showing its characteristic spherical shape and the crown-like surface proteins. The particle is rendered in shades of brown and orange against a blue background.

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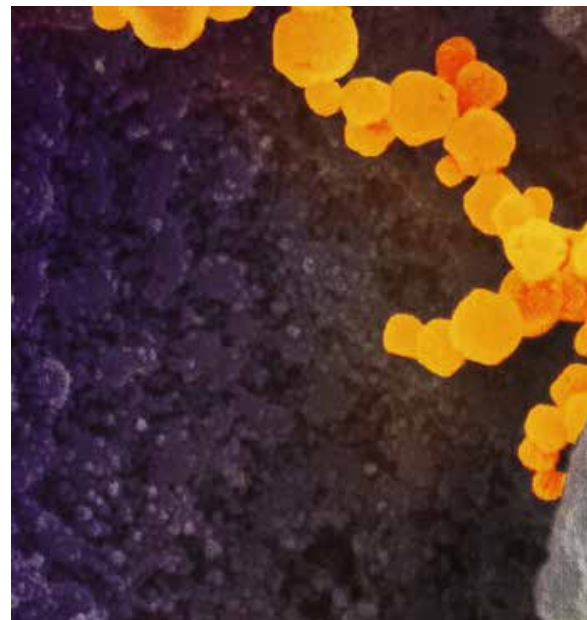
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# A SMALL ARMY OF RESEARCHERS RACES TO BUILD A CORONAVIRUS INTERACTOME

By John Arnst



As institutions shuttered across the U.S. ahead of shelter-in-place orders, Nevan Krogan’s lab at the University of California, San Francisco, raced to gather the last bits of data they needed to assemble a protein interaction map to identify drugs that might work against SARS-CoV-2, the virus that causes COVID-19.

“We actually collected the last sample for the map about six hours before they shut everything down,” said Krogan, a professor in the department of cellular and molecular pharmacology at UCSF and the director of the university’s Quantitative Biosciences Institute. “It was really a race against the clock, and it was a testament to the scientists in the lab essentially working for days on end without sleeping.”

In a study uploaded to the preprint site bioRxiv last week, Krogan and 93 co-authors list 69 drugs that might be effective in targeting COVID-19, the coronavirus that is testing the limits of healthcare systems and safety nets around the world. To identify these drugs, they built an interactome that showed how 332 human proteins interacted with proteins from 26 of the virus’ 29 genes.

“It’s a kind of a blueprint of how the virus comes in and hijacks and rewires the host during the course of infection,” Krogan said. “What happens is you put a hook on each one of (the viral genes) and you express the genes in human cells, and then what you do is pull out, fish out, the corresponding protein with that hook, and then you see by mass spectrometry which other human proteins are physically interacting or physically talking to the viral proteins.”

Krogan conceived and coordinated the collaborative effort, which was carried out by scientists from 22 labs at the Quantitative Biosciences Institute as well as from the University of Michigan, the University of California San Diego, the Icahn School of Medicine at Mount Sinai, the Howard Hughes Medical Institute, the Fred Hutchinson Cancer Research Center, the European Molecular Biology Laboratory and the Institut Pasteur. When it came to determining which drug targets could interact with the viral proteins, Krogan looked to UCSF chemists Brian Shoichet and Kevan Shokat.

“For the last 10 years, we’ve been working on getting drugs for undruggable targets,” Shokat said. “I looked in the map for weird targets that nobody thinks of as traditional drug targets.”

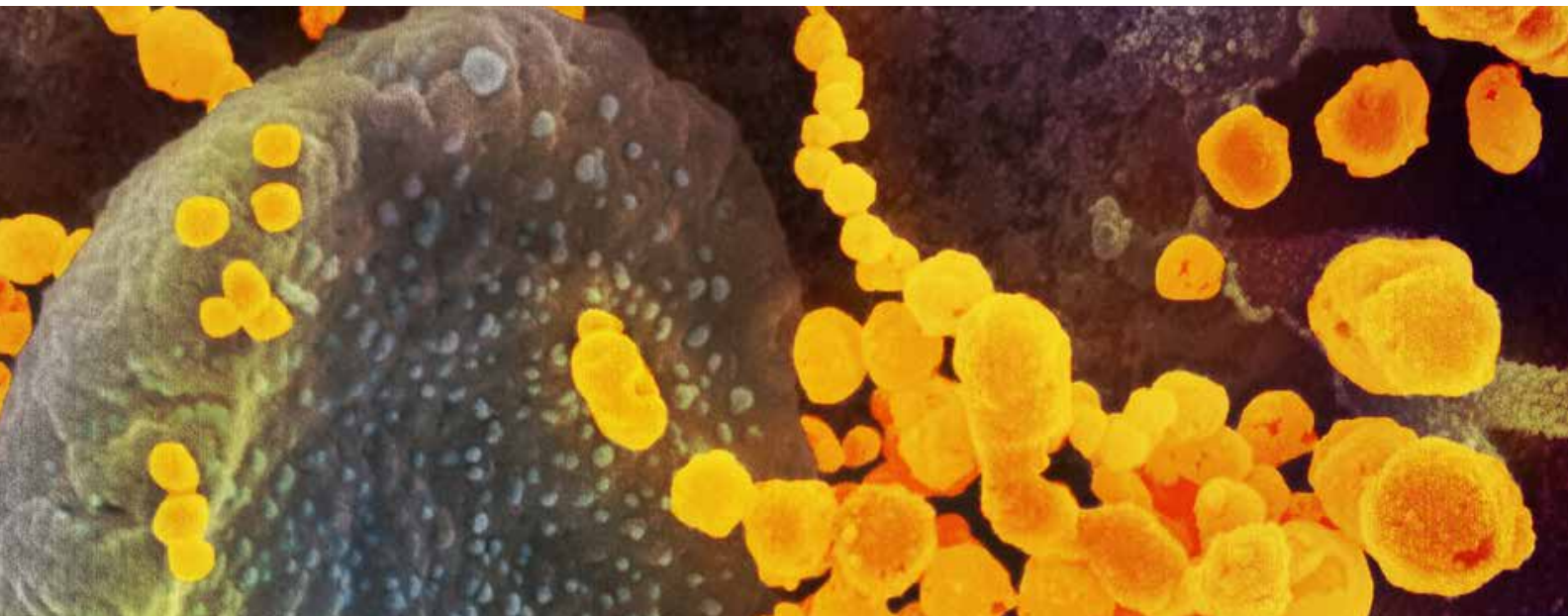
That meant the target list included not only the immunosuppressant rapamycin and the drugs chloroquine and remdesivir, which are being evaluated against SARS-CoV-2 in clinical trials around the world, but also cancer drugs such as dabrafenib and natural products such as WDB002, a cyclic polyketide synthase, that are being evaluated for clinical use.

All of those drugs are being evaluated against the coronavirus in the biosafety-level 3 labs at the Institut Pasteur in Paris. There, Marco Vignuzzi and his lab members, including postdoctoral fellows Bjoern Meyer, Veronica Rezelj and Cassandra Koh, must work one or two at a time due to the city’s continuing lockdown.

“We are currently testing 20 compounds,” Meyer said. “Overall, I think the whole panel will include something



NIAID/RML



**This scanning electron microscope image shows SARS-CoV-2 (round gold objects) emerging from the surface of cells cultured in the lab. The virus shown was isolated from a patient in the U.S.**

along the lines of 65 or 69 compounds.” Their efforts are being duplicated, for the sake of corroboration, by Kris M. White and Lisa Miorin at the Icahn School of Medicine at Mount Sinai in New York.

The collaboration includes researchers at UCSF who hadn’t previously brought their skills to bear on viral problems, such as structural biologist Natalia Jura.

“We were just so motivated to contribute that everybody really put on hold what they were doing ... and just started reading papers about coronaviruses and accumulating expertise in this area,” Jura said. “As a structural biologist, I was most interested in understanding what is known about how viral proteins interact with the host proteins.”

Most of the paper’s authors are now analyzing data remotely, with little access to their labs, according to Krogan.

“We’re having regular Zoom calls with scientists — I think last time there were 100 different scientists on the Zoom call discussing this map,” he said. Krogan and colleagues at the UCSF-affiliated nonprofit Gladstone Institute previously assembled drug interaction maps for HIV and for the Ebola, Zika and dengue viruses with much longer timeframes.

“Normally, that takes a few years,” he said. “Well, we expedited this for a couple of weeks. And that’s a testament in my opinion to the collaborative effort that was underway.”

Shokat is impressed by the speed with which the group was able to pull together its data.

“Usually we have six months, nine months to do

it. But here you had two weeks,” he said. “It was really outstanding. You just wake up at 7, work till 11 and then check your phone until it’s bedtime. It’s crazy, everybody’s spirit has been amazing.”

The scientists in San Francisco must work at a distance from each other and from their labs, but their colleagues in New York and in Paris continue to evaluate compounds against the coronavirus in their level 3 labs, the second-highest level of biosafety containment. As Krogan and colleagues whittle down their list of drugs, he hopes that even more scientists will take advantage of their interaction map to find new leads about both SARS-CoV-2 and drugs that might work against it.

“It’s a very rich data set, and they can make predictions about the biology of virus that we didn’t find, and they can also make predictions about other drugs and compounds,” he said. “What I’m hoping for here, the silver lining in all of this, is that we’re setting a new paradigm of how to do science. And hopefully, this infrastructure stays in place so that we’re in a better position to tackle the next pandemic.”

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# Could an old malaria drug help fight SARS-CoV-2?

By John Arnst

Chloroquine might be getting new life as an antiviral treatment for the novel coronavirus that emerged in Wuhan, China in late 2019 and has since become a pandemic with more than 2.5 million cases worldwide. For decades, the drug was a front-line treatment and prophylactic for malaria.

In a three-page paper published in early February in *Cell Research*, scientists at the Wuhan Institute of Virology's State Key Laboratory of Virology write that both chloroquine and the antiviral remdesivir were, individually, "highly effective" at inhibiting replication of the novel coronavirus in cell culture. Their drug screen evaluated five other drugs that were not effective. The authors could not be reached for comment.

Though the paper is brief, John Lednicky, a professor at the University of Florida's Emerging Pathogens Institute, found its results intriguing. "It's interesting in that it really lacks a lot of details but, nevertheless, if you look at the data as presented, at least in vitro, it seems like chloroquine can be used as an early-stage drug," he said. "It would be very good if these types of experiments were repeated by more laboratories to see whether the same results occur across the board."

Chloroquine is a synthetic form of quinine, a compound found in

the bark of cinchona trees native to Peru and used for centuries to treat malaria. Chloroquine was an essential element of mass drug administration campaigns to combat malaria throughout the second half of the 20th century, and remains one of the World Health Organization's essential medicines. However, after the malaria parasites *Plasmodium falciparum* and *Plasmodium vivax* began exhibiting resistance to the drug in the 1960s and 1980s, respectively, it was replaced by similar antimalarial compounds and combination therapies. Chloroquine is still widely used against the three other species of plasmodium and to treat autoimmune disorders and some cases of amebiasis, an intestinal infection caused by the amoeba *Entamoeba histolytica*.

Chloroquine's antiviral properties were explored in the mid-1990s against HIV and in the following decade against severe acute respiratory syndrome, or SARS, which is closely related to the novel coronavirus. In 2004, researchers in Belgium found that chloroquine inhibited replication of SARS in cell culture. The following year, however, another team at Utah State University and the Chinese University of Hong Kong evaluated a gamut of compounds against SARS replication in mice infected with the virus, finding that chloroquine was only effective as an

anti-inflammatory agent. They recommended that it could be used in combination with compounds that prevent replication. Nevertheless, in 2009, the Belgian group found that lethal infections of human coronavirus OC43, a relative of SARS, could be averted in newborn mice by administering chloroquine through the mother's milk.

Chloroquine raises the pH in host-cell lysosomes, which interferes with viruses' attempts to acidify the lysosomes, a prerequisite to formation of the autophagosomes that cells use to eat themselves. In the *Cell Research* paper, the researchers found that the drug was effective at inhibiting the virus as it was both entering and exiting cells.

Craig Cameron is a virologist at the University of North Carolina at Chapel Hill. "There is mounting evidence that many viruses hijack this cellular autophagy pathway for the good of the virus, but it is not completely clear why," he said. "From this, one can imagine chloroquine as an antiviral."

The second compound, remdesivir, is a nucleoside analog discovered in 2016 that inhibits viral polymerase activity, shutting down transcription and synthesis of viral RNA. This gives it antiviral activity against a broad range of retroviruses, including Ebola (for which the drugmaker Gilead developed and



tested it, unsuccessfully, during the 2018-2020 epidemic in the Democratic Republic of the Congo) and coronaviruses.

“The fact that this drug works against this virus is not unexpected, especially *in vitro*,” Cameron said. “Accumulation in the lungs to a level that is effective is likely the bigger issue as a therapeutic for humans.”

The Wuhan Institute of Virology submitted a patent Jan. 21 for the use of remdesivir to fight the new coronavirus in China; this may set up a battle with Gilead over intellectual property rights. In their filing, the institute noted that they did not apply to patent chloroquine phosphate because it has been marketed in China and has an extant supply chain.

Lednický is optimistic about the prospects for treating the new coronavirus with remdesivir and chloroquine.

“What’s important is that the selectivity index is relatively high for both of them,” Lednický said. “In other words, they’re not expected to have a lot of side effects.”

The biggest question regarding

chloroquine he said, is at how many days into an infection it can be effectively administered to someone sick with the new coronavirus.

“As an analogy, Tamiflu works very well against susceptible influenza A virus strains as long as you take it early enough,” he said. “And that’s what we have to determine with chloroquine, whether it can be used when somebody has been sick for more than a few days. But the indication so far, based on this paper and past work with SARS, is that it might be a useful drug.”

However, both chloroquine and its less-toxic derivative hydroxychloroquine, marketed as Plaquenil and prescribed to people with autoimmune disorders including lupus, do carry risks of cardiomyopathy and heart failure in patients who are both older and pre-disposed to cardiac disease.

Over the last two months, the potential usefulness of chloroquine and its less-toxic derivative hydroxychloroquine as treatments for COVID-19 has become a highly politicized subject following a flawed

clinical trial by the French microbiologist Didier Raoult that caught the attention of President Trump. In late March, a man in Arizona died after ingesting a form of chloroquine used to clean aquariums; according to his wife, who also ingested the cleaner and lived, they took it after watching a White House press conference in which the president touted its effectiveness. Additionally, many people with lupus and arthritis who rely on hydroxychloroquine are now facing shortages of the drug.

As some doctors on the front lines are using the drug — one of very few tools in their medical arsenals against COVID-19 — for patients at various stages of the disease, various clinical trials have been launched to evaluate its effectiveness against the virus.

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# Anatomy of a molecule: what makes remdesivir promising?

Experts weigh in on the chemistry of the potential SARS-nCoV-2 antiviral

By Laurel Oldach

The World Health Organization in late January convened experts to discuss experimental therapeutics for patients with the emerging coronavirus with no name, no vaccine and no treatment. The panel reported that “among the different therapeutic options, remdesivir was considered the most promising candidate.”

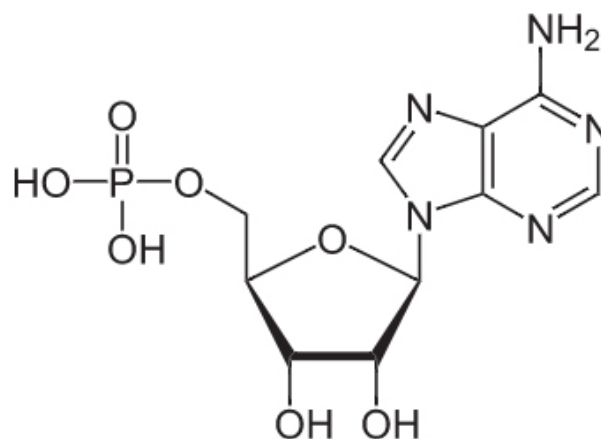
Within weeks, a clinical trial of the compound was underway in China. Results are expected in April; in the meantime, the outbreak of SARS-nCoV-2, the virus that causes COVID-19, has become a global pandemic.

Remdesivir is a nucleotide analog, one of the oldest classes of antiviral drugs. It works by blocking the RNA polymerase that coronaviruses and related RNA viruses need to replicate their genomes and proliferate in the host body.

The molecule originally was synthesized as part of a screen for inhibitors of the hepatitis C virus RNA polymerase. Its inventors at Gilead Sciences decided to move forward with a different nucleotide analog compound to treat hepatitis C. But RNA-dependent RNA polymerases are conserved between many viruses. Experiments in vitro, in cell culture and in animal models have shown that remdesivir has broad-spectrum activity against RNA viruses, including filoviruses (like the one that causes Ebola) and coronaviruses.

Remdesivir resembles the RNA base adenosine, shown here as a monophosphate.

The compound and ATP have some important differences, but some features are very similar. ASBMB Today spoke to medicinal chemist Katherine Seley-Radtke at the University of Maryland, Baltimore County, and structural virologist Craig Cameron at the University of North Carolina, Chapel Hill about what makes the molecule interesting.



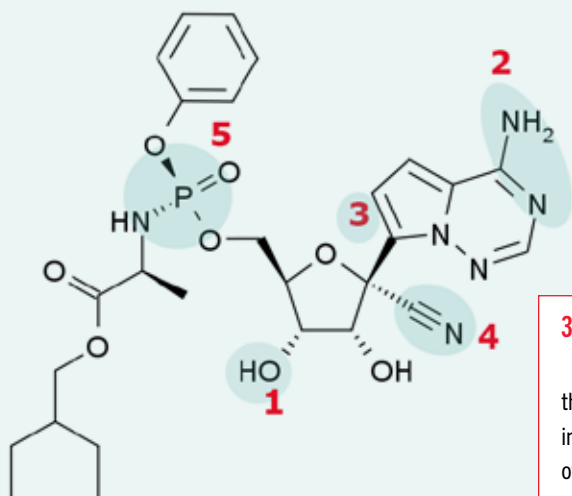
“ My whole career has had the RNA dependent RNA polymerase at the center of our studies, because it really is a very well validated drug target. —Craig Cameron ”



Craig Cameron



Katherine Seley-Radtke



### 1. 3' hydroxy group

Different classes of nucleotide analogs have different effects on polymerases. Remdesivir is in a class called nonobligate chain terminators, due to the presence of the hydroxy group at carbon 3 in the sugar. It should, in theory, be possible to add more nucleotides to a strand of RNA after remdesivir has been added.

“That hydroxy group is what is required for continued synthesis of nucleic acid, whether it be RNA or DNA,” said virologist Craig Cameron, who studies the interactions between nucleoside and nucleotide analogs and viral polymerases.

Recent research suggests that remdesivir, when mixed with coronavirus RNA polymerases *in vitro*, doesn't terminate the synthesis of a new RNA strand right away. Instead, Cameron said, “it takes a few cycles between nucleoside and nucleotide analogs and viral polymerases before you can see the termination effect.”

Those additional nucleotides may shield remdesivir from coronavirus proofreading enzymes that remove unnatural nucleotide analogs.

### 2. Base pairing to uracil

In adenosine in double-stranded RNA, this face of the molecule is involved in base pairing with uracil. The two nitrogens act as proton donor and acceptor, respectively, for hydrogen bonds to atoms in the uracil base.

Chemists think that remdesivir, by presenting a very similar binding face, gets incorporated into a growing RNA strand by viral polymerases.

### 3. C-nucleoside bond

Usually, the glycosidic bond connects the 1' carbon in the ribose ring to a nitrogen in the base. But in remdesivir (and some other nucleoside analogs) the sugar and the nucleobase are connected by a bond between two carbons.

“It definitely provides much greater stability (against) nucleases and other enzymes that can cleave the nucleobase from the sugar,” said Katherine Seley-Radtke, a medicinal chemist at the University of Maryland, Baltimore County who works on the design and synthesis of antiviral nucleotide analogues. With a C-nucleoside, “you'd have to break a carbon-carbon bond; whereas in a normal nucleoside you're breaking a hemi-aminal bond, which is far less stable. So having that carbon-carbon bond is a great advantage.”

### 4. 1' cyano group

Ask a group of chemists what jumps out at them about remdesivir, and most will start with this dramatic feature. Substitution at this carbon is unusual and probably possible only because of the strength of the C-nucleoside bond.

According to an article in the *Journal of Medicinal Chemistry*, the cyano group was initially added because a precursor molecule, monophosphate inhibitor of viral RNA polymerases, also blocked the mitochondrial RNA polymerase in mice. To make a molecule without such toxic side effects, chemists at Gilead tried a series of substitutions at the 1' carbon. The compound with the cyano group worked best: it still blocked the hepatitis C polymerase but was not incorporated by host-cell polymerases.

“You can't predict activity. You have to make it and test it,” Seley-Radtke said. “But even small changes can have amazing consequences.”

### 5. Phosphate

“You see all that flotsam and jetsam coming off at the 5' hydroxy?” said Katherine Seley-Radtke. Among medicinal chemists, this type of protecting group is casually known as “a McGuigan ProTide.” Designed by medicinal chemist Chris McGuigan in the 1990s, this type of protecting group and its variations are widely used to deliver nucleotide analogs into cells.

“It is a brilliant system, because it accomplishes two things,” Seley-Radtke said. “No. 1, an issue with nucleosides is that they're polar and their phosphates are even more polar.” Masking the highly negative phosphate groups with esters or amides reduces the molecule's overall polarity, letting it cross the plasma membrane into cells.

Second, to be recognized by polymerases, the analog needs to resemble a normal nucleotide triphosphate — which means it needs to be phosphorylated.

“The first phosphorylation, either by cellular or viral kinases, is oftentimes very difficult,” Seley-Radtke said. “A lot of those kinases are very, very picky in terms of recognition.” By arriving into the cell with its first phosphate already in tow, remdesivir and other nucleoside and nucleotide analogs and viral polymerases skip that rate-limiting step. After the protecting groups are cleaved, the nucleotide analog is a reasonable substrate for later nucleotide kinases.

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# SLIPPING PAST THE PROOFREADER

The virus family that causes SARS, MERS and COVID-19 has an unusual ability to evade treatment. Can new drug candidates overcome it?

By Laurel Oldach

Vials containing a solution of the nucleotide analog remdesivir are capped at a Gilead production facility.

In the early 2000s, when experts believed human coronavirus infection caused nothing worse than the common cold, Mark Denison struggled to land adequate federal grants to support his lab at the Vanderbilt University Medical Center.

A virologist and clinician, Denison had been studying coronaviruses since 1984, when only two of the seven coronaviruses currently known to cause disease in humans were known. Those two, along with several other coronaviruses, cause colds.



VANDERBILT UNIVERSITY MEDICAL CENTER

Mark Denison, a professor at Vanderbilt University Medical Center, has studied coronaviruses since the 1980s.

Denison initially found the virus he studied, which affects only mice, interesting because it leads to a mouse version of multiple sclerosis. Along the way, he became interested in how the virus replicated — but persuading funders to support his work was a real challenge.

In early 2003, he and his wife Laura were on vacation in Florida having a difficult conversation. “I think the work is important. I think the models are important,” he recalled saying. “(But) I don’t know if I can maintain a career.”

That was the day he learned about the pathogen behind the deadly respiratory disease SARS, which had been making headlines.

GILEAD SCIENCES

“I’m literally on the beach with my wife, and someone came down from the hotel and told me that I had a phone call,” he said. The call was from a colleague, sharing the news that the pathogen responsible for the disease had been identified, and it was a coronavirus.

Severe acute respiratory syndrome swept from southern China into 26 countries in 2002 and 2003, killing about 10% of the roughly 8,000 people it infected. Although the outbreak was contained, coronaviruses were recognized suddenly as a serious problem of potentially pandemic proportion.

Almost two decades later, the work done in Denison’s lab has turned out to be instrumental in developing a molecule, called remdesivir, that entered large-scale clinical trials just weeks after SARS-CoV-2, the coronavirus that causes COVID-19, was identified.

The molecule, it seems, can overcome coronaviruses’ superpower: their genome-proofreading ability. This ability isn’t found in other RNA viruses, and it makes coronaviruses resistant to a majority of drugs used against other RNA viruses.

When ASBMB Today went to print in mid-April, researchers expected to learn in the next few weeks whether remdesivir is an effective treatment for patients with COVID-19. In the meantime, Denison’s lab has continued to work to identify other molecules that might bypass viral resistance.

“This is a really key question for us: Is this a new class of drug that can allow us to better design more drugs that can bypass the proofreading function and inhibit the virus?” said Denison, who now directs the pediatric infectious diseases division at Vanderbilt.

### Not your average RNA viruses

Like many viruses that cause human disease, coronaviruses have a genome composed of RNA.

When the virus behind SARS was identified, one of the many experimental treatments clinicians tried using was a molecule



**Craig Cameron, a virologist at the University of North Carolina at Chapel Hill, studies RdRp molecular mechanisms in picornaviruses.**

called ribavirin. At the time, ribavirin was the first-line drug for many RNA viruses.

Ribavirin targets a viral protein called the RNA-dependent RNA polymerase, or RdRp, which is responsible for replicating the coronavirus genome.

Craig Cameron is a virologist at the University of North Carolina at Chapel Hill who studies RdRp molecular mechanisms in picornaviruses. “(RdRp) is a very well-validated drug target,” Cameron said. “And it is one of those targets that actually have the potential of having pan-viral antiviral activity.”

Ribavirin belongs to a class of antiviral drugs called nucleotide or nucleoside analogs.

Exactly how ribavirin works seems to vary from one virus to another, making it a good illustration of the many possible modes of action of nucleotide analogs. Some work by blocking the viral polymerase, terminating a growing strand of RNA. Some are mutagens, which slip into the growing viral genome, letting the polymerase continue, but introduce some molecular ambiguity to the next round of replication that causes a cascade of errors in later generations. Some block metabolic enzymes, preventing the synthesis or processing

of real ribonucleotides and thereby slowing down replication.

A systematic review of data from 30 clinical trials, conducted after the SARS epidemic, showed no conclusive benefit of ribavirin — or any other treatment that was tested — and some evidence that ribavirin had done patients harm.

Ribavirin was the first example. Since then, most nucleotide analogs tried against coronaviruses that cause SARS and Middle East respiratory syndrome, or MERS, have not been effective treatments. Referring to ribavirin and the classic nucleoside analog 5-fluorouracil, which works as a mutagen, Denison said, “Coronaviruses are completely,



**Bruno Canard started new research programs at the French National Centre for Scientific Research after the SARS outbreak.**

entirely resistant to those drugs. You can soak them in it, and they have no effect.”

### **Vigorous viral proofreading**

Bruno Canard is the principal investigator of a viral replication group at the French National Centre for Scientific Research. Before the SARS outbreak, Canard had focused on the structure–activity relationships of nucleotide analogs used to treat HIV and other viruses. Like many virologists, he was inspired by the near miss with SARS to start new research programs.

“We were surprised that ribavirin was pretty toxic and not very effective (against coronaviruses,” Canard said.

Both the CNRS team in Marseille and Denison’s group in Tennessee set out to understand more about the virus that caused SARS, and one of their major questions was why ribavirin, broadly effective against other RNA viruses, had failed against this one.

The answer lay in the virus family’s large genome and how it evolved to protect itself.

“The reason (RNA viruses) are thought to be so successful is because their polymerases make mistakes,” Denison said. “They lack the ability to correct mistakes, so they generate mutant swarms of viruses that are ready for adaptation in different environments.”

Structural biologists describe RNA-dependent RNA polymerases as resembling a cupped hand, with the fingers and thumb protecting the enzyme’s active site. As each new nucleobase in the template strand enters the active site, the polymerase coordinates a new incoming ribonucleotide by matching it against its counterpart in the existing strand. If the fit is right, the enzyme catalyzes a bond formation in the RNA backbone. If the fit is close enough, many viral RNA polymerases will catalyze a bond anyway. An error rate that can be as high as one mistake per 10,000 bases lets those mutant swarms arise. But for coronaviruses, the replication error rate is lower.

Coronaviruses have some of the longest genomes in the RNA viral world. Whereas their closest cousins have genomes averaging 10 kilobases, coronavirus genomes are three times as long. With so much genetic material to copy, if coronaviruses mutated at the same rate as other RNA viruses, they would accumulate so many mutations that they would barely produce any viable progeny.

As researchers in the field came to understand the coronavirus RdRp better, they found that the polymerase by itself could not explain the disconnect. Virologist François Ferron, a staff scientist at CNRS, has worked on coronavirus replication since the SARS outbreak. “The viral RNA polymerase is quite





**Virologist François Ferron, a staff scientist at CNRS, has worked on coronavirus replication since the SARS outbreak.**

loose, meaning it has a tendency to make a lot of mistakes,” he said. “Maybe a little bit more than the regular (cellular) RNA polymerase.”

This led researchers to suspect that coronaviruses might have some way of recognizing and correcting errors.

An international team conducting a study of the SARS viral genome identified a number of potential RNA-processing enzymes based on their homology to other known enzymes. In 2006, Canard’s group worked with members of that international bioinformatics team to show that one of those enzymes, like its homologs, could cleave double-stranded RNA and was required for successful viral replication.

“There was a speculation that (coronaviruses) might encode a proofreading function that would allow them to stabilize a big genome, and there was a predicted place in the genome where that might occur,” Denison explained. “That really led us to try the genetic experiments.”

In 2007, his group found that in viruses lacking the protein encoded at that same location, a protein called nsp14, coronaviruses from a mouse model virus accumulated mutations at a rate similar to other RNA viruses. And strains of the virus without nsp14, they found, were sensitive to ribavirin.

Following up on that work, the French group zeroed in on how nsp14 worked in a test tube. “We didn’t work on the virus, like Mark Denison was beautifully doing,” said Canard. “We just concentrated on that enzyme ... and we found out that it could actually excise ribavirin.”

The CNRS team published an enzymology study that confirmed that nsp14 can identify and remove mismatches between bases at the end of a growing copy of viral RNA; in 2018 they followed up with confirmation that when ribavirin is incorporated in a growing RNA strand, nsp14 protein can scoop it out of the stalled strand, letting replication resume.

As the researchers worked out the enzymology, a pressing question arose: Did their findings mean that all nucleotide analogs would be useless against coronaviruses?

“This question is actually key right now in the development of nucleoside analog inhibitors,” Canard said.

### Evading viral proofreading

This is where remdesivir comes in.

“From my perspective, the (remdesivir) story started in 2013,” Denison said. “We had discovered that coronaviruses encode the only known RNA proofreading system ... (and) I wanted to test whether there were any nucleosides out there that could be active in the setting of coronavirus proofreading.”

Denison heard from Cameron about a research collaboration with Gilead Sciences. Cameron was working on understanding the precise mechanism of action of a group of nucleotide analogs the company was using to treat hepatitis C, an RNA virus that infected tens of thousands of people each year.

Before the race to drug hepatitis C, according to Adrian Ray, a medicinal chemist who used to work at Gilead, “The nuc space for RNA polymerases and for RNA viruses was really not heavily explored.”

In the course of trying to beat competitors to the lucrative hepatitis C market, Gilead had developed a large library of RNA-dependent RNA polymerase inhibitors, including the molecule that would come to be known as



**Maria Agostini, a grad student in Mark Denison's lab, was one of the researchers who worked on remdesivir.**

remdesivir. A compound closely related to remdesivir had made it to early clinical tests for hepatitis C, but had faltered, in part because like remdesivir it needed to be administered by injection. Gilead changed strategies, buying a biotech startup to gain access to the startup's orally available nucleotide analog, which became a key component of Gilead's hepatitis C cocktail.

Working with the RNA-dependent RNA polymerase from poliovirus, Cameron had begun work that would show that the molecule was a non-obligate chain terminator, a type of nucleotide analog that the polymerase ought to be able to incorporate into a growing strand and keep going — but could not.

Intrigued, Denison contacted Gilead to ask permission to try that approved drug, called sofosbuvir, against mouse coronaviruses.

“That was their world-changing drug that cured hepatitis C,” Denison said. “They weren't going to let a little-known virologist working on a coronavirus use their drugs.” But after a series of introductions by Cameron and several discussions, Gilead agreed to let his lab work with a different series of molecules, the ones that had been developed in-house and shelved for hepatitis C. They had shown promising results in early studies as a candidate treatment for other viral infections, including against Ebola virus.

The candidate molecules arrived. Denison and his trainees had no idea what they were. But they went ahead and tested them. What they found was exciting: In mouse cell culture, the drugs could block coronavirus replication.

“So we asked our Gilead collaborators, ‘What is that (compound)?’ They said, ‘We’re not going to tell you, but we’re going to send you 60 prodrugs, chemical modifications of the same compound,’” Denison said.

One of that second batch of molecules proved to be remdesivir. Graduate student Maria Agostini, who had recently joined Denison's lab, was one of the researchers who worked on understanding its strong activity.

“We’ve worked with a couple of potent compounds, but remdesivir was really one of the first I had worked with,” Agostini said. “When you were looking at the cells, you could visually see less evidence of viral replication going on.”

Whereas cells in her control dishes were visibly infected, suffering bad cytopathic effects, the cells treated with remdesivir after infection survived well. By growing many generations of the virus in cells treated with subtherapeutic concentrations of remdesivir, selecting for mutations that would let the virus evade the drug, Agostini and colleagues Erica Andres and Clint Smith demonstrated that it would take mutations in the viral poly-



**Mathias Götte's lab in Canada has studied how remdesivir works on polymerase enzymes from the MERS coronavirus.**



**In a remdesivir production facility, Gilead employees work in personal protective equipment.**

merase to confer resistance to remdesivir — and that those mutant viruses were less able to infect hosts than the wild type.

Gilead supplied the drug free of charge, and the National Institutes of Health funded the researchers through a program aimed at developing treatments for emerging infectious diseases.

“This points out the value of collaborative science,” Denison said. “This was a company that committed to helping us do this when no one was interested in coronaviruses, and a grant mechanism that allows some flexibility in terms of expanding it.”

Recently, Mathias Götte’s enzymology lab in Canada has looked at how remdesivir works on polymerase enzymes from the coronavirus that causes MERS. Researchers in Götte’s group determined that the compound stops the polymerase, acting as a chain terminator — but not immediately.

Andrea Pruijssers, a virologist who directs the antivirals research program in Denison’s group, said, “(Remdesivir) somehow evades recognition by the proofreading enzyme.”

Instead of stopping the polymerase as soon as it is incorporated, remdesivir seems to let



**Andrea Pruijssers directs the antivirals research program in Mark Denison’s group.**

the enzyme keep going for a few more cycles but then causes it to stall. Researchers suspect that the molecular stumble may be caused by an unusual structure in the template-copy RNA duplex.

“They think that, at that point, the nucleoside analog that has already been incorporated is shielded from the proofreading enzyme,” Pruijssers said.

COURTESY OF ANDREA PRUIJSSERS



Members of the Denison lab at a less pandemic time: (Left to right) Maria Agostini, Jim Chappell, Jennifer Gribble, Andrea Puijssers, Laura Stevens, Tia Hughes, Mark Denison, Xiaotao Lu.

In the lab of Denison’s longtime collaborator Ralph Baric at the University of North Carolina, Chapel Hill, researchers found that remdesivir was an effective treatment for mice infected with SARS. Those results were promising enough to advance remdesivir into a study of MERS in monkeys, published in February by researchers at the Rocky Mountain Laboratory of the NIH. The drug showed some benefit in reducing the severity of the illness, provided the monkeys were treated prophylactically.

In terms of drug development, remdesivir “has sort of met every milestone along the way, from our perspective,” Denison said.

**Similar drug class, different result**

When Puijssers started in the Denison lab in 2017, they had another molecule to investigate, beta-D-N4-hydroxycytidine, or NHC for short, that was being tested at the Emory Institute for Drug Development as a potential broad-spectrum antiviral drug.

Agostini led the first study of that drug as well, showing its activity in tissue culture. In March, researchers from the Baric and Denison labs published a followup in *Science Translational Medicine*, showing that NHC can block replication in the viruses that cause MERS and SARS — and also the coronavirus

that causes COVID-19.

“It’s interesting,” Puijssers said. “(NHC) doesn’t act as a chain-terminator. It incorporates into the genome and then causes lethal mutagenesis.”

Through its ability to base-pair with more than one nucleotide in the complementary strand, NHC introduces a cascade of errors in successive rounds of replication. Eventually, viral progeny don’t have the information they need to make a new virus.

Whereas remdesivir stops the polymerase in its tracks, causing few new mutations, deep sequencing experiments in the few viruses that emerged after NHC treatment showed that the drug causes numerous mutations.

“We identified two compounds that structurally fall into the same class of nucleoside analogs but act very differently on coronaviruses,” Agostini said.

They were particularly encouraged because the work showed that NHC has some therapeutic efficacy in the mouse model of MERS — and that it can block even remdesivir-resistant strains of coronavirus.

In an interview in early March, Puijssers said NHC was still relatively untested as a therapeutic. “It’s hard to develop a mutagen, because the FDA doesn’t usually like the idea of mutation unless it’s for a life-threatening disease.”

But the pandemic changed things. Emory has partnered with Miami biotechnology company Ridgeback Biotherapeutics to develop the molecule, and Emory has filed an application with the U.S. Food and Drug Administration for permission to begin first-in-human trials to test the molecule's safety in humans.

Denison described the pivotal role Agostini played: "In five years of graduate school, Maria tested and developed the detailed in vitro analysis on two potential drugs to treat this pandemic coronavirus — and got them all the way through that in vitro preclinical development."

It's a remarkable and highly unusual feat. Drug development is known for its high failure rate. Of course, many drug candidates that appear promising in preclinical studies falter in large human trials.

### Facing the pandemic

After arguing for a decade that the world must be ready for a pandemic, Denison said in early March, it was strange to be facing it.

"It's really weird that we worked on this for the past six years, and the drugs were just getting through, and they were just ready to go," he said. "We'll see what the outcome is."

He has some concerns about how to interpret data from clinical trials testing how well remdesivir works for COVID-19 in humans, the first of which were expected to be released

in April as a trial at the China–Japan Friendship Hospital in Wuhan concluded. (Other trials, sponsored by Gilead, the NIH and the World Health Organization, launched later.)

First, animal data from other coronaviruses suggest that the drug is most effective when it's delivered prophylactically, after the animals are exposed but before they begin to develop symptoms. In the context of a global pandemic, this would be difficult to achieve in humans. At some point in the course of infection, an extremely strong immune response begins to do more harm than the virus; at that point, Denison said, it may be too late for an antiviral to help.

Second, the data from the first few trials are likely to be nuanced and require careful interpretation — which Denison worries public discourse is not well prepared for. Early human trials of remdesivir's sister compound in hepatitis patients showed dramatic differences among individuals in antiviral response, and remdesivir itself showed limited benefit compared to other candidate therapies in a clinical trial in Ebola patients. "People tend to have a winner or loser mentality," he said. "They've called remdesivir 'that failed Ebola drug,' right? It didn't fail in the Ebola trial; it just wasn't advanced because it didn't show as much benefit as the other two compounds."

Whatever the outcome of clinical trials of remdesivir and NHC, Denison said he hopes this crisis will underline the importance of funding research into potentially pandemic viruses before outbreaks begin.

"Trying to maintain basic investigations and drug development against something that's a high, high, high impact but low, low, low probability is really hard in our world. Really hard," he said. "We've just never given up on this idea that we had to have these things ready and have them in the bucket."

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Denison, pictured in January with the spring 2004 issue of the Vanderbilt University Medical Center's Lens magazine.

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# Scientist uses community organizing skills to mobilize researchers against COVID-19

By Laurel Oldach

**A**round the world, scientific researchers are seeking ways to channel their abilities and energy in the fight to contain the spread of COVID-19. When Michael Wells, furloughed from his laboratory and wanting to help, launched a national volunteer database, it took off quickly.

“I think it’s grown about 100 people since we started talking,” Wells, a postdoctoral fellow at the Broad Institute in Boston, said 15 minutes into a phone interview on March 20, just two days after the online questionnaire for the database was launched.

## Building a database

Twelve years ago, Wells ran the Obama primary campaign on his college campus at the University of Notre Dame and, during the summer, he worked for Obama in Ohio. Using skills honed during his time as a campaign volunteer and an Obama fellow, Wells and an ad hoc team of collaborators have recruited more than 8,300 researchers who want to contribute to the COVID-19 effort.

The list includes volunteers’ locations, laboratory experience, access to supplies that could be donated and — by request, for vetted public health organizations only — names and contact information. Wells and his team are now tackling the more

difficult task of putting the list into the hands of people who need it.

This isn’t Wells’ first experience responding to a disease outbreak. In 2015, as a postdoc starting out in a lab that studied brain organoids, he had planned to work on autism. But then the Zika virus outbreak spreading from Brazil to other parts of North and South America began to make headlines. With much of his extended family living in El Salvador, Wells said he saw “an opportunity for me to not only learn all these new techniques, but also potentially do something that could have a direct impact on people in my life.”

After four years of postdoctoral research and several publications on Zika and the developing brain, Wells recently began to consider seeking a faculty job. But once again, a virus changed his plans. Scrolling social media feeds for news about the pandemic after his laboratory shut down, Wells saw calls from diagnostic labs in other parts of the country for people with molecular biology skills. He waited a while for something similar to pop up in Boston but then decided to build it himself and, while he was at it, to make a tool that could be used across the country. He recruited musician friends to promote it on social media.

Word spread quickly. Now, with

thousands of volunteers registered and the tide of new arrivals slowing, Wells and colleagues he met during a stint as a Society for Neuroscience policy fellow are working to make local governments aware of the resource.

## Local responses

With vacillating federal government leadership, much of the country’s response to the COVID-19 epidemic is happening at the state and local level. Wells sees that reflected in how he has distributed the volunteer database to those who might be able to use it.

“It seems like individual counties in individual states are responding differently to the virus,” he said.

For some, that is a source of some comfort. Derek Crowe, a graduate student at the University of Rochester is working to coordinate local volunteers with the health department.

“I actually trust the local government a lot more than the national government to get things done,” he said. Seeing local government, healthcare workers and hospital staff working around the clock “indicates to me that there is leadership that approaching this situation with seriousness and professionalism.”

With the situation changing rapidly, it can be difficult for members



**Michael Wells is using the community organizing skills he learned in an election campaign to build a database of researchers who want to help in the fight against COVID-19.**

of the public to find current information on testing. Crowe said that doctors in his area are only testing people with symptoms, because of a shortage of diagnostic supplies.

“If the issue isn’t that there aren’t enough tests but that there aren’t enough human resources to get them done, we want to be able to fill that gap,” he said.

Monroe County, New York, where Rochester is located, has two large universities, and most of the volunteers in the area are graduate students or principal investigators at the University of Rochester or Rochester Institute of Technology. According to Wells, who lives in Boston, the larger concern is for less densely populated areas with a lower concentration of universities and biotechnology companies.

Already, a public health laborato-

ry in Island County, Washington, in search of laboratory personnel and a hospital administrator in Laurel, Mississippi, who needed help sourcing UV lamps have requested access to regional subsets of the database. That diversity of purpose, Wells said, is part of the point.

“We don’t know what they are going to need it for; they don’t know what they are going to need it for yet. The focus is on getting it into their hands and letting them figure out the best way of activating all this scientific energy.”

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COURTESY OF MICHAEL WELLS

**“If the issue isn’t that there aren’t enough tests but that there aren’t enough human resources to get them done, we want to be able to fill that gap.”**

## Researchers retool genomics labs to provide virus testing

By *Laurel Oldach*

**R**esearchers at San Francisco's Innovative Genomics Institute announced on March 30 that they were opening a COVID-19 testing center able to provide at least 1,200 tests each day for patients in San Francisco. The IGI is one of several academic institutes whose laboratories have switched focus to contribute to the COVID-19 response.

Labs that conduct high-throughput genome sequencing at IGI, Boston's Broad Institute and San Francisco's Chan-Zuckerberg Biohub retooled recently to provide clinical testing for SARS-nCoV-2, the virus that causes COVID-19. These overhauls by volunteer scientists and administrators added capacity for thousands of tests and rapid turnaround time to help public health departments determine how many people are infected.

Jennifer Doudna, a professor at the University of California Berkeley and a Howard Hughes Medical Institute investigator, founded and leads the IGI.

"Imagine setting that up — a process that would normally take months to years — in a couple weeks. It's really extraordinary," Doudna said in an IGI press release.

Doudna and colleague Fyodor Urnov, also a UC Berkeley professor and a technical director at the



**Postdoctoral fellows Enrique Shao and Jenny Hamilton work in a converted diagnostics lab, now being used for COVID-19 testing, at the Innovative Genomics Institute in San Francisco.**

IGI, put out a call for volunteers in mid-March after hearing about the diagnostic testing effort at the neighboring Biohub. Within hours, 800 members of San Francisco's biomedical research community, mainly graduate students and postdocs, responded.

Jenny Hamilton, a postdoctoral fellow in Doudna's UC Berkeley lab, led the technical team that transformed the genomics core into a clinical testing laboratory, and validated the test results, in just two weeks.

"The room that we're using was previously part of a genomics core facility on campus, and because of that it had some robotics for high-throughput experiments already installed," Hamilton said. "Because the campus is shut down

and nobody's doing high-throughput sequencing experiments right now, we've been able to quickly reconfigure the room."

Using liquid-handling robots and reagents bought and donated from multiple sources, Hamilton and her team set up and validated a mostly automated pipeline for extracting RNA from patient samples and conducting a standard reverse transcription polymerase chain reaction, or RT-PCR, assay for SARS-nCoV-2. Advisers from industry helped the researchers program the robotic pipeline.

Some widely used reagents, such as disinfectant and qPCR master mix, have been difficult to come by. According to Alexandra Amen, another postdoc in the Doudna lab who helped run the lab-conversion



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effort, “The hardest thing is sourcing materials that are in low supply.”

As testing began, volunteer researchers planned to operate the diagnostic lab, testing samples collected from patients at UC Berkeley’s medical center and other hospitals in San Francisco’s East Bay. They hoped to return results of 1,200 to 4,000 tests daily within 24 hours, improving on turnaround times that Kaiser Health News reports reported could take three days to a week. As for funding, the team said through a spokesperson, “We hope to fund the IGI’s testing lab through donations to enable us to serve those without insurance.”

Ordinarily, the institute focuses on genome engineering. Its research programs work to isolate new CRIS-

PR systems from microbes, improve genome editing tools, genetically engineer crops and diagnose human diseases.

“All of our laboratories do PCR every day,” Doudna stated in the IGI release. “But for this test we need to go above and beyond to ensure we can provide accurate detection.”

Researchers didn’t know initially whether the effort was entirely legal. Clinical laboratories must be licensed by state and federal governments to ensure that they report valid results. But given the COVID-19 public health emergency, the IGI release stated, the Centers for Disease Control and Prevention, the U.S. Food and Drug Administration and the California Department of Public

Health have relaxed some restrictions on who may test for and report new cases of the novel coronavirus.

Nonetheless, some logistical barriers remained in place as ASBMB Today went to print in mid-April. The journal Nature reported on April 9 that even as California testing pipelines remained backlogged, many hospitals had declined free diagnostic testing from the IGI because the lab lacked software that commercial diagnostic labs use for electronic health records.

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# “We are doers. We want to get involved.”

## How basic scientists at University of Washington contributed to diagnostic testing for COVID-19

By *Laurel Oldach*

The basic science laboratories at the University of Washington School of Medicine in Seattle are under the same roof as the clinical care facilities but separated by long hallways. In early March, when Seattle was the first American hotspot but before Washington’s governor issued shelter-in-place orders, those halls were very quiet. Faculty members and trainees with children and those at high risk of contracting COVID-19 shifted to remote work, and the remaining scientists carefully avoided close contact.

“It’s a really weird combination of intense emotional distress and being deserted. Normally, I think, when a place is deserted, it’s empty of emotion, too,” said Sharon Gordon, the university’s associate dean for research and graduate education.

At a time when normality felt like a distant memory, Gordon became one of many basic scientists helping with an unusual effort: recruiting volunteer scientists to help keep diagnostic labs running during Seattle’s COVID-19 outbreak.

### Reassigning basic scientists

Normally, basic scientists and clinical lab workers overlap very little. Because of federal regulations, diagnostic tests must be carried out

by government-certified laboratory technicians. However, testing rates for the novel coronavirus SARS-nCoV-2 lagged badly in the United States compared with other countries. As the number of people with respiratory symptoms grew, demand for testing strained the university’s laboratory medicine department.

The first shortage was hardware; the interim chair of the pathology department circulated a request for specific PCR machines early in March.

In subsequent weeks, the lab’s personnel became overwhelmed. As the university prepared to launch a drive-up testing center, Gordon said, “there was the recognition that the state testing lab, in combination with the university’s testing lab, just didn’t have the capacity — and that outside-the-box thinking was going to be necessary.”

Luckily, the UW community includes a large number of scientists who know their way around a thermocycler. After consulting with faculty and department chairs, the dean of research sent an email on March 12 requesting volunteers under age 40 to help out in the labs at the department of laboratory medicine.

The diagnostic tests themselves still had to be performed by certi-

fied technicians. But the roughly 150 volunteers — most of whom are graduate students, postdoctoral fellows or junior faculty — helped with ancillary tasks, from restocking shelves to logging samples as they enter the lab.

“Something that’s very heart-warming is everybody pulling together within the University of Washington to make this happen,” said Paul Scott, the chair of the university’s pharmacology department. “It started with an idea, and it’s expanded very quickly into action.”

Meanwhile, other members of the University of Washington community found ways to contribute to the outbreak response. Rapidly-developed message boards within the UW community matched healthcare workers in need of childcare and people at higher risk of infection with delivery needs to people who want to help. Research labs crowdsourced reagents and coordinated donations. The stringent Food and Drug Administration protocols that clinical laboratories follow often specify the manufacturer and type of reagents or consumables that may be used. One Friday, the UW virology department put out an urgent request for pipette tips; that Saturday morning, it reported that donations from academic groups, including



an influenza surveillance study, had allowed it to continue diagnostic tests until a manufacturer's shipment came in.

Before Washington's governor issued a shelter-in-place order on March 23, Gordon said, the advice to stay at home and avoid social

contact was difficult for the scientists she knows to follow, even though its importance was clear. "We are doers. We want to get involved," Gordon said. "But if you put 100 people in a room to get involved, you would be spreading the virus."

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



# On the front line: Pandemic insight from a health care worker

By Justin R. Lovett

**W**orking in a hospital emergency department in the midst of a pandemic, I am learning a new routine. As COVID-19 numbers increase in Texas, our protocols get stricter. The state had more than 7,300 confirmed cases on April 6, and we have seen dozens at the hospital where I work. Our infectious disease team is working diligently to ensure the safety of the staff, so our protocols are changing continuously.

Before the pandemic, I got dressed at home and then drove to the hospital for my shifts as an emergency medicine technician. Now, I have to wear civilian clothes to the hospital and then change into scrubs and put on shoe covers, a surgical mask and a surgical cap. At the end of the shift, I change back into my civilian clothes and go home, strip those clothes off at the laundry, shower and put on fresh clothes. Then I am free to walk about my house. I do this to contain any potentially infectious particles I may have come into contact with.

The personal protective equipment described above is standard for interacting with any patient, whether or not they show COVID-19 symptoms. If you enter the emergency department with a toothache, you'll see us wearing scrubs, shoe covers, caps and masks. This is for safety so we do not spread particles from our previous patients to new ones. PPE, always important, is essential during this crisis; however, faced with shortages everywhere, we are rationing our PPE gear.

When I am caring directly for a patient who shows symptoms and meets criteria for COVID-19 testing, I have to wear a gown, gloves, an N95 respirator, boot covers, shoe covers over the boot covers, goggles, a hood, a face shield and a surgical mask over the respirator. This is a lot to put on each time you enter a patient's room.

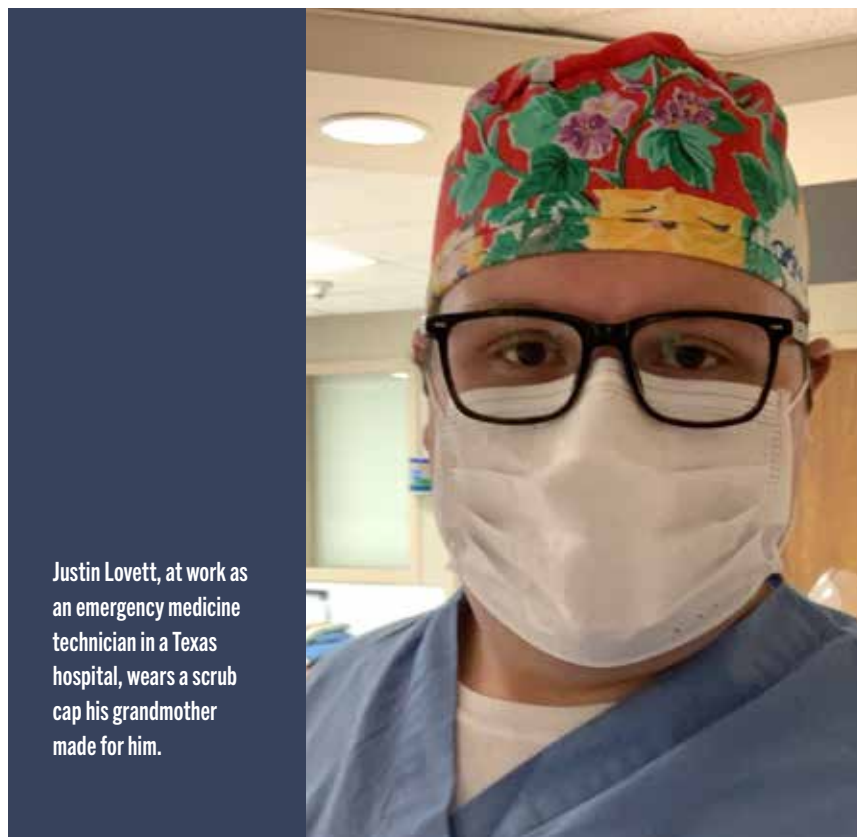
Most health care workers share a concern about what happens when we run out of PPE: When we can no longer wear PPE with infectious patients, what do we do? Already, we get one single-use surgical mask for a 12-hour shift. That mask provides standard droplet protection. However, when we have COVID-19 patients at the hospital, we need to take precautions against both droplets and airborne particles. N95 respirators are the most secure protection against infectious particles. The hospital allots a single N95 mask for 8 hours of use. We pick and choose when we wear them, because we cannot order any more.

We have a strict no-visitor policy in the ED; all patients and staff are screened prior to entry, even patients coming in on an ambulance. The screening includes a temperature check and a questionnaire; the results determine which patients need to wear a surgical mask. Before we had the screening process, patients would grab handfuls of masks and leave with them. Each employee gets a dated sticker that we must display stating we have been screened on the current day.

As the number of patients increases, emergency departments and critical care units have become overcrowded, and we have extra staff on standby. In the month of March, I worked a total of eight shifts. In April, I am working 16 shifts to help with this influx of patients.

I sometimes feel it is a matter of "When will I contract this virus?" as opposed to "I hope I don't contract this virus." That's an ominous feeling. The community has been incredibly supportive of the ED staff, sending us food and other tokens of appreciation. Though the feeling is ominous, it is reassuring knowing we have the support of our community.

In addition to working on the front line in the ED, I am a student, and the pandemic also has affected how my classmates and I learn. This semester, I am enrolled in 18 hours of coursework ranging from Biochemistry II to Calculus. It has been a struggle for students and professors to transition these intensive courses to a distanced platform and ensure the same quality of instruction. The professors have been amazing and continuously check in on us along the way. Now we have lecture videos and Zoom office hours. My main concern beyond adjusting to an online platform is my senior research. Research is an integral part of our curriculum in the chemistry department. Before spring break, I was in the purification process of important samples for my senior thesis, which had to stop. Luckily, I am working with a sturdy protein, so my fingers



JUSTIN LOVETT

Justin Lovett, at work as an emergency medicine technician in a Texas hospital, wears a scrub cap his grandmother made for him.

are crossed that I'll return to viable samples. Otherwise, it's back to square one of purification.

Working increased shifts in the ED means more time away from loved ones. We have to keep our distance because we work in a high-risk environment and do not want to infect anyone. We don't know how long this will last. I wonder sometimes when normalcy will return. Because of my work, I made the cautious decision to remain away from my family. I have not seen them in person for a couple of weeks, and I wonder when I will get to see my siblings, nieces, nephews and parents.

I look forward to the day when we can all gather around the fam-

ily table for Mom and Grandma's Southern home cooking, to laugh, play games and hug one another like we used to do. We all communicate daily via group message and the occasional phone call. This time has been especially hard on my parents, who have four children working in health care. We've planned a group Facetime so we can see each other. My grandmother is keeping busy by making us all scrub caps.

I am thankful for my team in the emergency department. We took an oath to put patients first and to help others. That is what we are doing, working diligently to provide the best care we can to all patients. We take risks caring for COVID-19 patients,

and we make sacrifices.

This new reality has taken an emotional and physical toll on all health care workers. However, we are banded together as a community to help fight this pandemic.

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**Justin R. Lovett** is a senior chemistry major at Stephen F. Austin State University and serves as the recruitment chair for SFASU's ASBMB Student Chapter. Justin works in Odutayo Odunuga's lab, where he enjoys researching the biophysical properties of protein structure and function. He plans to pursue an academic career in biophysical chemistry.



# Quarantined thoughts

By Makayla K. Portley & Marya S. Sabir

**W**e used to think science stopped for no one and nothing, but now that feels only partially true. During these uncertain times of mandated social distancing and a 24-hour COVID-19 news cycle, we've been reflecting on how different our lives are compared to four weeks ago.

Back then, we were in the lab working diligently on finishing confirmatory PCRs for a large whole-genome sequencing study and organizing patient samples for another large study. Now, our days are filled with daily 9 a.m. lab meetings via Zoom, other conference calls (so many virtual platforms — and let's be honest now, we all have a favorite), learning bioinformatics, and making loaf after loaf of fresh sourdough bread (yum).

As we do our best to navigate these unprecedented times, we remember the intimate idiosyncrasies of being a bench researcher and how much these are tied to our identities as scientists. Each researcher has a unique set of senses with which we perceive the fascinating world of bench science. Here are some sensory wet lab experiences that we're missing during our mandatory telework days.

### Sight

- We miss the fluorescent lighting of the lab, even though it usually causes us headaches after about four hours.
- We miss seeing other passionate scientists (AKA fellow nerds). Our political science major friends don't share the same zest for neurological disease research wormholes.



COURTESY OF MAKAYLA PORTLEY

With her lab closed for now, Makayla Portley can spend more time in her kitchen baking tasty treats.

- We miss the sight of the qPCR machine generating its multicolored curves in real time. Even when the experiment fails, it's still pretty.
- We miss the way that our tube racks look when they're finally organized and all oriented the same. exact. way. It takes dedication, but it is fulfilling.
- We miss the sight of the lab's messy benches after a hard day's work.

### Smell

- We miss the aroma the autoclave produces during its cycle, which is mysteriously similar to bread baking.
- Quite inexplicably, we miss the faint scent of mice coming from the behavioral testing room.
- We miss the smell of Trizol.

- Just kidding, no one ever smells Trizol because it is always used in a perfectly ventilated fume hood through which no odor escapes ... And we don't miss it.
- We miss the smell of the baked goods shared in the lunchroom by our wonderful lab mates. Another chance to smell baked bread.
- We miss the odor of rotten eggs and burnt rubber — oh wait, that's just beta-mercaptoethanol being used outside the hood.

### Touch

- We miss the cool benchtop on a warm day.
- We miss the weight of a pipet in our hands.
- We miss the weird feeling of hand sweat inside our non-latex gloves (not that much, though).

- We miss our itchy, too-warm lab coats.
- We miss holding hundreds of tubes as we attach adhesive labels to the lids. We suspect this fondness will be short-lived when we return to the lab.

## Hearing

- We miss the sounds of our Maxwell extracting DNA from brain tissue (it's just normal machine sounds for which the exact onomatopoeia is not yet coined).
- We miss the sound of the cell counter focusing. We don't know why, but it's such a specific, whirring sound that holds a special place in our hearts.
- We miss the sounds of scientists

excited about successful experiments: gasps or general praise of science, cells, an antibody — whatever is involved.

- We miss hearing the freezer beeping madly to alert us that it's gotten slightly too warm. Coincidentally, that sound also haunts our dreams.
- We miss the only sound in the lab at 2 a.m. — the hissing of liquid nitrogen tanks in the corridor. We only recently realized this wasn't coming from lab ghosts.

## Taste

We miss the taste of the gummy bears that come with our primer orders from Eurofins.

Beyond that, we're hoping this one doesn't apply to anyone these days since mouth-pipetting is strongly frowned upon.

Here's to being able to do bench science again — soon.

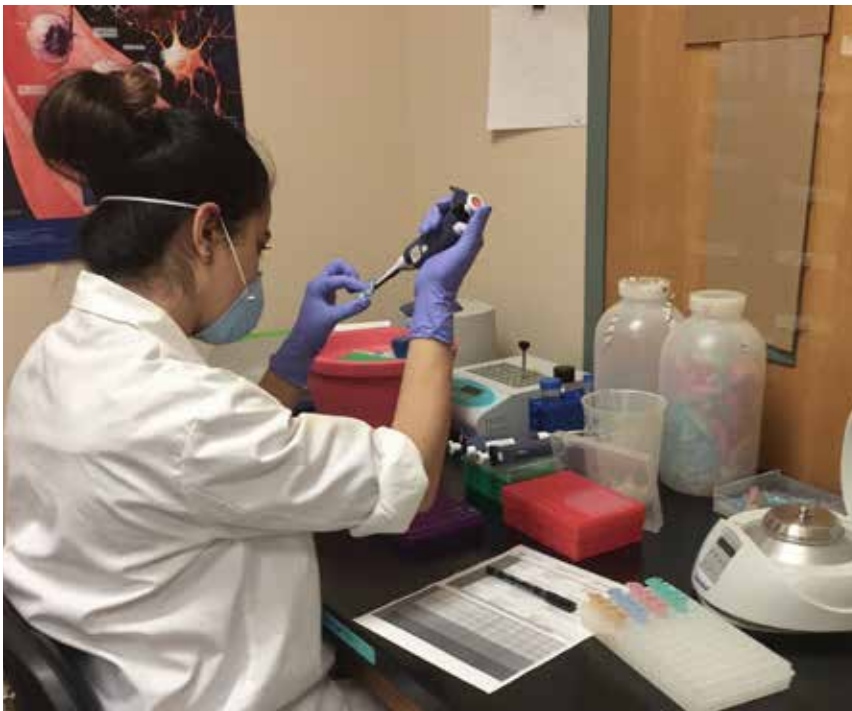
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COURTESY OF MARYA SABIR



Marya Sabir works in the lab before the COVID-19 pandemic shuttered her institution.

**“We miss holding hundreds of tubes as we attach adhesive labels to the lids. We suspect this fondness will be short-lived when we return to the lab.”**

# A new city, a new job and a global pandemic

Plus, a natural disaster for good measure

By *Elizabeth Stivison*

**O**n the evening of Feb. 27, my friend Germaine and I finished packing up my U-Haul. We hugged my roommates goodbye, and, along with my dog, Milo, piled into the truck to leave New York City.

I'd lived for seven years in Upper Manhattan while earning my Ph.D. at Columbia University and nearly my whole life within a few hours' bus ride of the city. As much as I complained about NYC, it was my home. I felt excited, but also a bit nervous, to be leaving to start my postdoc at Vanderbilt University.

As we drove away, I was filled with love for my community and neighborhood that I was leaving. What I didn't know was that my new city and new postdoc life would be nothing like I expected. Within a few weeks' time, I would narrowly escape a devastating tornado, and the COVID-19 pandemic would turn the world upside-down.

### Three weeks earlier

"Milo got out of his leash and ran away!" my dog sitter, breathless from running, told me on the phone. I was down in Nashville looking for an apartment.

Panicked, I hung up, bought the first plane ticket home, and immediately started calling people I knew from the dog park. I called Katie, whose small Muppet-like dog likes to wrestle with Milo; she went to look. I called Trena, whose big

stubborn dog lets Milo lick his face. She had just arrived home from a trip and was jetlagged, but she went to look too. I texted Kelly, owner of a big curly-furred puppy. She was out of town, but her husband and daughter went to look. I called my roommates, my friend Joy (by then in tears) and my neighbor Amanda. They all looked. My labmate and friend Amr drove down from the Bronx to look in his car.

Suddenly, it seemed like every dog owner and friend in my neighborhood was looking. Numbers I didn't even recognize were texting me where they were looking. A group text emerged. As I sat in my hotel, waiting until it was time to leave for the airport, people were updating each other on who had seen Milo and where.

"He's in the northwest corner of the playground, but he ran off."

"Saw him running north from the subway stop."

"Oh, Milo! That little white dog? I know that dog! The girl loves him so much," a guy at the corner bodega told my friend.

Roger, the owner of a golden retriever who Milo loves, looked until almost 2 a.m., even though he was flying to Mexico a few hours later.

Around 5 a.m. the next day, as I was in the airport waiting for my flight, the texts and updates started again. By the time I landed, I was armed with maps of Milo sightings.

I finally spotted him in a ceme-

tery, and he came running when he saw me.

I texted the group and everyone was overjoyed and relieved. I felt like I was George Bailey in the end of "It's a Wonderful Life," when his friends and family come together to save him. My pup, the little goofy love of my life, had been saved by my community.

But, unlike George Bailey, I didn't earn this support in any real way: I never saved any bank from the Depression or helped anyone buy their home.

And, perhaps stupidly, I was leaving this caring community in a few weeks for a new job.

### Welcome to Nashville

Germaine and I arrived at my new apartment in Nashville on March 2. We piled all my boxes in the living room, set up my bed and an inflatable mattress for her, returned the U-Haul and went to sleep.

During the night, I woke to the sound of sirens. "Man, I was really hoping Nashville would be quieter than New York City," I thought.

In the morning, everyone was texting me: my mom, my old roommates, my friends. "I heard there was a tornado in Nashville. Are you OK?" I told them all I was fine.

I went into the living room and said, "Germaine, I think there was a tornado last night ... nearby." We looked on the map together and saw





Elizabeth Stivison poses with her dog, Milo, in front of the U-Haul she used for her move to Nashville.

that it was about 3 miles from us. “I didn’t know that’s what those sirens meant!” I said.

Welcome to Nashville!

The next day, after saying goodbye to Germaine, I heard on the radio about a case of COVID-19 in New York, and it was near where I used to live and work. I texted my former roommate, Katherine.

“I know! It’s starting ...,” she wrote.

“Wash your hands!” I told her.

### Amenities for making acquaintances

My apartment in New York had been a four-bedroom, so I knew I’d want to be able to see people in my new building in Nashville. I also knew I’d need a dog park nearby so that Milo could play and get his

energy out and so I could meet other dog owners. I chose a building with common rooms, a café, an office with Internet and a coffee machine, next door to a big dog park.

I was excited to meet people and see what the Music City was like. I decided I’d help after the tornado by supporting local businesses by my patronage. I went to an art event and met a sweet and kind couple whose street was destroyed by the tornado, but somehow their house was undamaged. We exchanged numbers and planned to meet up soon.

I went to the dog park each day and slowly began meeting people. I loved the feeling of arriving and finally recognizing faces, dog and human. I exchanged numbers with a few people and made plans to bring

our dogs at the same time.

### Things changed quickly

On March 13, my former lab-mates forwarded me an email that said: “The hospital has a critical need for surgical masks ... for all labs that have surgical masks, please bring them down ... there will be a box for depositing them when you enter the suite. PLEASE BRING THEM NOW.”

The next day, they texted me that the lab at Columbia was closing.

I emailed my new boss at Vanderbilt to make sure I could still come in on Monday for my first day of work. He said I could but that the labs might close soon, so I should start thinking about remote projects and only do minimal lab work that was

## PERSPECTIVES

essential to my project.

March 16: My first day of work in my new lab! Also the first day my old lab at Columbia was officially shut down.

“I think the lab will be closed soon,” my boss told me.

I started making cell lines to use later, and Vanderbilt banned Ph.D. students from coming in.

My apartment building closed all the common rooms, and the city closed the dog park.

On March 22, the mayor of Nashville issued a safer-at-home order. I texted another postdoc in my lab, “What does this mean for lab?” She didn’t know.

Our PI told us that, so far, Vanderbilt considers labs essential. As a lab, we decided a few things.

First, that we will try to not overlap in lab. Second, that we will probably be shut down soon, though we don’t know when. Third, that we’ll have Zoom lab meetings once a week to keep us all connected. “So we don’t come back in a few months a bunch of strangers!” our PI said.

After learning how to do tissue culture, I started going into lab every few days, always checking to make sure no one else would be there, and did my work alone. When I couldn’t figure something out, I’d Zoom with my boss and show him my problems.

“Is this the correct media?” I’d ask, holding the bottle up to the camera.

One of the few times my boss and I were in lab at the same time (we both wore masks), he was teaching me how to freeze cells for liquid nitrogen storage, and while waiting for the media to be ready, he told me about his daughter.

“She’s been bugging us to get a pet. She wants a dog so badly. But we agreed she could start with a mouse,” he said.

“You should get her a hamster instead!” I said with conviction. “Mice are stinky. Hamsters don’t stink as much. I always had hamsters

COURTESY OF ELIZABETH STIVISON



Elizabeth Stivison, at left, her friend Germaine and Milo take a selfie on their way to Nashville. “We took several days for the drive down and explored the snowy forests in Virginia, a cider brewery in Asheville, North Carolina, and hiking trails in the Smoky Mountains,” Elizabeth wrote. “This picture is from our motel in the Smokies, which were beautiful even in winter.”

growing up.”

He laughed, and we resuspended the cells in freezing media, to be stored in liquid nitrogen. “Now, these have to go at -80, overnight, then they can be moved to LN2 tomorrow,” he said.

### Starting to feel familiar

I occasionally take the bus to the lab instead of walking, and I am always the only rider. The driver, under his mask, usually smiles at me and recognizes me. “Hello again!” he says when I get on. “You done for the day?” he says when I see him again on my way home.

One time I asked him, “Many other people out today?”

“Well, including you, I had three people on the bus today.”

One day, a person I recognized from the dog park waved when he saw me walking Milo. We walked together, staying six or more feet apart. His store has closed. We let our dogs play.

I thought of my friends in New York and how our lives are extremely different now. People were dying and hospitals overflowing there. And there I was in a sunny park, chatting almost normally.

### Lab community from afar

On our lab’s first Zoom meeting, we talked about how the lab will probably have to close soon, but again, none of us knew when. It felt a little like “Goodnight, Wesley, sleep well. I’ll most likely kill you in the morning,” from “The Princess Bride.”

After our PI told us what he was working on, he said, “Also, I’m basically home-schooling my daughter. I’m with her from 8 to 12, and my wife is with her from 12 to 4. And also, I have to finish this hamster cage I started building.”

“A hamster cage! You got a hamster!” I said. I was so happy my advice was taken seriously, even if it wasn’t science-related advice.

“Yes, her name, or his, I’m not sure, is Hamilton.” He sent us all a photo of the light brown fuzzy critter.

Milo then walked into the room and started to chew my backpack straps. “Hey, Milo, don’t eat that please,” I said.

“Is that your dog? Show us your dog,” they said.

I turn the laptop to capture Milo, careful to hide the pile of still-unpacked boxes and miscellaneous mess around my living room. Everyone “aww”ed at his cute face.

When it was my turn to share, I talked about making my new cells lines and trying to get a handle on the literature. “It’s a little frustrating,” I said, “because I’m used to reading papers in my field and understanding them. I keep having to read these over and over again, not getting it.”

“You know, text me or call me with any questions,” my boss said. “Ideally you’d be reading in lab and could just pop into my office with questions.” I left the lab meeting feeling less alone.

After the meeting, I saw that Milo had, in fact, chewed through my backpack strap. I tied it back together, temporarily fixing it, but the knot came out the other day.

### Fear from a distance

On April 2, my former labmates at Columbia texted about an email they had received from a professor involved in coordinating the university’s response to COVID-19. It asked for volunteers to transport patients at the hospital. There are too many patients, and the hospital can’t afford to let doctors and healthcare workers walk away to transport patients.

“The fact that basic scientists are being asked to serve in a patient-facing role underscores the seriousness of the situation at the hospital,” the email stated. “I honestly never thought that this would happen. The need is real, but so are the risks. Think this through.”

My instinct was to tell them all, “No, don’t do it!”

One labmate texted me, “I don’t know what to do. I want to help, but I’m also scared. I’m scared that, in an emergency situation, I won’t understand what people want me to do.” English is not her first language, and I can imagine that urgent orders coming from mouths hidden beneath masks might make it really hard to understand what to do and where to go.

I told her I understood and that she didn’t have to go.

### ‘You lazy slacker’

I really like my new lab, as weird as things have been, and want to do a good job here.

“I’m not doing my best, though,” I said, on the phone to my sister. “I feel so stupid. I’m not understanding stuff quickly and not focusing. I read papers and just nothing sticks. I’m really afraid of disappointing my new boss! And I don’t want my boss to regret hiring me. You know they say when Isaac Newton was sent home to quarantine during the plague, that’s when he discovered some basic physics laws, right? I’m such a disappointment to science!”

My sister, always able to see through bullshit, replied, “You mean you aren’t doing your best in a new city alone in the middle of an unprecedented global pandemic and economic disaster? I can’t believe it! God, Beth. You lazy slacker.”

It made me feel a little better.

## Far from danger?

My friends in New York are facing a terrifying situation that I am not a part of. I feel like I abandoned them during this impossibly hard time. I text my sympathy, but it isn't quite the same. I watch the numbers in the news articles climb.

Here, I'm waiting for something. Waiting for things to get worse, or waiting for things to get better. Waiting for the lab to close, and waiting for the lab to reopen. Waiting for the outbreak to hit us like it's hitting New York, or waiting for proof that our social distancing is saving us from that outcome.

I hear more about healthy people dying from the virus in NYC, and I

wonder if I might be one of them if it gets bad here. I wonder who would take care of Milo if I had to go to the hospital.

I am, technically, quite alone. "I'm sorry you had to move here to a new city and then not be allowed to make any friends," my PI tells me. But, somehow, I don't feel fully alone.

Whether it's the bus driver who recognizes me, the dog owners who wave, the Skype and Zoom calls with my lab here, or friends in NYC, I feel OK here. An up-in-the-air type of OK, though.

I sit here in a type of limbo, with my heart and mind open, knowing it will get both better and worse.

If we survive this, then one day this empty lab in the empty building will be my work home, this apartment building with its closed rooms near the closed park in this city full of closed stores and restaurants will really become my home, and these people I see occasionally and from a distance and through screens will become my friends.

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**ASBMB**

## COVID-19 Special Edition Podcast

ASBMB Public Affairs Director Ben Corb interviews members of the community about their experiences with the ongoing pandemic.

**PIPETTES & POLITICS**

[asbmb.org/career-resources/online-resources](https://asbmb.org/career-resources/online-resources)

# Is more science the medicine we need to cure the world's struggling economy?

By *Maurizio Crestani*

As part of “Life in the time of COVID-19,” I reported on the situation in Italy for the ASBMB Today website in the middle of the COVID-19 outbreak in mid-March. Here I am, some six weeks later, to share more thoughts.

When I first wrote, Italy was completely closed, except pharmacies, hospitals and food stores. Milano, usually a very active and alive city, was like a desert. My university was closed; teaching, meetings, exams and thesis defense were being done via teleconferencing. I was working from home, and my research team was using the time to analyze data from our experiments, running bioinformatic analyses of our RNA-seq

and ChIP-seq experiments.

As you have probably heard, the situation here in Italy is slowly getting better, but we are aware that the pandemic is far from over. Intensive care units no longer are overcrowded, as they were a few weeks ago. People are starting to think that we could gradually return to our jobs. As I write this in early May, the lockdown is being partially lifted.

Nonetheless, we must be cautious, as we have learned that this virus is a tricky one: We have found out that people who are positive for the virus but show no symptoms will be a real problem. According to some studies performed in small communities in selected areas of Italy,

asymptomatic SARS-Cov-2–positive subjects turned out to be much more numerous than we expected, and they may have contributed substantially to the spread of the virus. Not that it's their fault, of course, but there's no doubt we need to identify them in order to prevent other uncontrolled waves of the infection.

We also need to verify who has been exposed to the virus and has developed antibodies, although we still don't know whether we develop immunity after infection. And of course, we need medications and a vaccine. In Italy, studies are underway to test different therapeutic options, such as infusion of plasma from hyperimmune subjects who were pre-



LUCA VOLPI / WIKIMEDIA COMMONS

The facade of the headquarters of the Università degli Studi di Milano, as seen from the garden of Largo Richini.

## ESSAY

viously infected by the virus and were successfully cured, an antibody against IL-6 used in rheumatoid arthritis, antivirals for Ebola and more. We are also testing vaccines in collaboration with other countries. One vaccine seems quite promising and, if safe and efficacious, it will be produced by a big pharmaceutical company adopting a not-for-profit model.

In an unpredictable emergency, science and scientists are doing their best to find solutions to benefit the entire community. We hope the new knowledge stemming from this effort will be available not only for one country but worldwide.

We must also face another challenge: The world economy has been struck hard by a tiny microorganism, and that financial crisis is a threat for the near future. I am not an economist, but I am sure that one recipe to help fight the economic crisis

and loss of jobs around the world could be investing in fundamental research. Basic science is the engine that moves the pipeline of innovation and new technological developments, and we need new ideas for creating jobs and helping to fight the economic depression resulting from the pandemic.

I worry that politicians may forget or underestimate the importance of investing in basic science in any field, from biomedical research to engineering to physics. For this reason, I think we should launch a call for increased funding in scientific research, as an investment to counteract the financial crisis in all countries.

The American Society for Biochemistry and Molecular Biology could help start a planetary initiative aimed at convincing politicians and governments to increase

research funding. The members of the ASBMB have the energy, the resources and the contacts to start this initiative. Scientists around the world should subscribe to a manifesto calling for funding fundamental science as an investment in the planet's future and a prosperous economy that could benefit societies at all levels. Because, after all, we are one world.

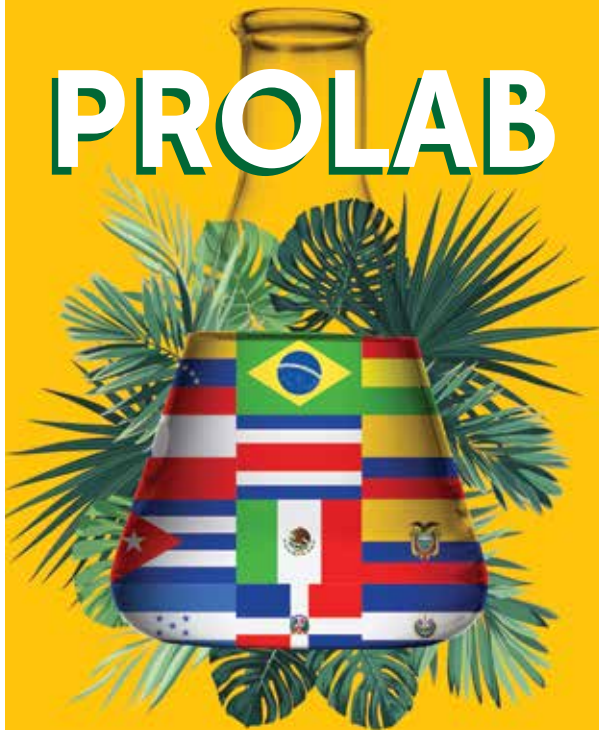
I'd like to hear from my ASBMB colleagues about this proposal. We must be creative and take steps to realize the dream of a better world. Science can certainly help do so.

Cheers from Milano!

**Maurizio Crestani** ([maurizio.crestani@unimi.it](mailto:maurizio.crestani@unimi.it)) is a professor of biochemistry at the Università degli Studi di Milano. His research focuses on epigenetic regulation of adipose tissue physiology in the context of obesity and Type 2 diabetes.



# PROLAB



## PROMOTING RESEARCH OPPORTUNITIES FOR LATIN AMERICAN BIOCHEMISTS

The Promoting Research Opportunities for Latin American Biochemists (PROLAB) program allows Latin American graduate students and postdoctoral fellows to spend up to six months in U.S. or Canadian laboratories.

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# CLASSIFIEDS

## Benjamin Goldberg Professor and Head of the Department of Biochemistry and Molecular Genetics Member Company, UIC College of Medicine



The University of Illinois College of Medicine invites nominations and applications for the position of Benjamin Goldberg Professor and Head of the Department of Biochemistry and Molecular Genetics (BMG). BMG has 20 faculty members with active research in a variety of areas including biochemistry, epigenetics, structural biology, gene expression, and signaling. BMG faculty employ model organisms and innovative genetic and biochemical approaches to study fundamental mechanisms, and perform translational research to treat human diseases. In this role, the new Head of BMG will have the opportunity to build upon the strengths and catalyze the expansion of the Department.

[careers.asbmb.org/job/benjamin-goldberg-professor-and-head-of-the-department-of-biochemistry-and-molecular-genetics/53242179](https://careers.asbmb.org/job/benjamin-goldberg-professor-and-head-of-the-department-of-biochemistry-and-molecular-genetics/53242179)

## Assistant Professor - Immunology-Immune Signaling, University of Nebraska-Lincoln Department of Biochemistry



Within the center, UNL is seeking applicants for a nine-month (academic year) tenure-leading Assistant Professor faculty position (75% research and 25% teaching) in the Department of Biochemistry addressing the sequence of immune signaling events that are activated in individual cells following the association of cell surface molecules during cell-cell contact and the relationships to the detection of soluble molecules of either host or pathogen origin. The ideal candidate will also have expertise in computational immunology that would deploy system-wide quantitative data to probe immune-system functions using metabolomics, proteomics and/or transcriptomics. The deployment of such technologies would be expected to provide novel integrative analyses that would transform such data into valuable biological insights of immune system function.

[careers.asbmb.org/job/assistant-professor-immunology-immune-signaling/53738920/](https://careers.asbmb.org/job/assistant-professor-immunology-immune-signaling/53738920/)

## Instructor - Physical Chemistry Tennessee Technological University Department of Chemistry



The Department of Chemistry at Tennessee Tech University invites applications for an Instructor of Physical Chemistry position available at Tennessee Tech University. The department offers an ACS-certified undergraduate degree as well as a master's degree in chemistry and will begin transitioning to a new, state-of-the-art science building during the 2020-2021 academic year. This is a one-year temporary, non-tenure-track appointment to begin August 1, 2020.

[careers.asbmb.org/job/instructor-physical-chemistry/53707946/](https://careers.asbmb.org/job/instructor-physical-chemistry/53707946/)

## Postdoctoral Research Associate (Glycobiology/Biochemistry/Microbiology) University of Kentucky



The Department of Molecular and Cellular Biochemistry at the University of Kentucky is recruiting post-doctoral fellows to study structure, biosynthesis and function of cell wall in pathogenic streptococci: *Streptococcus pyogenes*, *Streptococcus mutans* and *Streptococcus agalactiae*. These projects will utilize cutting-edge microscopy techniques, protein expression and purification, GC-MS analysis of cell wall composition, construction of bacterial mutants and molecular biological and biochemical techniques (PCR, cloning, western blot, etc).

[careers.asbmb.org/job/postdoctoral-research-associate-glycobiologybiochemistrymicrobiology/53430309/](https://careers.asbmb.org/job/postdoctoral-research-associate-glycobiologybiochemistrymicrobiology/53430309/)

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