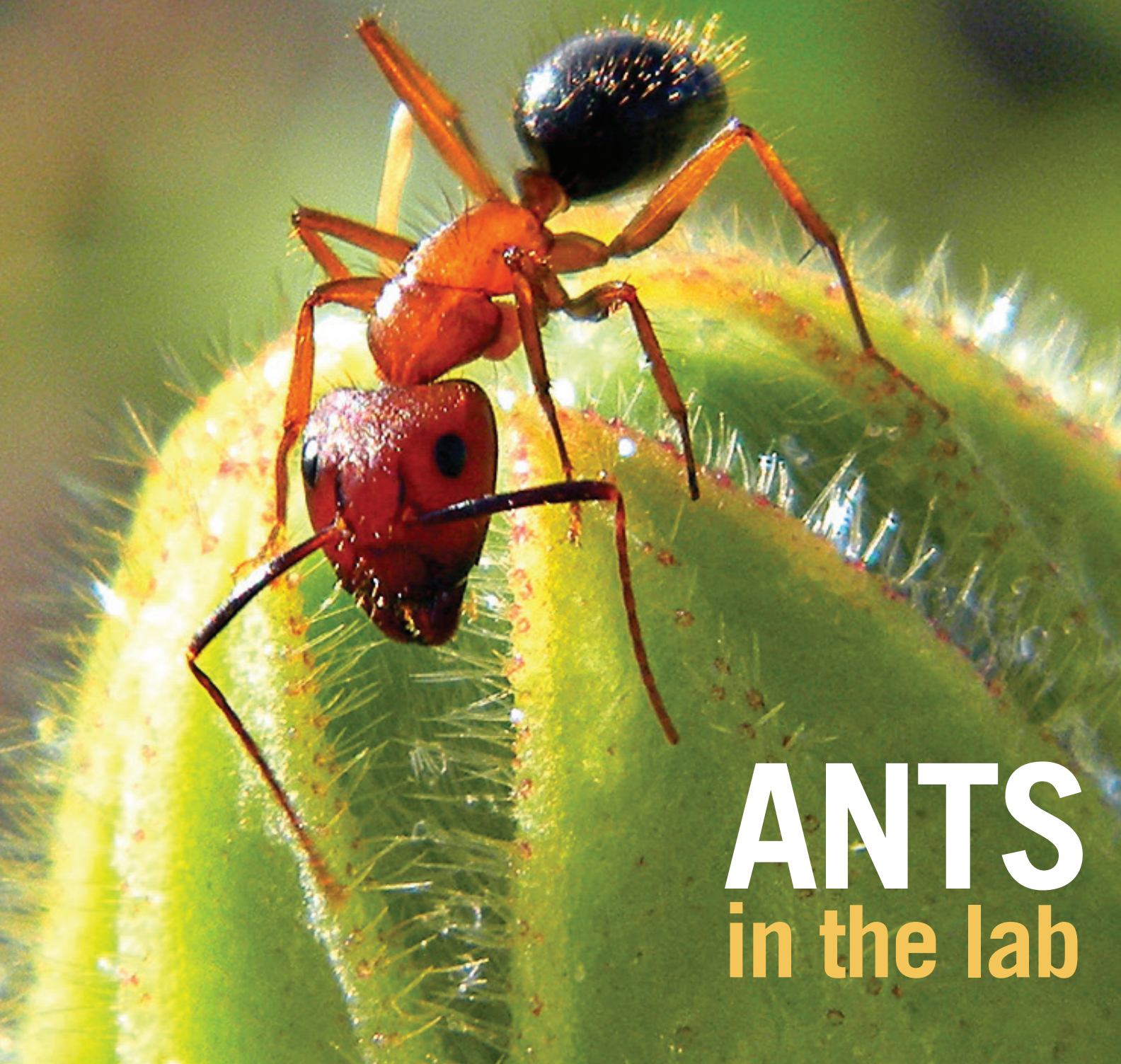


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ASBMB TODAY

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NEWS

2

EDITOR'S NOTE

Ending an elemental year

3

PRESIDENT'S MESSAGE

Beware the unintended consequences of mandatory open access

5

MEMBER UPDATE

10

RETROSPECTIVES

10 *Roberta F. Colman (1938 – 2019)*

14 *Sydney Brenner (1927 – 2019)*

18

NEW MEMBERS

20

LIPID NEWS

Crystal building blocks of triglycerides

21

YEAR OF (BIO)CHEMICAL ELEMENTS

Rounding out the year with nickel and zinc

22

JOURNAL NEWS

22 *Tor comes to the fore in autophagy*

24 *Paving the way for disease-resistant rice*

25 *Secrets of fat and the lymph node*

26 *When prions are personal*

28 *From the journals*

ON THE COVER

A carpenter ant climbs on the bud of a native sleepy hibiscus at Sweetbay Natural Area in Palm Beach Gardens, Florida.

BOB PETERSON/WIKIMEDIA COMMONS

FEATURES

34

ANTS IN THE LAB

Using social insects to study behavior and aging

42

OXYGEN SENSING AND ALTITUDE

Semenza shares 2019 Nobel Prize

48

GIFT GUIDE



PERSPECTIVES

56

NIGHT SHIFT

The nightlife of a scientist–mother



ANNUAL MEETING

51

2020 MEETING TO HIGHLIGHT JLR JUNIOR ASSOCIATE EDITORS

RAY BLIND	52
ROTONYA CARR.....	53
BRANDON DAVIES	54
GISSETTE REYES–SOFFER	55

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Ending an elemental year

By *Comfort Dorn*

Readers of a certain age may remember Tom Lehrer's song "The Elements," in which the then-Harvard math professor and musical satirist pattered-sang, a la Gilbert and Sullivan, the name of every element in the periodic table.

When I was a musical theater nerd in high school, I co-directed a musical revue in my senior year. The other directors and I thought we had the whole thing precast, but during auditions, a hitherto unremarkable singer bowled us over with her rendition of this serious tongue twister. (I'll link to a video of Lehrer singing it on the ASBMB Today website so you can hear for yourself how impressive this was.) We borrowed a lab coat and a wall-sized copy of the periodic table from the school's science department to hang behind her. At every performance, that song brought the house down. The big chart disappeared after closing night, and one of my fellow directors either had to pay for it or forfeit her diploma.

That was the last time I thought about the periodic table until an ASBMB Today planning meeting late last year when Quira Zeidan, the society's education and public outreach coordinator, told us that 2019 was the 150th anniversary of the year Dmitri Mendeleev first published his tabular display of the elements.

She wasn't just sharing science trivia. In her heart of hearts, Quira

is a teacher, and she offered to write a series of articles for ASBMB Today highlighting elements of significance in the biochemical realm.

There's nothing an editor likes better than the promise of a timely series (and guaranteed content), so I was delighted, but Quira gave us something more than that. As regular ASBMB Today readers know, she has provided a wonderfully coherent series of lessons that clearly explain everything from where the elements originate to their roles in human health. Every month, I've looked forward to learning something new from this series. And on page 21 of this issue, with nickel and zinc, I'm sad to see it end.

This month may mark the end of the (bio)chemical elements in ASBMB Today, but plans are afoot to build educational programs around these 11 articles — complete with experiments. If this resource would be useful to you or any of your colleagues, contact Quira at qzeidan@asbmb.org.

Thanks to all our readers for celebrating the International Year of the Periodic Table with us — and thank you, Quira, for being as cool a teacher as Tom Lehrer.

Comfort Dorn

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



CORRECTION

The Lipid News article in the November issue contained incorrect terminology. It should have stated that platelet activating factor is a plasmanylncholine.

Beware the unintended consequences of mandatory open access

By *Gerald Hart*

In 2018, a group of research funding organizations with the support of the European Research Council, or ERC, launched cOAlition S, a plan to require full open access to published research papers on work they had funded.

Their mandate: “With effect from 2021, all scholarly publications on the results from research funded by public or private grants provided by national, regional and international research councils and funding bodies, must be published in Open Access Journals, on Open Access Platforms, or made immediately available through Open Access Repositories without embargo.”

Most major funding agencies in Europe have endorsed this plan.

While the American Society for Biochemistry and Molecular Biology favors moving toward a model where scientific literature is freely available to everyone (open access), the fact remains that someone has to pay for the reviewing, redaction, quality control and eventual publication of research findings. Under the current system, most publication costs (at least in the U.S.) are born by library subscriptions, helping keep authors' costs to a minimum. At U.S. universities, library subscriptions are paid by indirect costs (finance and accounting, or F&A) that funding agencies provide to the universities within grants.

As stated in one of the Plan S 10 key principles, “Where applica-

While the American Society for Biochemistry and Molecular Biology favors moving toward a model where scientific literature is freely available to everyone (open access), the fact remains that someone has to pay for the reviewing, redaction, quality control and eventual publication of research findings.

ble, Open Access publication fees are covered by the Funders or research institutions, not by individual researchers; it is acknowledged that all researchers should be able to publish their work Open Access.”

Thus far, U.S. funding agencies, such as the National Institutes of Health and the National Science Foundation, have not adopted Plan S, but it seems likely that open access eventually will become mandatory worldwide for scientific literature.

ASBMB journals are already open access. In the *Journal of Biological Chemistry*, the *Journal of Lipid Research*, and *Molecular & Cellular Proteomics*, the papers in press, or PIPs, go online the day they are accepted, and they remain online for free indefinitely. However, this model is not acceptable to Plan S proponents, who demand that the final redacted versions of papers also must be available for free.

Another key principle listed in

Plan S: “The Funders do not support the ‘hybrid’ model of publishing. However, as a transitional pathway towards full Open Access within a clearly defined timeframe, and only as part of transformative arrangements, Funders may contribute to financially supporting such arrangements.”

If open access for final versions of papers is mandated across the board, libraries will no longer need to pay to subscribe to journals. In the U.S., all costs of publication will need to be borne by authors, generally from direct costs from grants. The cost to authors to publish likely will increase substantially.

Mandated open access benefits for-profit publishers, several of whom already are making lots of money from open-access journals. These publishers, especially the so-called high-impact journals and their cascade journals, can receive exorbitant funds to publish a paper, and the more papers they publish, either in the parent journal or its cascade siblings, the more money they make. One side effect is that the quality of publications might drop because more money is to be made by publishing more papers.

In contrast, complete open access likely will have a deleterious effect on scientific societies, and small societies with limited budgets will be hit particularly hard. Most societies are nonprofit, but they do use some of the funds generated by their journals to support science, such as travel awards for students, community

PRESIDENT'S MESSAGE

outreach and education, as well as to advocate for government support of scientific research. Open access not only will eliminate funds used for these functions, but many specialty journals published for or by small societies likely will cease to exist due to lack of revenue.

If complete open access of the type mandated by Plan S is adopted within the U.S., then the NIH, the NSF and other U.S. funding agencies must follow a model like that set

forth by the European agencies and provide funds to help defray the cost of publication. Perhaps indirect costs (F&A) supporting library subscriptions might be redirected to help keep costs low for authors publishing in open-access journals?

It is also important that we scientists not allow the for-profit publishers to demand exorbitant fees to publish in their journals. These publishers can, and often do, demand lots of money to publish simply


because we scientists continue to play the impact factor game — even though nearly all of us agree that a journal's impact factor says nothing about the quality of papers published in it.

Gerald Hart

(gerald.hart@uga.edu) is a professor and Georgia Research Alliance eminent scholar at the University of Georgia and president of the ASBMB.



Call for 2021 ASBMB Symposia proposals



Planning a meeting can be daunting. The ASBMB offers its members the opportunity to work directly with its meetings department to plan and promote niche scientific meetings through the ASBMB Symposia program.

asbmb.org/special-symposia/proposals/



Member update

By ASBMB Today Staff

Hartl, Lee win Breakthrough Prize

Two of the five winners of the 2020 Breakthrough Prize in Life Sciences are members of the American Society for Biochemistry and Molecular Biology.



Hartl

F. Ulrich Hartl, managing director of the Max Planck Institute of Biochemistry, and **Virginia Man-Yee Lee**, a professor in Alzheimer's research at the University of Pennsylvania, are among the recipients of the \$3 million award, one of three awarded annually by the

Breakthrough Prize Foundation and known collectively as the "Oscars of Science." The foundation also selected recipients in physics and mathematics.

Hartl shares the honor with Arthur L. Horwich of the Yale School of Medicine and the Howard Hughes Medical Institute, for discovering functions of molecular chaperones in mediating protein folding and preventing protein aggregation, which can be a precursor to cancer and neurodegenerative diseases.



Lee

Lee is a John H. Ware endowed professor in Alzheimer's research at the Perelman School of Medicine, director of the Center for Neurodegenerative Disease Research and co-director of the Marian S. Ware Center for Alzheimer's Drug Discovery Program. She is honored for discovering TDP43 protein aggregates in frontotemporal dementia and amyotrophic lateral sclerosis and for showing that different forms of alpha-synuclein in different cell types underlie Parkinson's disease and multiple system atrophy.

Jeffrey M. Friedman and David Julius also received the life sciences prize. The recipients were honored at an awards ceremony in November at the NASA Ames Research Center in California.

Cell biology society names fellows

Five members of the American Society for Biochemistry and Molecular Biology are among the 16 fellows elected to the American Society for Cell Biology in 2019. The fellows, who are selected by their peers, are recognized not only for their contributions to research involving cell biology and to its community of scientists but also for their commitment to the mission of the ASCB. Congratulations to these ASBMB members:

David Asai, senior director for science education, Howard Hughes Medical Institute, Chevy Chase, Maryland.

Mary Dasso, senior investigator in the Section on Cell Cycle Regulation, National Institutes of Health, Bethesda, Maryland.

Erin Dolan, professor of biochemistry and molecular biology and Georgia Athletic Association professor of innovative science education, University of

Georgia, Athens.

Vassie Ware, professor of biological sciences and co-director, HHMI biosciences program and distance education program, Lehigh University, Bethlehem, Pennsylvania.

Susan Wentz, professor of cell and developmental biology, provost, interim provost and vice chancellor for academic affairs, Vanderbilt University, Nashville, Tennessee.

The 16 new fellows will be recognized at the ASCB/European Molecular Biology Organization meeting to be held in Washington, D.C., this month.



Asai



Dasso



Dolan



Ware



Wentz

National Academy of Medicine elects new members

Five members of the American Society for Biochemistry and Molecular Biology are among the 90 new regular members and 10 new international members elected to the National Academy of Medicine.

The newly elected members include:



Davidson

Beverly L. Davidson, professor of pathology and laboratory medicine, Perelman School of Medicine, University of Pennsylvania, and director, Raymond G. Perelman Center for Cellular & Molecular Therapy, Children's Hospital of Philadelphia.



DuBois

Raymond N. DuBois Jr., dean of the college of medicine and professor of biochemistry and medicine, Medical University of South Carolina, Charleston.



Gutkind

J. Silvio Gutkind, professor of pharmacology and associate director of basic science, Moores Cancer Center, University of California, San Diego.



Palczewski

Krzysztof Palczewski, director of the Center for Translational Vision Research, Irving H. Leopold chair in ophthalmology and a professor of physiology and biophysics at the University of California, Irvine School of Medicine.



Rustgi

Anil K. Rustgi, professor of medicine and director, Herbert Irving Comprehensive Cancer Center and associate dean of oncology, department of medicine, Vagelos College of Physicians and Surgeons, Columbia University, New York City.

The newly elected members bring the NAM's total membership to more than 2,200 and the number of international members to approximately 180.

Velasquez, Torres land Gilliam fellowship



Velasquez



Torres

Erick Velasquez, a Ph.D. student in the biochemistry, molecular and structural biology program at the University of California, Los Angeles, and **Jorge Torres**, a professor in the department of chemistry and biochemistry at UCLA are among this year's

44 pairs of Gilliam fellows, selected by the Howard Hughes Medical Institute.

Gilliam fellowships for advanced study are unique in supporting advisor-student pairs rather than professors or trainees in isolation. Designed to foster diversity and inclusion in science and train future scientific leaders, the awards support fellows in their later years of graduate school and provide training for their faculty mentors.

Under Torres' supervision, Velasquez plans to apply machine learning to proteomics data sets to understand protein-protein interactions in mitosis.

Torres studies proteins that direct the assembly and function of the mitotic spindle and uses multidisciplinary approaches to develop new anti-cancer drugs. He received the American Society for Biochemistry and Molecular Biology's 2019 Ruth Kirschstein Diversity in Science Award.

Fleming recognized for diversity work



Fleming

Karen Fleming, a professor of biophysics at Johns Hopkins University, received the university's Provost's Prize for Faculty

Excellence in Diversity in May.

The \$50,000 prize recognizes faculty efforts to promote gender and racial diversity. In Fleming's case, that advocacy work includes starting a journal club for gender equity, teaching fellow Hopkins professors about best practices for inclusive pedagogy and holding equity workshops at scientific society meetings.

"We all need to plug the leaks in the STEM pipeline through our actions and words each and every day," Fleming said in her remarks on receiving the award.

Fleming, whose research focuses on membrane protein folding and the involvement of chaperones in that process, serves as an associate editor of the *Journal of Biological Chemistry*.

Brown University honors Gordon



Gordon

Sharona Gordon, a professor of physiology and biophysics at the University of Washington in Seattle, was awarded Brown University's 2019 Horace Mann Medal.

The prize, named after a politician and education reformer who attended Brown in the early 19th century, recognizes significant contributions of Brown graduate alumni to

Biophysical Society announces honors

American Society for Biochemistry and Molecular Biology members **G. Marius Clore**, **Dan Herschlag** and **Alexandra C. Newton** are among the recipients of the 2020 Biophysical Society awards. ASBMB members **Cynthia Wolberger** and **Hao Wu** have been named 2020 BPS fellows.

Clore, a National Institutes of Health distinguished investigator and chief of the Protein Nuclear Magnetic Resonance Section of the National Institute of Diabetes and Digestive and Kidney Diseases, will receive the BPS Innovation Award in recognition of his contributions to the development of nuclear magnetic resonance imaging for determining 3D structures of macromolecules in solution and his work on the development of paramagnetic and relaxation-based NMR experiments to characterize rare, transient and previously invisible states of macromolecules.

Herschlag, a professor of biochemistry at Stanford University, will receive the society's Founders Award for his fundamental contributions to RNA folding and enzymology. "The Founders Award allows us to call attention to outstanding achievements in biophysics that are now accepted and used by others, whether that acceptance was immediate or over a period of years," BPS President Dave Piston stated. "Dan's work on RNA folding and enzymology has had a ripple effect on the field, leaving a lasting impact on the entire breadth of molecular biophysics."

Newton, a professor in the department of pharmacology at the University of California, San Diego, will receive the BPS Award in the Biophysics of Health and Disease in recognition of her paradigm-shifting discoveries that showed how disease mutations that inhibit protein kinase C activity cause cancer while those that activate PKC are drivers of neurodegenerative diseases.

Wolberger is a professor of biophysics and biophysical chemistry at the Johns Hopkins University School of Medicine. Her research in ubiquitin signaling and regulation of transcription has transformed understanding of molecular mechanisms underlying genes regulation through elegant structural studies.

Wu is the Asa and Patricia Springer professor in the department of biological chemistry and molecular pharmacology at Harvard Medical School. Her use of structural immunology has revised the view of intracellular signaling and cellular organization through discovering supramolecular signalosomes formed by innate immune signaling proteins, mechanisms that govern cooperative assembly, and proximity-driven enzyme activation.



Clore



Herschlag



Newton



Wolberger



Wu

MEMBER UPDATE

their fields and was conferred at the university's commencement ceremony in May.

Gordon, whose research focuses on the physiology of ion channels in the TRP family, serves as the editor-in-chief of the *Journal of General Physiology*. Last year she founded *Below the Waterline*, a grassroots organization aimed at improving the culture of science by addressing gender harassment, and she published a study on the development of scientific identity among postdocs.

In their announcement of the prize, the award committee noted Gordon's commitment to the scientific community along with her own scientific achievements.

Boehning moves to Rowan University



Boehning

Darren Boehning, until recently a professor of biochemistry and molecular biology at the University of Texas Health Science

Center at Houston, has joined the Cooper Medical School of Rowan University in Camden, New Jersey. He will serve as head of the school's department of biomedical sciences and assistant dean for research.

Boehning's research focuses on apoptosis, investigating how the inositol triphosphate receptor calcium channel contributes to cell death. This receptor is not only dysregulated

in certain cancers, where it contributes to resistance to apoptosis, but also in traumatic injury, which increases its activity and can contribute to stress-induced diabetes.

While leading that research, Boehning also held several leadership roles at UTHealth, most recently directing two graduate programs. His accolades include awards for teaching excellence and for being an outstanding faculty member.

Biophysical Society elects Moores to council



Moores

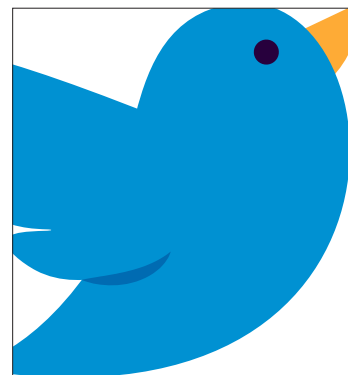
Carolyn A.

Moores of Birkbeck College, part of the University of London, has been elected to the governing council of the

Biophysical Society. She will begin a three-year term in February 2020.

A professor of structural biology whose lab studies microtubule organization and dynamics, Moores runs the biological sciences department at Birkbeck and recently was appointed interim dean at the college. She also is the academic head of the electron microscopy and image processing lab.

With more than 9,000 members around the world, the Biophysical Society develops and shares knowledge in biophysics. Its members elected a new president-elect and four council members, including Moores, in August.



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IN MEMORIAM

John Oates

John Oates, a physician–scientist on the team that discovered the first blood pressure–lowering drug and who went on to become a pioneer in the study of prostaglandins, died in July in Nashville at age 87.

Oates was raised in Fayetteville, North Carolina, by a former schoolteacher mother and lawyer–historian father. He earned his bachelor’s degree in 1953 at what was then Wake Forest College (now University) and his M.D. in 1956 at the college’s Bowman Gray School of Medicine.

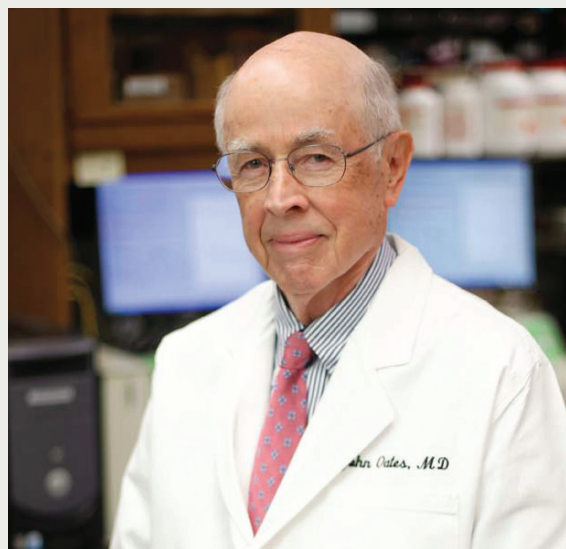
He did a stint in the Merchant Marines, at which time he was based in and became fond of New York, and went on to complete his residency at the New York Hospital–Cornell Medical Center.

Though he was prepared to join the U.S. Air Force as part of the so-called “doctor draft” that sent thousands of medical professionals to the Korean War battlefield, he learned from a peer that working at the National Institutes of Health was an alternative. His chair arranged for him to take a position at the National Heart Institute, according to a 2013 interview in the *Journal of Clinical Investigation*.

In 1959, he and colleagues at the NIH were studying the synthesis and metabolism of aromatic amines (for example, norepinephrine and serotonin) to better understand their roles in high blood pressure. They discovered, quite unexpectedly, that the Merck drug methyldopa (brand name Aldomet), which the company had synthesized as part of a cancer research screen, lowered blood pressure in animal models.

“The pharmacologists at Merck had completed toxicology studies and commented to us that they had given rabbits doses of up to one gram per kilogram without lowering blood pressure or having any adverse effect,” he told Vanderbilt University’s Leigh MacMillan in 2005. “They said it can’t possibly be pharmacologically active.”

Methyldopa ended up being used to treat severe hypertension and, though more effective therapies for high blood pressure have since emerged, still is used today in certain cases, in particular during pregnancy.



Oates moved to Vanderbilt University in 1963 and is credited with founding one of the first divisions of clinical pharmacology, which he led until 1996.

Oates’ team at Vanderbilt did groundbreaking research on prostaglandins, members of the eicosanoid family derived from fatty acids. They determined the role prostaglandins play in renin release by the kidneys, showing that, parallel to the adrenergic nervous system, they affected renin release and blood pressure regulation.

They also found that prostaglandin D2 is a major inflammatory mediator produced by mast cells, which kicked off drug-development studies for allergic rhinitis and asthma.

Oates also is recognized for elucidating the concept of first-pass metabolism, which affects drug concentration. And, in his later years, his group studied small molecules that could be used for diseases driven by oxidative stress, including Alzheimer’s and coronary artery disease.

Oates’ publication list is long, his awards numerous, and his academic progeny widespread. He is survived by his wife, Meredith, three children and four grandchildren.

Roberta F. Colman (1938 – 2019)

By Hal White & Judith G. Voet

Roberta (Bobbie) Colman, Willis F. Harrington professor emerita of chemistry and biochemistry at the University of Delaware, joined what then was the UD chemistry department in 1973 as its fifth biochemist and remained there until her retirement in 2009.

In 1985, Bobbie became the first woman to receive the Francis Alison Award, UD's highest faculty honor, and the university awarded her an honorary doctor of science degree at commencement in 2014. Her honorary degree citation recognized her for her roles as a revered educator and prolific researcher and also saluted her work in mentoring women and minority students.

The citation concluded, "Your pioneering undoubtedly changed and enriched the scientific world in academe; it also has enriched the larger society because of the many contributions that you have made to your field."

Bobbie's distinguished career in research started in high school when she received a Westinghouse Science Talent Search Award. She graduated from Radcliffe College *summa cum laude* and went on to graduate school at Harvard University, where she earned a Ph.D. under the direction of the renowned physical organic chemist Frank Westheimer. After post-doctoral fellowships at the National Institutes of Health and Washington University in St. Louis, she joined the faculty in the department of biological chemistry at Washington University in 1966. A year later, she became an assistant professor in the

department of biological chemistry at Harvard Medical School. She left Harvard as an associate professor in 1973 to become a full professor of biochemistry at UD.

During her highly productive career, Bobbie published more than 260 articles in journals such as the *Journal of Biological Chemistry*, *Biochemistry*, *Archives of Biochemistry and Biophysics*, *Nature Genetics* and *Protein Science*. Many of her publications dealt with the structure of the active sites of enzymes and the function of various amino acid side chains in enzyme catalysis. She pioneered the use of particular reactive nucleotide analogs as affinity labels to probe enzyme active sites. As a world authority on the structure and function of nicotinamide adenine dinucleotide-linked and nicotinamide adenine dinucleotide phosphate-linked isocitrate dehydrogenases and other enzymes such as glutamate dehydrogenase, pyruvate kinase, glutathione S-transferase and adenylosuccinate synthase, she established numerous collaborations and received many honors.

Bobbie was a fellow of the American Association for the Advancement of Science and a member of numerous professional societies. Among other positions, she was treasurer of the American Society for Biological Chemists (the precursor of the American Society for Biochemistry and Molecular Biology) from 1981 to 1985. She served on the ASBMB Executive Council from 1993 to 1996, and in 1996 she received the Herbert A. Sober



PAUL KENDE

Pictured here in June 2012, Bobbie Colman had a colorful fashion sense.

Award from the ASBMB for scientific achievement. She served as chair of the division of biological chemistry of the American Chemical Society from 1998 to 2000. She was on the editorial board of *Archives of Biochemistry and Biophysics* for 27 years, including 17 years as an executive editor. She was an associate editor of the *Journal of Protein Chemistry* for six years and served on the editorial boards of several other journals including the *Journal of Biological Chemistry* and *Protein Science*.

Throughout her career at UD, Bobbie maintained a well-funded research group of about 10 people, including research assistants, undergraduates, graduate students, postdoctoral fellows and visiting faculty members. Nearly 30 graduate students completed their dissertations under her guidance. Many of these associates have gone on to distin-

EVAN KRAPE



University of Delaware Board of Trustees Chairman Gil Sparks presents Bobbie Colman with an honorary doctor of science degree at the university's 2014 commencement ceremony.



COURTESY OF JUDITH G. VOET

Enjoying a meal together in February 2019 are, from left, Bobbie and Bob Colman, Don and Judy Voet, Paul and Frances Kende, and Liz and Ed Thornton.

guished careers elsewhere. In addition, she was the program director of UD's NIH-funded chemistry-biology interface graduate program from 1993 to 2009. Students in her laboratory received excellent training. In addition to her graduate students and postdoctoral fellows, many of the undergraduates who worked in her laboratory became co-authors on scientific publications.

Graduate students and undergraduates from over the years remember Bobbie as their teacher in graduate-level biochemistry core courses. She also taught elementary biochemistry for nonmajors and mechanisms of enzyme regulation.

After being one of the only women in her college science classes and

then discovering early in her career a large salary discrepancy between herself and similarly qualified male faculty members, Bobbie took a special interest in nurturing and enabling the careers of women and underrepresented minority scientists. She did this through mentoring students in her own laboratory and through service on national committees such as the Committee on Women in Biochemistry and the Educational Affairs Committee of the ASBMB.

Bobbie enjoyed traveling. With her husband, Robert, she used summer vacations to travel the world from the Antarctic to Asia and Africa. In each country, she took in the local culture and natural history and returned with photographs to share.

Her fashion sense was very colorful and often extended to clothing acquired on her travels.

After her retirement in 2009, Bobbie regularly attended classes at UD's Osher Lifelong Learning Institute, where she continued to cultivate her many interests.

She is survived by her husband; her children, Sharon and David; and her two grandchildren, Lexi Greenberg and Jason Greenberg.

Hal White (halwhite@udel.edu) is a professor emeritus of chemistry and biochemistry at the University of Delaware.

Judith G. Voet (jvoet1@swarthmore.edu) is the J.H. Hammons professor emerita of chemistry and biochemistry at Swarthmore College.



To their friends, Bobbie and Bob Colman were "joined at the hip," attending movies, concerts and plays together, as in this April 2013 photo.

PAUL KENDE

BOBBIE COLMAN'S INFLUENCE

Mayura Dange, former graduate student: “She is the reason I am what I am ... Not only a U.S.-graduated scientist, but also a feminist, a travel lover, a hobbyist photographer Her scientific excellence is all over the web, but her personality was far beyond science labs and books She was a constant learner, who after her retirement at the age of 71, started taking music appreciation and architecture classes at the university. She would subtly emphasize how a woman has to take extra efforts to prove herself while strongly reminding us that being a woman does not entitle you to any freebies or sympathy. There are many life lessons I learned under her guidance, but more personal to me was when I had tried and failed over and over in one part of my project. She was someone who would never give up, but she told me ‘sometimes we have to let go of something that is not working out and focus on what is working. It’s not giving up, it’s being practical.’”

Anastasia Thévenin, doctoral student: “Rest in peace, dearest Dr. Colman — my Ph.D. adviser. I would not be where I am today without your help and guidance. You were the kindest, most caring person I knew, and your positivity was my guiding light during my Ph.D. You will always be the kind of scientist and a woman I will aspire to be.”

Mark Segall, former postdoctoral researcher: “Dr. Colman was an ideal mentor, extraordinarily knowledgeable, but also very willing to consider and discuss the ideas of scientists at earlier stages of their careers. She provided an environment that brought out the very best in her graduate students and post-docs. There was never a single day that I did not feel supported, encouraged and eager to move ahead with my project and determine the outcome of the next experiment. Even years after I left her laboratory, Dr. Colman remained extremely supportive and an enduring role model to me.”

Don Dennis, a faculty colleague for many years, remembers a conversation with a visiting speaker who noted that Dr. Colman was such a competent scientist and that she only talked about substantive issues. The visitor then wondered if she ever engaged in small talk. Dennis responded that she did, but she never initiated it because “she had more respect for others’ time than they did for themselves.” Dennis also noted that since the age of 17, Roberta routinely got and did not need more than five hours of sleep a night.

Judy Voet, who, with her husband, **Don**, and **Liz and Ed Thornton** and **Frances and Paul Kende**, was a close personal friend of Bobbie and Bob Colman, writes, “To us, they were joined at the hip. They took courses and studied together, took trips together, went to movies, concerts and plays together and gave wonderful dinner/slide-shows of their travels together. They even created a joint out-going phone message/greeting! Bobbie was a wonderful, creative cook and often coordinated meals to go with their travel presentations, with Bob being primarily the sous chef. But with the slide shows that ‘togetherness’ ended. They were each fiercely protective of their own photos, and we often wound up with a two-act show!”

Bobbie’s daughter, **Sharon Greenberg**, writes, “My mother was a person with a true love of life, discovery of the world and learning. She was a very positive, optimistic individual who instilled in me a passion for travel and learning. Her grandchildren loved her excitement and enthusiasm. We miss her immensely.”



Bobbie Colman, pictured here in 2004, took a special interest in nurturing and enabling the careers of women and underrepresented minority scientists.

Sydney Brenner (1927 – 2019)

By Terrence Sejnowski

Born in South Africa in 1927, Sydney Brenner started medical school at such an early age that he was too young to practice medicine at the conclusion of his training. This gave him time to take classes in anatomy and physiology that included bench experiments. He abandoned medicine and went on to write a master's thesis in the field of cytogenetics, which served him well when he became a molecular biologist. This was the first turning point in his remarkable life.

In 1953, Sydney was pursuing doctoral research at Oxford when he heard about the DNA model that Jim Watson and Francis Crick had constructed, based on experimental data from Rosalind Franklin. Along with Leslie Orgel and Jack Dunitz, he drove to Cambridge to see the model. He described this experience in a lecture near the end of his life:

“And I have to tell you that it was just a moment of absolute enlightenment, that's all I can say. I had seen the light, and I spent the whole of the next day, before we went back, talking to Jim Watson ... And I resolved to work on this subject and, of course, there wasn't much I could do at that time. I started to think, as indeed we began to talk then, about the genetic code. What is this code? What does this sequence mean?”

This was a second turning point. Francis Crick recruited Sydney to the Laboratory of Molecular Biology, or LMB, where he embarked on a series of experiments that eventually contributed to deciphering the genetic code. His discoveries proved that the

code was based on triplets of base pairs, which he called codons, and he found two of the stop codons.

This led to a third turning point. Sydney shared an office at the LMB with Francis Crick, and they had long discussions about biological questions. What do you do for your next project after discovering the structure of DNA and working out the genetic code? Francis decided to focus on the human brain, and Sydney inaugurated a new model organism, *Caenorhabditis elegans*, a roundworm that is one millimeter long and has only 302 neurons. He wanted a species that could serve as a Rosetta stone for decoding how neurons give rise to complex behaviors. The neurons' small size and other technical problems delayed that study until optogenetic techniques were invented, but in the meantime the worm's genetics were the starting point for many breakthroughs in understanding how a creature develops from an embryo by following every cell in its body over time.

Sydney was famous for his wit. He received the Nobel Prize for physiology or medicine in 2002 for establishing *C. elegans* as a model system. At the Nobel banquet, he delivered a short after-dinner talk:

“But now I come to what I want to say. And the best way I can say it, is to tell you about a letter I've received. A Nobel Prize winner gets many letters. This was from a student in China. His e-mail said: 'Dear Dr. Sydney Brenner, I wish also to win a Nobel Prize. Please tell me how to do it.' I have been considering the reply which will

*say something like this: First you must choose the right place for your work with generous sponsors to support you. Cambridge and the Medical Research Council will do. Then you need to discover the right animal to work on — a worm such as *C. elegans* for example. Next, choose excellent colleagues who are willing to join you in the hard work you will need to do. How about John Sulston and Robert Horvitz for a starter. You must also make sure that they can find other colleagues and students. Everybody will have to work hard. Finally, and most important of all, you must select a Nobel Committee which is enlightened and appreciative and has an excellent chairman with unquestioned discernment.”*

Sydney once counseled me not to retire until I had my next job lined up. This was his way of keeping active in science long into his 80s. After retiring from the LMB, he had an experimental project in Singapore sequencing the highly compact genome of the fugu, a pufferfish. He was the founding president of the Okinawa Institute of Science and Technology, a distinguished professor at the Salk Institute and a senior fellow at both the Janelia Research Campus of the Howard Hughes Medical Institute and the Crick–Jacobs Center for Theoretical and Computational Biology at the Salk Institute. Sydney had reinvented himself again, this time as a Johnny Appleseed for science. He wrote in “My Life in Science,” his autobiography: “I think my real skills are in getting things started. In fact, that's what I enjoy most, the opening game.



OIST/WIKIMEDIA COMMONS

Sydney Brenner speaks at a 2011 symposium at the Okinawa Institute of Science and Technology.

And I'm afraid that once it gets past that point, I get rather bored and want to do other things."

Sydney gave three lectures at the Salk Institute on "Reading the Human Genome" in 2009. They were a tour de force, delivered without a single slide or prop. He did not need props to hold an audience spellbound. He said that no human ever had read the entire human genome, base pair by base pair — only computers. Sydney made it his goal to do just that and in so doing discovered interesting similarities between stretches of DNA in different genes and across species.

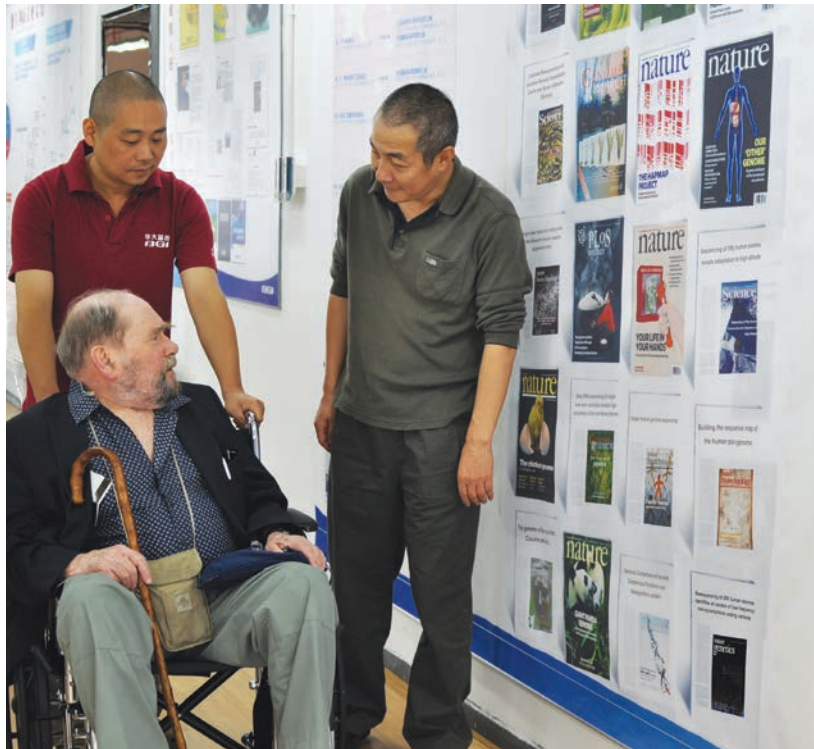
Sydney was skeptical about the rise of omics in biology. In a *Science*

magazine editorial, "Understanding the Human Brain," he wrote: "Like most fields in biology, neuroscience is succumbing to an 'epidemic' of data collecting." At a symposium at the University of California, San Diego, on the emergence of omics, when asked which of all the omics was the most important, his immediate reply was "economics." On another occasion he was asked about the use of pipelines for drug discovery. His comment was "High throughput: No input, no output." Despite these comments, we should remember that he was responsible for the complete reconstruction of the *C. elegans* brain from electron microscopic sections in 1968, a

pioneering piece of 21st century connectomics in the 20th century.

In October 2017, I served as interlocutor for four lectures Sydney gave to a small group of young researchers in Singapore, during which he reminisced about his career and the art of doing science. He stressed the importance of giving younger scientists resources to set out in new directions as he had done early in his career. The average age of researchers receiving their first National Institutes of Health grant is now 45, halfway to retirement. At the Crick-Jacobs Center at Salk, we hatched a scheme to give promising young scientists a junior fellow position directly after their Ph.D.,

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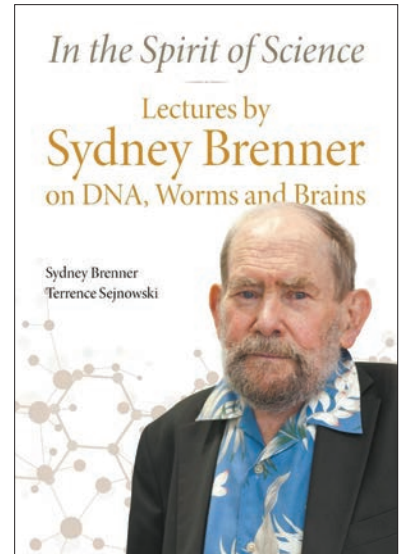


Wang Jian, founder of the genome sequencing company BGI, shows Sydney Brenner around the BGI headquarters in Shenzhen, Guangdong, China, in November 2010.

providing them with independence and mentoring, bypassing years of postdoctoral apprenticeships. These fellows flourished and went on to brilliant careers. The Salk Institute extended the fellows program to other research areas with equal success. Sydney's influence lives on there and at other institutions he helped launch and advise.

I visited Sydney in Singapore in January 2017 along with family and friends from all stages of his life to celebrate his 90th birthday. He was no longer able to travel, but he was well cared for by his family and Singaporean friends and was staying at the Shangri La Hotel. He was using a wheelchair, and his health was failing, but he was as lively as I ever have seen him. I asked him to tell us my favorite Sydney Brenner story, "Francisco Crick in Paradiso":

"I shared an office with Francis Crick for twenty years in Cambridge. At one time he was interested in embryology and spent a lot of time thinking about imaginal discs in Drosophila. One day, he threw the book he was reading down onto his desk with an exasperated cry. 'God knows how these imaginal discs work.' In a flash I saw the whole story of Francis arriving in heaven and Peter welcoming him with 'Oh Dr. Crick, you must be tired after your long journey. Do sit down, have a drink and relax.' 'No,' says Francis, 'I must see this fellow, God; I have to ask him a question.' After some persuasion, the angel agrees to take Francis to God. They cross the middle part of heaven, and finally right at the back, across the railway tracks, they come to a shed, with a corrugated iron roof, surrounded by junk. And in the back part, there



COURTESY OF TERRENCE SEJNOWSKI

Sydney Brenner's last lectures, delivered in Singapore in 2017, were published in book form in 2018.

is a little man in overalls with a large spanner in his back pocket. 'God,' says the angel, 'This is Dr. Crick; Dr. Crick, this is God.' 'I am so pleased to meet you,' says Francis. 'I must ask you this question. How do imaginal discs work?' 'Well,' comes the reply, 'We took a little bit of this stuff and we added some things to it and ... actually, we don't know, but I can tell you that we've been building flies up here for 200 million years and we have had no complaints.'

Sydney Brenner died in April, joining Francis Crick in Paradiso. He had an enormous impact on science and influenced many careers. We have lost a great scientist and a good friend.

Terrence Sejnowski (terry@snl.salk.edu) holds the Francis Crick chair at the Salk Institute for Biological Studies and is a distinguished professor in the division of biological sciences at the University of California, San Diego.

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Crystal building blocks of triglycerides

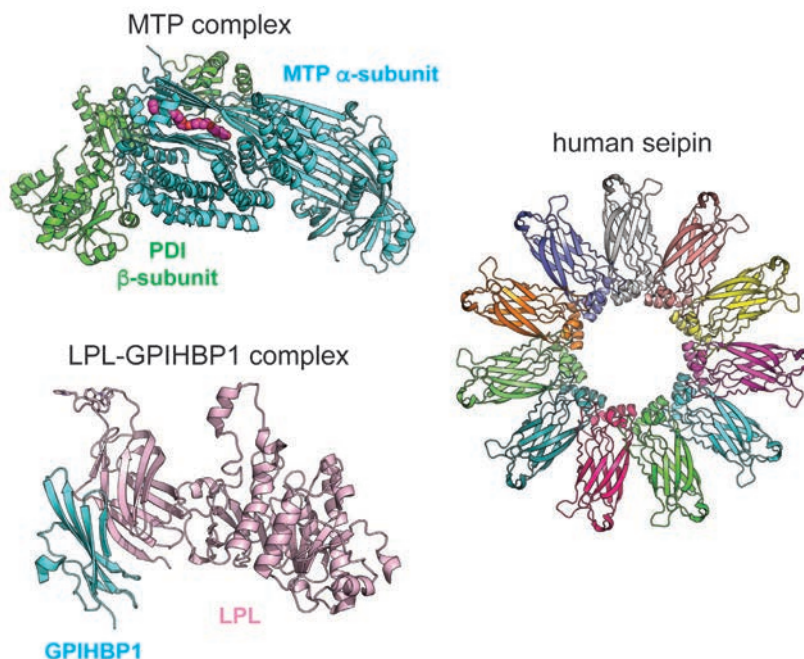
By Michael Airola

Francis Crick once said, “If you want to understand function, study structure.” Do you agree? I certainly do, and I would argue that most lipid biologists do too. Just consider the effort to define chemical structures for the many thousands of lipids that exist and the hypotheses about individual lipid function that this structural information has generated.

What has lagged behind is the characterization of the structures of the proteins that modify, transport or interact with these lipids, but times are changing. For example, when I started my postdoc in Yusuf Hannun’s lab, only a handful of sphingolipid-metabolizing enzymes had been structurally characterized, and these were mainly from bacteria. While many questions remain open (hey, ceramide synthase — we can’t wait to see what you look like!), work from several labs has defined the structures and mechanisms for many human enzymes in sphingolipid metabolism.

A similar revolution appears to be happening with triglycerides. As most of you know, triglycerides serve as a reservoir for energy storage, but when they accumulate excessively, they can cause health problems, including obesity, diabetes and heart disease. Three new structures in particular have caught my attention.

The most recent is a crystal structure of microsomal triglyceride transfer protein complex, which transfers neutral lipids into apolipoprotein B-containing lipoproteins. The arduous crystallography required to conduct this work is impressive.



Beautiful structures of proteins involved in triglyceride metabolism and storage.

The researchers revealed an unexpected lipid-binding cavity and provided insight into disease mutations as well as pharmacological inhibition of this therapeutic target.

The second is the crystal structure of lipoprotein lipase, or LPL, the major lipase that clears triglycerides in the blood. Gabriel Birrane and colleagues and Risha Arora and colleagues separately determined the LPL structures, overcoming the relative instability of LPL by complexing it with its binding partner glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1. These structures, along with other biochemical data, suggest LPL is active as a monomer, challenging the long-standing paradigm that LPL was only active as a dimer.

The last notable structure is that of seipin, a homo-oligomeric integral

membrane protein that is a key player in the formation of cytoplasmic lipid droplets. Two groups (Renhong Yan and colleagues and Xuewu Sui and colleagues), using cryo-electron microscopy, found that 11 or 12 seipin molecules (dependent on the species) come together to form a ring that spans the endoplasmic reticulum membrane, can bind phosphatidic acid and may stabilize the formation of nascent lipid droplets.

What’s next? Who knows, but I’m darn sure we’re all gonna love it.

Michael Airola (Michael.airola@stonybrook.edu) is an assistant professor of biochemistry and cell biology at Stony Brook University.



MICHAEL AIROLA

Rounding out the year with nickel and zinc

By Quira Zeidan

To complete our celebration of the 150th anniversary of Dmitri Mendeleev's periodic table, we look at nickel and zinc, two metallic elements with chemical symbols Ni and Zn and atomic numbers 28 and 30, respectively.

Nickel can exist in oxidation states ranging from -2 to +4. The most abundant — Ni^{+2} — combines with common anions such as sulfate, sulfide, carbonate, nitrate and hydroxide. In contrast, zinc predominates in the oxidation +2 almost exclusively, acting as a strong reducing agent. Zinc forms binary compounds with most nonmetal and metalloid elements with the exception of noble gases.

Nickel is produced with iron in the final stages of nuclear reactions during violent explosions deep inside supergiant stars. As a result, these two elements are mixed abundantly in the interior of meteorites. The astrophysical origin of zinc is not entirely understood, but it might have involved the asymmetric explosion of the universe's earliest supernova.

Nickel makes up only 0.008% of the Earth's crust and occurs often as an alloy with iron in the planet's core. It also exists in minerals in combination with sulfur and arsenic. Zinc is the 24th most common element in the Earth's crust, where it is found primarily as zinc sulfide and as a binary alloy with metals including aluminum, gold, iron, lead, silver and nickel. Mineral weathering disperses small amounts of zinc into soil, seawater and the atmosphere.



This ribbon diagram shows the 3D structure of the enzyme urease in coordination with two nickel ions depicted in green.

Both nickel and zinc are essential for life and are present in many organisms. Nickel is recognized and transported into the cell by a variety of mechanisms: nonspecific influx across membrane proteins in bacteria and yeast, high-affinity uptake via transporters and permeases in certain bacteria, and incorporation through channels that preferentially carry other divalent cations — such as magnesium and calcium — in fungi and humans. Inside cells, nickel is inserted into the active site of many enzymes such as hydrogenase, nickel superoxide dismutase, carbon monoxide dehydrogenase, cis-trans isomerase and urease. Toxic excess intracellular free nickel is neutralized by binding to negatively charged molecules such as polyphosphate and sequestration of nickel-containing complexes into vacuoles.

The nickel-containing protein urease is important in the pathophysiology of liver cirrhosis, peptic ulcers and urinary stones. Urease is produced by bacteria that infect the gastrointestinal and urinary tracts, including *Helicobacter pylori* and

Proteus mirabilis. It breaks down urea and produces ammonia, which increases the pH of the surrounding environment from neutral to basic and becomes toxic in the liver, the stomach lining, the kidneys and the blood stream.

Cells transport, use and sequester zinc much as they do other divalent metals. Photosynthetic bacteria of the genus *Acidiphilium* contain a purple chlorophyll pigment that uses zinc as cofactor instead of the more common magnesium. Zinc-dependent phospholipases C in *Clostridia*, *Bacillus* or *Listeria* species may contribute to toxicity by breaking down host cell membranes. The coordination of one or more zinc ions by particular amino acids forms a zinc-finger motif that stabilizes the 3D structure of many proteins that bind DNA, such as nucleases and transcription factors.

Quira Zeidan
(qzeidan@asbmb.org) is the ASBMB's education and public outreach coordinator. Follow her on Twitter @quirazeidan.



E. JABRI ET AL/WIKIMEDIA COMMONS

Tor comes to the fore in autophagy

By Martin J. Spiering

Healthy cells are expert recyclers, rapidly breaking down worn-out or surplus macromolecules and reusing their building blocks. Several pathways, such as the proteasomal degradation route for protein breakdown, specifically pick out those damaged or expendable molecules.

These selective degradation pathways usually operate in cells that have ready access to nutrients. But when cells encounter crises such as severe nutrient shortages, they activate an emergency recycling strategy. In these cells, a bulk degradation pathway indiscriminately breaks down macromolecules and entire cytoplasmic organelles and ribosomes.

This process is called autophagy (Greek for “self-eating”) — or sometimes, more specifically, macroautophagy to distinguish it from specialized forms of autophagy that are more restricted and selective. It’s the rough equivalent of a wood chipper that shreds chairs, tables and credenzas wholesale for use in plywood or as fireplace fuel.

Autophagy also represents an important quality-control mechanism that eliminates long-lived proteins and damaged organelles in some cells, such as neurons, whose total destruction by other processes such as apoptosis would harm the organism.

Defects in autophagy have been linked to neurodegenerative diseases and cancer, highlighting that this recycling mechanism is essential for keeping cells healthy and alive. However, how the cellular nutrient status is communicated to the autophagy machinery was long unknown.

In a 1998 paper published in the **Journal of Biological Chemistry** and now recognized as a JBC Classic, Takeshi Noda and Yoshinori Ohsumi at the National Institute for Basic Biology in Japan uncovered this missing link, reporting that the target of rapamycin, or Tor, protein in yeast suppresses autophagy in cells that are growing in nutrient-rich conditions.

A facile biological system

Researchers had known since the early 1990s that two Tor proteins of *Saccharomyces cerevisiae*, or budding yeast, respond to the nutritional state of the cell and regulate cell cycle progression. Noda and Ohsumi’s discovery that Tor also controls autophagy was a milestone in unraveling how bulk degradation is regulated in eukaryotic cells.

Ohsumi chose yeast for his main studies in part because it has a large vacuole (a structure analogous to the lysosome in mammalian cells) that is easy to study by light microscopy. In 1992, his team discovered that in nutrient-starved cells of yeast mutants that cannot degrade proteins via the proteasomal pathway, the vacuoles quickly fill up with spherical structures.

These membrane-bound structures contained ribosomes, mitochondria, lipids and cytosolic enzymes, suggesting that they were signs of autophagy; the researchers named them autophagic bodies.

Noda, the first author of the Classic paper, was a graduate student in the Ohsumi lab. During peer review of the 1992 paper, he said, the



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Yoshinori Ohsumi and colleagues discovered that the Tor protein controls autophagy in yeast cells.

referees asked for additional experiments to verify that what he and Ohsumi saw under the microscope was indeed autophagy.

The extra work paid off. “We clearly showed that cytoplasmic enzymes are incorporated into the isolated vacuole during this process,” Noda said; these additional findings convinced the referees and secured the paper’s publication.

The referees’ requests prompted Noda to develop more specific and sensitive methods. “After the experience with the first paper, I realized that we needed a quantitative assay for measuring autophagy activity,” he said.

A revised view

In a follow-up paper, Noda and others in the Ohsumi lab developed an assay that measures the activity of a genetically engineered alkaline phosphatase, or ALP, that becomes active only when moved to the yeast

vacuole as it is during autophagy.

“Having this system in hand, I got interested in studying the regulatory mechanism of autophagy in more detail,” Noda said.

Noda came across a 1996 paper from Michael Hall’s group at the University of Basel, Switzerland, reporting that Tor in yeast controlled cellular processes that typically are induced in response to starvation.

“As autophagy is induced by starvation, I was eager to use our ALP assay to test the hypothesis that Tor might also regulate autophagy,” Noda said.

Noda and Ohsumi grew yeast cells in nutrient-rich culture conditions that typically inhibit autophagy. The researchers then added the Tor inhibitor rapamycin to the cell cultures. Using their ALP-based autophagy assay, they detected autophagy

in the Tor-inhibited cells, and using light microscopy, they also observed the tell-tale autophagic bodies in the vacuoles.

Using a yeast strain that carried a mutated TOR2 gene encoding a temperature-sensitive Tor2 variant, the authors firmed up these observations, finding that the TOR2-mutant strain exhibits autophagy when grown at temperatures that inactivated the mutated Tor2 variant.

“Our discovery of Tor’s role in autophagy revised prevailing views at the time, showing that Tor regulates not only anabolic processes, but also catabolic ones,” Noda said. “This coupling of anabolic and catabolic processes has been a key game changer in the research field.”

In search of a mechanism

They next turned to the question of how Tor might control autophagy. The Ohsumi lab previously had generated 14 autophagy-deficient yeast strains, and Noda found that rapamycin did not restore autophagy in these mutants, indicating that these genes, called ATG, all act downstream of Tor.

The Classics paper could not resolve the question of how Tor might regulate the ATGs, but there was a promising hint — Tor was known to have a kinase domain essential for cell cycle regulation. This suggested that Tor might control autophagy by phosphorylating and thereby inhibiting autophagy-associated proteins such as the ATGs.

This was borne out by a 2000 study published by Ohsumi and

colleagues reporting that Tor phosphorylates the autophagy-related yeast protein Atg13, interfering with Atg13’s ability to activate another kinase, Atg1, required for autophagy induction.

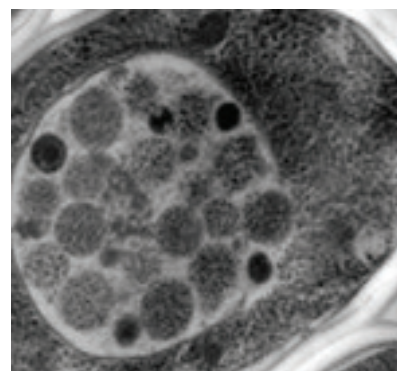
A 2009 paper by the Ohsumi lab reviewed how using the facile yeast system has helped pinpoint many other key players in autophagy.

Despite great strides in clarifying autophagy mechanisms in both yeast and mammalian cells, more work is needed. In particular, to prevent self-destruction, cells must avoid excessive degradation during autophagy, Noda said, meaning they need to have mechanisms that terminate autophagy at the right time.

“We are currently investigating this question,” Noda said, “and already got some good candidate molecules” that might stop autophagy.

For work that helped uncover the molecular mechanisms in autophagy, Ohsumi was awarded the Nobel Prize in physiology or medicine in 2016.

JBC Associate Editor Paul Fraser at the University of Toronto nominated the paper as a Classic. Read this and other JBC Classics at jbc.org



When yeast cells are depleted of nutrients, autophagic bodies (small dark spherical structures) start to accumulate in their vacuoles (light gray structure). Noda and Ohsumi showed that the Tor protein inhibits autophagy in nutrient-rich conditions.

JOURNAL OF BIOLOGICAL CHEMISTRY

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Paving the way for disease-resistant rice

By Jonathan Griffin

Researchers have uncovered an unusual protein activity in rice that might give plants an edge in the evolutionary arms race against rice blast disease, a major threat to rice production.

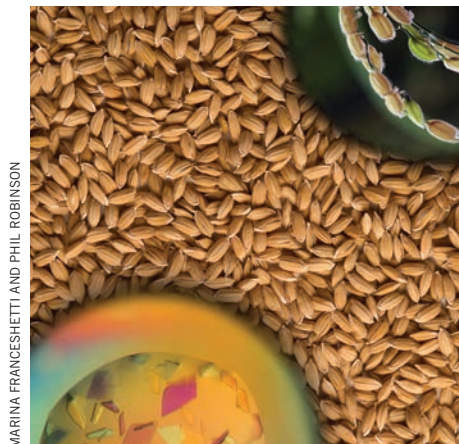
Magnaporthe oryzae, the fungus that leads to the disease, creates lesions on rice plants that reduce the yield and quality of grain, causing a loss of up to a third of the annual global rice harvest.

A sustainable approach to ward off the fungus has not yet been developed. Cost and environmental concerns limit the use of toxic fungicides. And a phenomenon called linkage drag, where undesirable genes are transferred along with desired ones, makes it difficult to breed varieties with improved disease resistance that still produce grain at a desired rate.

Gene-editing technologies that precisely insert genes in rice plants eventually could overcome linkage drag, but first, genes that boost rice immunity need to be identified or engineered.

Mark Banfield at the John Innes Centre and a team of researchers in Japan and the U.K. report in the **Journal of Biological Chemistry** that a particular rice immune receptor — from a class of receptors that typically recognize single pathogenic proteins — triggers immune reactions in response to two fungal proteins. The genes encoding this receptor could become a template for engineered receptors that detect multiple fungal proteins and thereby improve disease resistance.

Rice blast fungus deploys proteins



MARINA FRANCESCHETTI AND PHIL ROBINSON

Protein crystals and a rice panicle depicted against a backdrop of rice grains represent the structural biology and plant pathology aspects of a study that found a new way to combat rice blast disease.

known as effectors inside rice cells. In response, rice plants have evolved genes that encode nucleotide-binding leucine-rich repeat proteins, or NLRs, which are intracellular immune receptors that bait specific fungal effectors. After an NLR receptor's specific fungal effector binds to the bait, signaling pathways are initiated that cause cell death.

The cells “die in a very localized area so the rest of the plant is able to survive,” Banfield said. “It’s almost like sacrificing your finger to save the rest of your body.”

After learning that the fungal effectors AVR-Pia and AVR-Pik have similar structures, the researchers sought to find out whether any rice NLRs known to bind to one of these effectors might also bind to the other, Banfield said.

The team introduced different combinations of rice NLRs and fungal effectors into tobacco (a model for studying plant immunity) and also used rice plants to show if any unusual pairs could elicit immune responses. An AVR-Pik-binding rice NLR called Pikp triggered cell death in response to AVR-Pik as expected,

but the experiments showed that plants expressing this NLR also partially reacted to AVR-Pia.

Looking at the unexpected pairing using X-ray crystallography, the authors saw that the rice NLR possessed two separate docking sites for AVR-Pia and AVR-Pik.

Pikp causes meager immune reactions after binding AVR-Pia; however, the receptor’s DNA could be modified to improve its affinity for mismatched effectors, Banfield said. “If we can find a way to harness that capability, we could produce a super NLR that’s able to bind multiple pathogen effectors.”

As an ultimate endgame, gene-editing technologies could be used to insert enhanced versions of NLRs — such as Pikp — into plants, Banfield said, which could tip the scale in favor of healthy rice crops.

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Secrets of fat and the lymph node

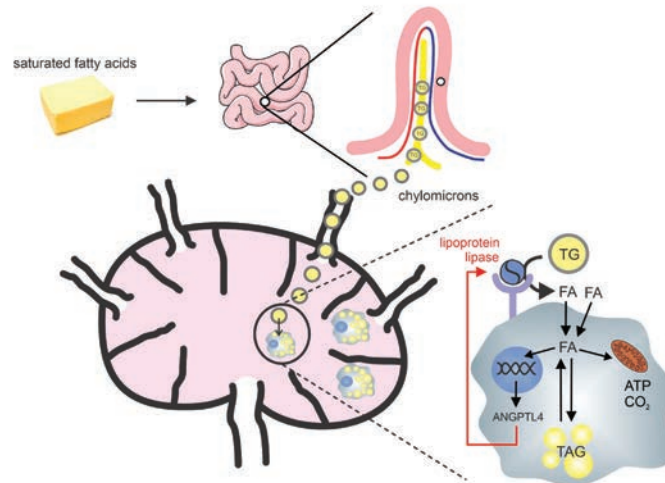
By Laurel Oldach

When you eat a high-fat meal, your gut exports the fat into chylomicrons, which join the flow of lymph in the surrounding vessels. This combined fluid, which resembles cream, passes rapidly through the lymph nodes and into the blood stream, where the fat is absorbed by cells that need energy, like heart muscle cells, or that can store fat for the long term, like adipose tissue.

Sander Kersten, a professor and department chair at Wageningen University in the Netherlands, studies that rapid uptake system, which depends on a protein called lipoprotein lipase, or LPL for short. LPL breaks down triglyceride fat molecules, allowing them to be absorbed. Kersten's latest study in the **Journal of Lipid Research** shows that LPL regulation varies among tissues.

Too much fat in the blood can cause problems such as heart disease. Therefore, right after a meal, it is beneficial for adipose tissue to absorb fat rapidly for storage. That means bumping up LPL levels. But during a long fast, limited LPL activity in adipose tissue helps ensure that fat stays available to cells that need it for energy. It is important that our bodies can tune LPL activity in different systems in response to how much food we eat.

Some 20 years ago, as a post-doc, Kersten isolated a protein, ANGPTL4, that acts as a control dial for LPL. Later, his lab demonstrated that the protein targets LPL for degradation in adipose cells. Researchers since have found that



COURTESY OF SANDER KERSTEN

A cartoon Kersten uses for teaching shows how saturated fat from the diet enters the lymph node as chylomicrons and how lymph node resident macrophages respond to the fat.

ANGPTL4 fluctuates in response to fasting, cold exposure and exercise, helping to control the body's lipid use.

Drug developers hoped that reducing ANGPTL4 would be a good way to reduce the risk of heart disease, but this research hit a snag. Mice that were bred to have no ANGPTL4 appeared healthy at first, but that health was fragile.

"If you place these animals on a diet that's rich in fat, they develop complications which were unanticipated," Kersten said. Lymph carrying chylomicrons escapes into their abdomens, eventually killing the mice. Whether this would happen in humans if you blocked their ANGPTL4 isn't known — it's an experiment no one is willing to risk.

The Kersten lab's latest paper examines why loss of ANGPTL4 has this effect. The work focuses on macrophages, the cells that populate the lymph node. Like fat cells, macrophages express ANGPTL4, and like fat cells, they turn it up in response

to high fat in the bloodstream. But ANGPTL4 in macrophages appears to work differently than in fat cells. Although ANGPTL4 reduces LPL activity and fat uptake in macrophages, it doesn't seem to alter LPL level — suggesting that it does not act by targeting LPL for degradation but by another mechanism. Exactly how ANGPTL4 affects macrophages, Kersten said, remains to be determined.

"After 20 years of studying ANGPTL4, there are some things that are very, very clear about this protein," Kersten said. "And I'm happy to have contributed to that."

Other questions remain. "We're not still 100% sure about what is going on in the lymph nodes."

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When prions are personal

Researchers on a quest for a cure publish new assay for monitoring protein level in folding disease

By *Laurel Oldach*

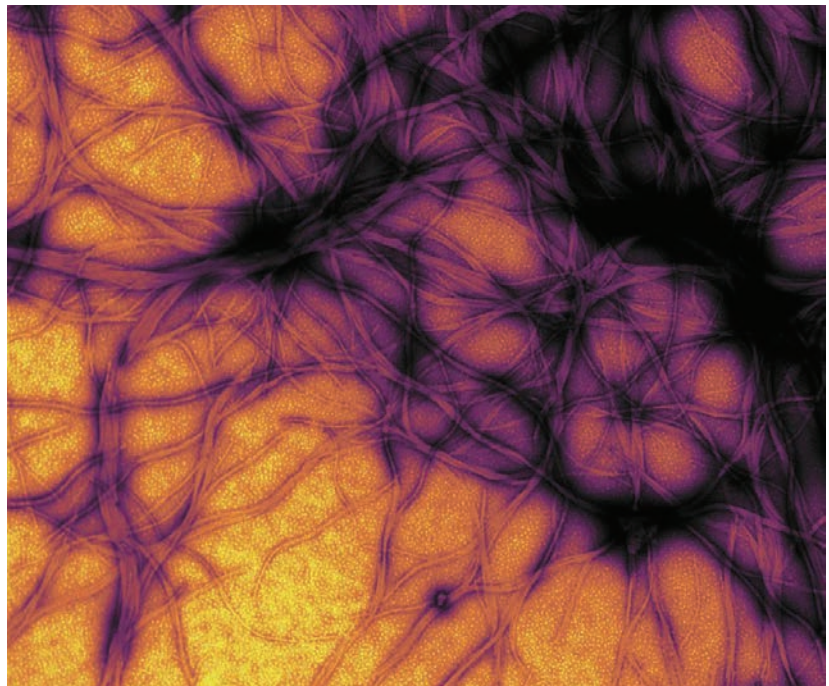
A research team with an especially personal stake in prion diseases has developed a new measurement that may be useful in testing the treatments they aim to pioneer.

Almost everyone produces the prion protein known as PrP, which is found in the brain and cerebrospinal fluid. Like most proteins, PrP folds into a characteristic structure when it is produced. But sometimes that structure can change. When one copy of PrP adopts a misfolded shape, other prion proteins it comes into contact with tend to adopt the same shape. The misfolded proteins spread like an infection, and they tend to clump together, damaging the brain.

For husband and wife team Sonia Vallabh and Eric Vallabh Minikel, prions became personal when Vallabh's mother died in her early fifties of a mysterious, rapidly advancing neurodegenerative disease. An autopsy showed that the culprit was a genetic prion disorder, a variant in PrP that makes the protein more likely to adopt a misfolded prion conformation. A test revealed that Vallabh, who is now in her thirties, had the gene too.

"She has a very high probability of developing the same disease by midlife," Minikel said. "And once it strikes, it's rapidly fatal."

After that genetic test, Vallabh and Minikel changed their lives. They started taking night classes in biology and took entry-level jobs in laboratories. They founded the Prion



NIH/ID

The prion protein forms fibrils like the ones shown here.

Alliance, a nonprofit dedicated to finding a cure. With support from leaders at Boston's Broad Institute, they enrolled in Harvard Medical School, and last spring they defended their Ph.D. theses, which focused on the mechanisms of prion disease, in back-to-back seminars. Now they're looking ahead toward testing treatments.

Researchers hope that if they can find a way to reduce the amount of prion protein in a person predisposed to prion disease, they can reduce the chances that person will develop the disease, or they might be able to delay the onset of symptoms.

But how will researchers know if

a potential treatment is working?

"The first and most basic thing you do in a clinical trial that's the first in humans is you try to find a dose that is potent and tolerated," Minikel said.

To measure a drug candidate's potency, researchers usually test for how much it affects its target. In this case, that would mean looking for a drop in PrP after treatment. However, in the normal course of this disease, the amount of detectable PrP drops dramatically after a person begins to show symptoms.

"It's very nonintuitive ... trying to lower a thing that already goes down at the onset of disease,"

Minikel said.

If disease progression and an effective drug candidate had the same effect on circulating PrP level, researchers would need to test the drug long before the disease began. And they weren't even sure if the PrP drop in the test results reflected reality. The most common test relies on an interaction between PrP and an antibody that recognizes its shape. As PrP refolds, the researchers wondered, could it become invisible to the antibody while still present in the cerebrospinal fluid?

As part of his thesis work, Minikel helped develop a new test to resolve this question. With colleagues at the Broad Institute who specialize in proteomics, he came up with a way to detect PrP that doesn't depend on the protein's shape. Instead, using a mass spectrometry technique called multiple reaction monitoring, the approach breaks the protein into bits and measures its constituent parts.

That means that even if the protein has changed shape, the assay can still detect it. The work recently was published in the journal **Molecular & Cellular Proteomics**.

Using this new assay to measure biobanked samples from patients, Minikel and his colleagues confirmed that PrP in the cerebrospinal fluid drops in the course of prion disease. Where the PrP goes is still an open question. But with greater confidence that it is indeed dropping when disease starts, the team has a roadmap for the best possible clinical tests for the drugs that they're starting to develop: They need to test potential drugs in people at risk of prion diseases who have not yet shown symptoms.

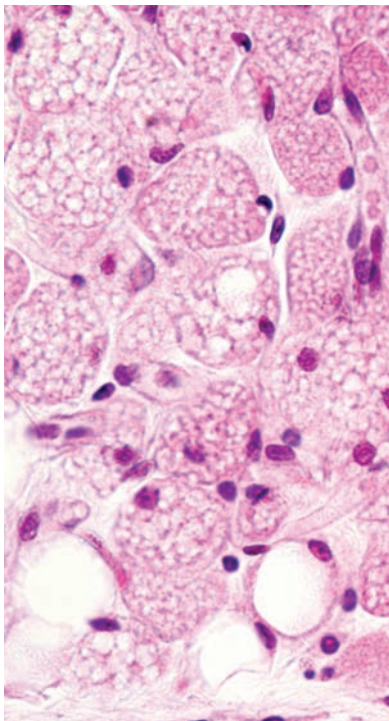
Working with a commercial partner, Vallabh and Minikel have started testing drug candidates in mice using antisense oligonucleotides, a technology that should suppress the production of prion protein. They

hope it will reduce the damage done by misfolded PrP. The early trials give Minikel hope, he said: Mice with genetic prion disorders, if treated before they show symptoms, survive longer without disease.

Even if this drug candidate doesn't prove effective, Minikel looks with pride at the groundwork they've laid.

"We've made tremendous progress in making this a what people in the industry would call a 'developable disease,'" he said. "And I think that's a really promising step forward no matter what happens with the antisense oligonucleotides."

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From the journals

By John Arnst, Jonathan Griffin, Angela Hopp, Kian Kamgar-Parsi & Laurel Oldach

Probing progesterone-producing cells in pregnancy

Extravillous trophoblasts, or EVT_s, support formation of the placenta, and EVT dysfunction has been associated with pregnancy complications. However, the unique characteristics of EVT_s compared to other cell types such as villous cytotrophoblasts, or vCTB_s, are not well understood. Research published in the **Journal of Lipid Research** provides new information on the metabolic characteristics of these key cells.

Austria- and California-based researchers led by Sigrid Vondra genomically profiled EVT_s and vCTB_s from first-trimester human placentas and found higher cholesterol levels in EVT_s as well as significant differences in genes associated with cholesterol metabolism. They found that EVT_s have higher levels of the enzyme HSD3B1, which is responsible for a final step in producing progesterone (a key pregnancy hormone) from cholesterol. Through additional analyses, the researchers discovered that EVT_s produced and secreted high levels of progesterone to support placental health and that they relied on their higher cholesterol levels to support this biological role. Perhaps most significantly, they found that HSD3B1 levels were decreased in placental samples from miscarriage, linking the EVT_s' progesterone production directly to pregnancy health. Further studies could provide warning signs and drug targets for healthy pregnancy management.
DOI: 10.1194/jlr.P093427

Profiling stem cells in differentiation

Mesenchymal stem cells, or MSCs, can differentiate into various cell types and have strong therapeutic potential for autoimmune disease and other disorders, but their development from embryonic stem cells remains poorly understood. In a recent paper published in the journal **Molecular & Cellular Proteomics**, a global research team led by Anja Billing of Weill Cornell Medicine-Qatar writes that they improved a protocol for developing MSCs from ES cells and then used this system to profile changes in the transcriptome, proteome and phosphoproteome during differentiation. The work identifies numerous regulatory changes that include changing expression of HOX transcription factors, long noncoding RNAs and signaling proteins. The multiomics approach also allowed the authors to appreciate, for example, that the proteins most phosphorylated are also the most strongly upregulated.
DOI: 10.1074/mcp.RA119.001356

How protein stability shapes disease

Mutations in SECISBP2 — a protein necessary for selenoprotein synthesis — are linked to human disease, but patients with these mutations exhibit a high degree of phenotypic heterogeneity. To gain insight into how different mutations influence SECISBP2 function and clinical phenotypes, Wenchao Zhao

of the Institut für Biochemie und Molekularbiologie and colleagues established two mouse models, each with a specific mutation that disrupts one of SECISBP2's two selenoprotein-producing functions. In the **Journal of Biological Chemistry**, they write that they found that while one mutation nullified SECISBP2 function, the other mutation had tissue-dependent effects, suggesting that differing clinical phenotypes may be caused by varying SECISBP2 stability in different tissues.
DOI: 10.1074/jbc.RA119.009369

Functions of a kidney regulator enzyme

Cytochromes CYP27B1 and CYP24A1 are known regulators of vitamin D in the kidney. However, the regulatory mechanism of the latter enzyme, which carries out separate functions in renal and nonrenal tissues, has not been clear. Mark B. Meyer, Seong Min Lee and colleagues in Wisconsin and Canada used ChIP-Seq and CRISPR/Cas9 genome editing to probe the genomic basis of CYP24A1 regulation in kidney and nonrenal target cells, or NRTC_s. They uncovered regulatory regions downstream of the *Cyp24a1* gene that, when specifically deleted, revealed a chromatin-based mechanism responsible for the CYP24A1's differing functions in the kidney and NRTC_s. Their study was published in the **Journal of Biological Chemistry**.
DOI: 10.1074/jbc.RA119.010173

Chasing tails: improving structural analysis of histones

Histones are essential for chromatin organization, but structural details for their N-terminal tails — which play a crucial role in epigenetic regulation by way of post-translational modifications — have proven elusive for crystallographic characterization. To obtain these structural details, researchers at the Broad Institute and the National Institute of Standards and Technology turned to hydrogen/deuterium-exchange mass spectrometry.

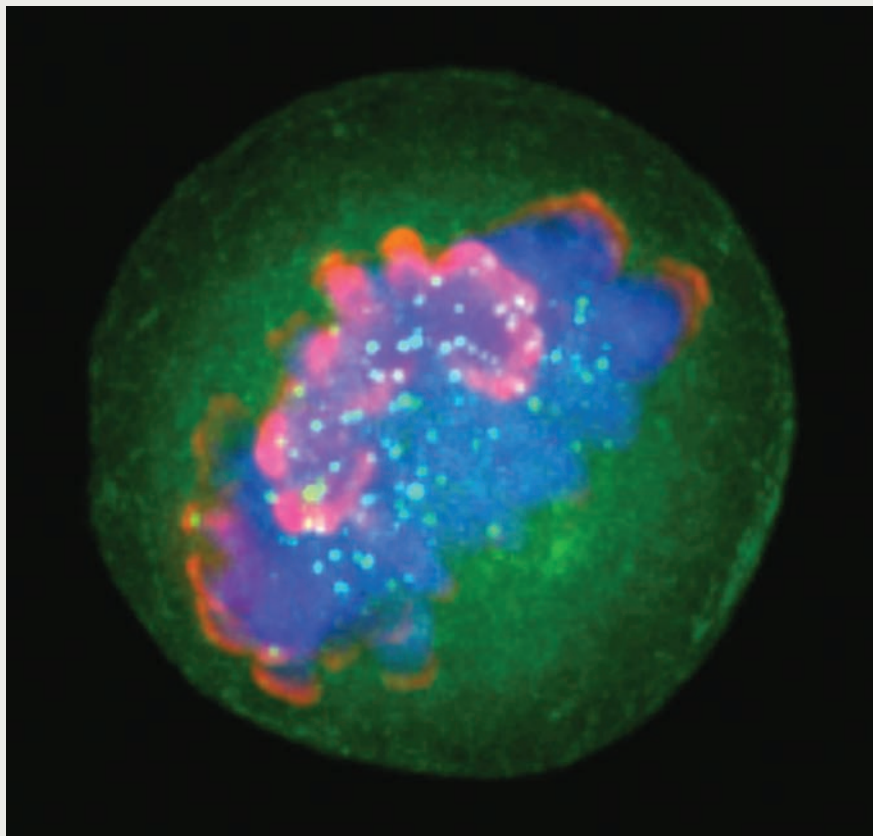
The technique, abbreviated as HX-MS, takes advantage of the tendency of hydrogens in certain proteins to trade places constantly with nearby hydrogen atoms when in aqueous solutions. When these proteins, such as histones, are exposed to heavy water that contains deuterium, a hydrogen isotope twice the mass of normal hydrogen, they wind up incorporating it in exposed positions on their surface. Once there, the deuterium atoms then can be used to probe protein conformation.

Malvina Papanastasiou and colleagues treated the four core histones — H2A, H2B, H3 and H4 — with the protease cathepsin-L, which helps improve coverage of histone tails, before subjecting them to HX-MS.

They found that cathepsin-L demonstrated unique cleavage patterns for each of the histones that were pH-dependent and that it generated overlapping N-terminal peptides about 20 amino acids long for the core histones H2A, H3 and H4. Taken together, the authors believe these results prove the protease’s suitability for the analysis of histone tail dynamics.

“Overall, this novel strategy opens new avenues for investigating the dynamic properties of histones that are not apparent from the crystal structures, providing insights into the structural basis of the histone code,” they write in their recent paper in the journal **Molecular & Cellular Proteomics**. DOI: 10.1074/mcp.RA119.001325

—John Arnst



Histones such as H3, shown here in pink during the metaphase stage of mitosis, package and order DNA in structural units called nucleosomes.

LAURA TRINKLE-MULCAHY

Sterol metabolism in the nematode

The metabolism of cholesterol is fundamental to eukaryotic life, as cholesterol contributes to hormone signaling, metabolism and maintaining cell structure. Given its importance in cellular function as well as its complexity, the cholesterol metabolism pathway is the subject of significant research to identify key divergences and elucidate major evolutionary points in eukaryotic life. Wenxu Zhou, Paxtyn Fisher and a team in W. David Nes' lab at Texas Tech have studied the cholesterol metabolism pathways of nematode worms (a common, well-characterized test organism) to elucidate the specific processes therein.

In research published in the **Journal of Lipid Research**, the researchers used a variety of biochemical and spectroscopic tools to follow the evolution of cholesterol and sterol intermediates in the worms. They already knew that sterol metabolism occurs along two evolutionarily divergent branches in the worms, leading to either C4-methyl stanol or C4-methyl stenol products. Experiments in this study showed that the enzyme sterol C4alpha-methyltransferase was responsible for regulating sterol flux through these divergent pathways via a novel mechanism. This additional knowledge of the cholesterol pathway could provide insights into the evolutionary development of eukaryotic sterol metabolism.

DOI: 10.1194/jlr.RA119000317

Does this receptor really bind sugars?

Recent work has shown that a domain of the immunoglobulin E-binding receptor CD23 resembles

a mammalian sugar-binding domain, but there have been conflicting reports regarding the receptor's sugar-binding activity. Sabine A. F. Jégouzo, Hadar Feinberg and colleagues in the U.S. and U.K. used solid-phase binding competition assays, glycoprotein blotting experiments and glycan array analysis to investigate the binding activity of various mammalian CD23s, they write in the **Journal of Biological Chemistry**. While no sugar binding was detected for human CD23, a range of sugars were found to bind to cow and mouse CD23. The findings suggest that CD23 may play various roles across different species. DOI: 10.1074/jbc.RA119.010572

Glycan markers assigned with beam search

Many antibodies used to recognize stem cells recognize glycan epitopes on surface proteins or lipids. To understand these reagents better, an international team led by Nian Wu of Imperial College London used glycans synthesized in the lab to determine what these antibodies bind to with greatest efficacy. Using a computing approach called a beam search, which enables rapid searching through large data sets, in this case a glycan microarray, the authors resolve uncertainty about exactly what these antibodies bind to. The results, which were published in the journal **Molecular & Cellular Proteomics**, also shed light on stem cell glycobiology.

DOI: 10.1074/mcp.RA119.001309

How strep prepares to infect

Streptococcus pyogenes — the bacterium responsible for strep throat and a diverse array of other diseases — relies on a surface poly-

saccharide called group A carbohydrate, or GAC, to infect human hosts. In a paper published in the **Journal of Biological Chemistry**, Azul Zorzoli and Benjamin H. Meyer of the University of Dundee and colleagues in Scotland and Russia write that they used molecular and synthetic biology approaches, biochemistry, radiolabeling and other techniques to show that the enzyme GacB performs a critical step in GAC biosynthesis. The results also indicated that the enzyme is conserved across the *Streptococcus* genus, including those with other types of surface carbohydrates, and may provide an opportunity to target early steps of GAC biosynthesis in *S. pyogenes* infections.

DOI: 10.1074/jbc.RA119.009894

The upshot of blocking ubiquitination

Proteins modified by ubiquitin and small ubiquitinlike modifier, or SUMO, proteins are pivotal in myriad essential cellular processes and are elevated under proteotoxic conditions such as heat shock, but the reason why has not been clear. To understand better the basis for this effect, Zhe Sha and a team from Harvard Medical School and the Leiden University Medical Center blocked ubiquitination in human cell lines with a selective inhibitor of ubiquitin-activating enzyme. The treatment led to a large accumulation of SUMOylated proteins located in special nuclear bodies. These unexpected results, which were published in the **Journal of Biological Chemistry**, offer insight into the interplay between ubiquitination and SUMOylation under stress.

DOI: 10.1074/jbc.RA119.009147

Lipid effects on endoplasmic reticulum structure

The endoplasmic reticulum, or ER, is a key organelle in all eukaryotic cells and plays essential roles in cell signaling and protein synthesis. The structure of the ER is integral to its function, and a number of human diseases including Alzheimer's, Type 2 diabetes and certain cancers are associated with changes in that structure. Previous research primarily has focused on the role of proteins in maintaining ER structure, while the role of lipids (the main structural element of cell membranes) is less well studied.

A new paper by Gabriela Ulloa and an international team, published in the **Journal of Lipid Research**, highlights the important role that lipids play in mediating ER structure.

The researchers changed ER membrane lipid compositions in relatively inert sea urchin oocytes. By fluorescently labeling the ER membrane and using advanced microscopy techniques, they were able to follow changes in the proportion of two main types of ER structure: flat sheets and curved rods. Through this microscopy-based approach, diacylglycerol, or DAG, was identified as a key lipid in mediating ER structure, as the researchers found

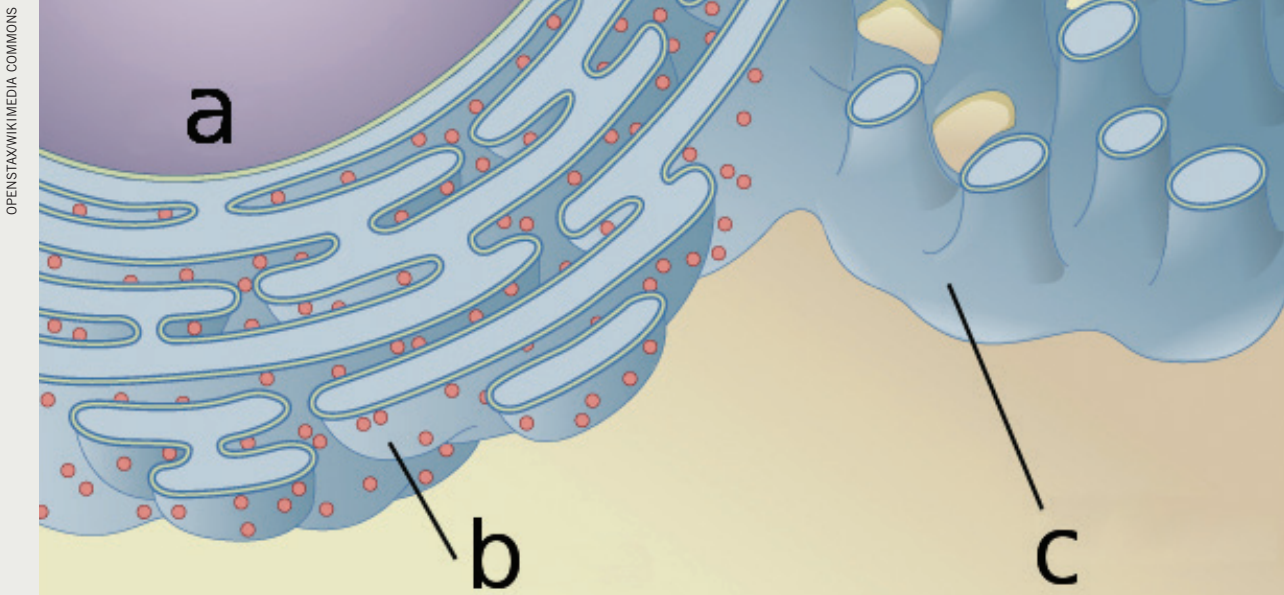
decreases in DAG skewed the rod-sheet split toward sheets.

Further experiments confirmed that the reintroduction of DAG recovered the normal balance, as did the addition of other lipids that energetically favor highly curved rodlike membranes, such as phosphatidylethanolamine. These ER structural modifications were independent of any changes in the number or type of proteins in the ER membrane, showing that the physical properties of the lipids themselves were driving the structural reformatting of the ER directly.

Beyond contributing to a deeper understanding of ER structural modifiers, this research could have applications in medicine. While most drugs target specific proteins, little drug development has targeted lipids directly to exert therapeutic benefit. With further study and more precise techniques, lipid-based targets for future therapies could emerge as a promising avenue in the treatment of ER-structure-associated human pathologies.

DOI: 10.1194/jlr.RA119000210

—Kian Kamgar-Parsi



The endoplasmic reticulum surrounds the nucleus (a), and has a structure including both sheetlike (b) and rodlike (c) sections that contribute to its function.

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Breaking down bacterial biofilm adhesion

Cholera is caused by consuming water or food contaminated with the bacterium *Vibrio cholerae*.

Like nearly all other bacteria, *Vibrio cholerae* forms a biofilm — a bacterial community stitched together with a glue of polysaccharides, proteins and nucleic acids. It produces these biofilms in water while it awaits its thirsty host and then, once ingested, to protect against the acidic environment of the stomach, allowing it to survive and enter the small intestine, where it produces the toxin that causes severe diarrhea, dehydration and even death.

Becoming a biofilm has its benefits. Bunches of bacteria are less vulnerable than singletons to predation by protozoa and bacteriophages. They're also more potent: Biofilms pack higher doses of bacteria and hyperinfective cells.

Scientists at Wesleyan University have been studying the bits and pieces of *Vibrio cholerae* biofilms found in water and the gut, and they recently reported a new finding about two components of the biofilm matrix in the **Journal of Biological Chemistry**.

Previous studies have suggested that the matrix proteins RbmC and Bap1 have redundant functions. When either is deleted, the biofilm grows as usual; when both are

deleted, though, the cell clusters cannot attach to surfaces.

The study by Katherine Kaus and colleagues in Rich Olson's lab at Wesleyan, however, suggests there may be nuanced, though important, differences in RbmC and Bap1.

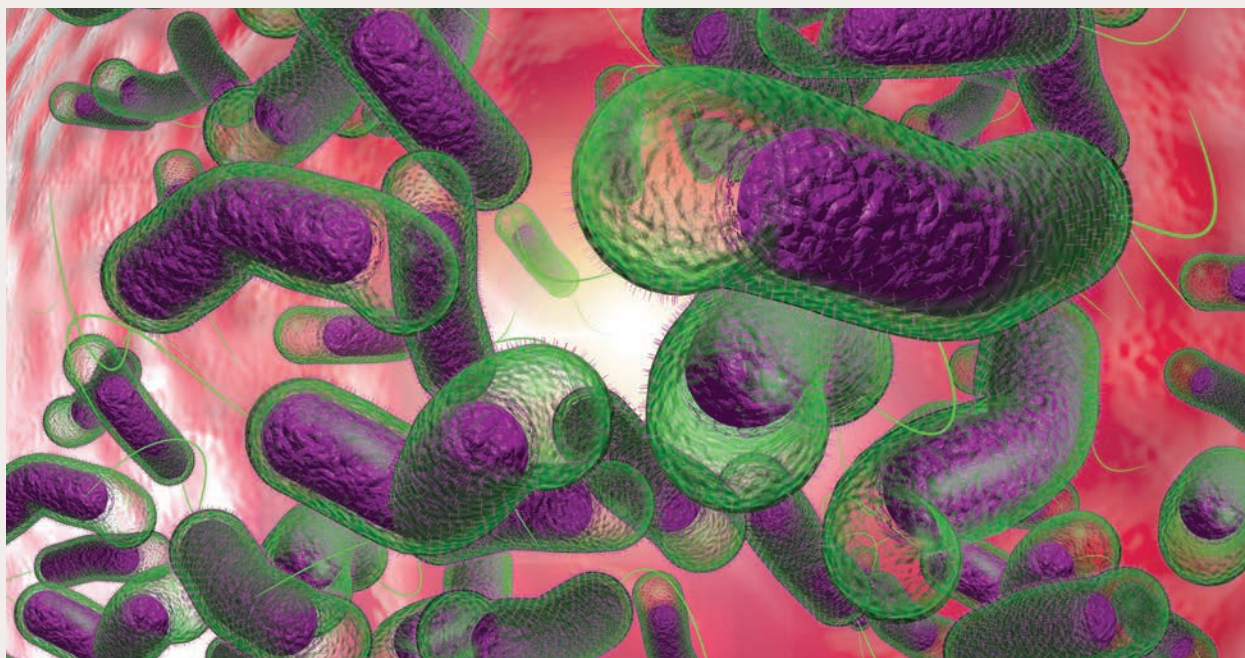
The team found that Bap1 has a different binding activity than RbmC; Bap1 prefers anionic polysaccharides over complex N-glycans. These results indicate that Bap1 and RbmC may play critical but different roles in biofilm surface attachment.

"These studies in conjunction with structures of Bap1 complexed with carbohydrate ligands will provide a framework for understanding the network of complex molecular interactions that underlie biofilm assembly and adhesion in *V. cholerae*," the authors wrote in *JBC*.

Kaus, now a postdoctoral researcher at the University of Texas Medical Branch in Galveston, said, "Our study is an exciting step forward in understanding the specific roles played by Bap1 and RbmC within the biofilm and how the slight differences in the two proteins might lead to important functional differences within the various environments encountered throughout the *Vibrio cholerae* lifecycle."

DOI: 10.1074/jbc.RA119.008335

— Angela Hopp



Elucidating a cervical cancer trigger

The degradation of tumor suppressor p53 by human papillomavirus, or HPV, oncoprotein E6 is a key step in the development of HPV-positive cervical cancer. E6 triggers the ubiquitination of p53 by associating with the ubiquitin ligase E6AP, but the function of the ligase is not well understood. By analyzing the p53 polyubiquitinated by E6AP in vitro, Yuji Masuda of Nagoya University and a team in Japan were able to elucidate details of the process. They found that p53 is multipolyubiquitinated with short chains and hypothesize that this is done in a stepwise manner. Together, the findings could inform the development of treatments for HPV-positive cervical cancer. The research was published in the **Journal of Biological Chemistry**. DOI: 10.1074/jbc.RA119.008374

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ANTS in the lab

Using social insects to study behavior and aging

By Alyson Smith



For more than a decade, researchers Danny Reinberg and Shelley Berger have studied ant communities to learn about links between epigenetics, gene expression and complex biological processes — and they have built their own cooperative scientific community in the process.

The two first met in the early 1990s, when Reinberg was a professor at the University of Medicine and Dentistry of New Jersey and Berger was a postdoctoral fellow at Harvard. Both studied transcription and gene expression, Reinberg by working out biochemical mechanisms and Berger by searching for new genes. At the time, Reinberg, Berger and other scientists were uncovering the nuts and bolts of epigenetics: how chemical tags attached to DNA and surrounding proteins control DNA packaging to specify which genes each cell within an organism expresses.

“We had very lively conversations debating the utility of biochemistry compared to genetics,” Berger recalled. “Over the years, I think it would be fair to say we developed a lot of respect for one another.”

Their shared interest in ants began in 2005 at an epigenetics conference in Mexico City when a strike tied up traffic and trapped them for hours in a cab they were sharing. They agreed that Reinberg’s experimental system of mammalian cells and Berger’s work with yeast limited their ability to dissect the role of epigenetic tags in complex processes such as neuroscience, aging and animal behavior. They needed a better model organism.

At one point, Berger’s eyes lit up. On a recent family vacation to Costa Rica, she had seen leaf-cutter ants in action. These ants run agrarian societies, finding and harvesting leaves that they use to grow their fungal food. As an undergraduate, Berger had learned that individual ants of the same species are closely related sisters: They share 75% of their DNA but can adapt radically different traits and behaviors when exposed to different environments.

“The vast differences in the way ants look and the way they act are due to epigenetic regula-



NEW YORK UNIVERSITY

As a Howard Hughes Medical Institute investigator, Danny Reinberg applied for the HHMI Collaborative Innovation Award, a four-year grant supporting investigators who form teams to pursue outside-the-box projects.



COURTESY OF SHELLEY BERGER

Shelley Berger, pictured here in her lab at the University of Pennsylvania, suggested to Danny Reinberg in 2005 that ants could be a powerful model organism to study epigenetics.

tion.” Berger said. “They have similar DNA, but during their lifetimes they can change because of environmental differences which lead to their aging differently or maybe even dying of different diseases.”

Berger suggested that ants held the promise of becoming a uniquely powerful model organism to study epigenetics in action. Reinberg instantly agreed that they should work on ants together.

In a recent paper in the *Annual Review of Genetics*, Reinberg shared some of what they’ve learned about the molecular mechanisms underlying social behavior since that cab ride.

A powerful model

Like termites, many bees and wasps, snapping shrimp, and naked mole rats, ants are eusocial, exhibiting the highest levels of cooperation found in animals. Ants and other

eusocial animals divide labor among two or more morphologically and behaviorally distinct castes; reproductive castes produce offspring while worker castes care for young, maintain and defend the hive, and forage for food.

Ant colonies are superorganisms: Each caste functions like an organ — an ovary, a reproductive tract, a muscle or a stomach — to accomplish what the colony needs to survive. Within its caste, each ant functions like a cell, relying on inter-organism communication and environmental cues to dictate behavior and maximize colony success. Their unique social structure makes ants wildly successful; they are found on nearly every landmass on Earth, and their global biomass rivals that of humans. Ants are also capable of feats of cooperation: foraging for food over long distances, building bridges with their own bodies and managing colonies of fungi or

KARL GLASTAD



Among carpenter ants, there are two worker castes. On the left is the minor forager, and on the right is the major soldier.

other insects to produce food.

With only one or a few reproducing queens in each ant colony, all colony members are closely related siblings. Despite similar genetics, castes may have distinct sizes, brains, body plans, behaviors and social interactions. Like genetically identical cells in a multicellular organism, the identity and behavior of individual ants depend less on DNA sequence than on how signal inputs at key points in differentiation and development act on that sequence.

Ants' unique genetic makeup allows Reinberg, Berger and their collaborators to study epigenetic factors behind development, behavior and other processes in isolation from the genetics.

Building a team

After forming their partnership during the cab ride, Reinberg and Berger knew they needed a large and unconventional funding source, because none of the ant genomes had been sequenced. In 2007, the Howard Hughes Medical Institute announced the Collaborative Innovation Award, a four-year grant funding HHMI investigators to form teams of scientists and pursue ambitious, outside-the-box projects. Reinberg, an HHMI investigator, suggested they apply.

Their first step was to find a collaborator who had experience working with ants in the lab. Berger's friend Laurence Zwiebel, an insect biologist at Vanderbilt, recommended ant biologist Jürgen Liebig of Arizona State University. Liebig was studying the carpenter ant *Camponotus floridanus* and the jumping ant *Harpegnathos saltator*. He was excited to combine his knowledge of ant biology with Reinberg's and Berger's experience in biochemistry and genetics to study behavior at the molecular level.

"You can study a whole society in a Petri dish or a shoe box when you work with ants," Liebig said. "This makes it much easier to study the organization of societies as you can control and replicate the experiments



When Shelley Berger and Danny Reinberg approached him about his work with ants, Jürgen Liebig, pictured in his lab at Arizona State University, was excited to combine his knowledge of ant biology with their experience in biochemistry and genetics to study behavior at the molecular level.

much better."

The carpenter ant has two types of workers (major and minor), while the jumping ant has two types of reproductive castes (queens and pseudoqueens). The scientists agreed that Berger would study the carpenter ant, and Reinberg would study the jumping ant — to exploit the species' unique caste structures and study different facets of epigenetics.

Liebig suggested that they study the epigenetics of aging in addition to behavior. In many ant species, the queen lives much longer than nonreproductive castes, sometimes up to 30 years. Liebig knew that carpenter ant queens live at least 17 years, while worker females live only two years. He also knew that when jumping ant queens died, nonreproductive workers could become reproductive pseudoqueens that maintained the colony and lived five times longer than normal workers. In the laboratory, Liebig had worked out protocols to switch jumping ant workers to pseudoqueens and back again, with concomitant changes in longevity.

The HHMI reviewers recognized that

studying epigenetics in ants could uncover mysteries behind human health, behavior and aging at a level not available in other model organisms. Reinberg and his team received the Collaborative Innovation Award in 2008 and 2012, jumpstarting their entry into ant epigenetics.

Making a model organism

By the time they received the HHMI funds, Reinberg had moved to the New York University School of Medicine and Berger to the University of Pennsylvania School of Medicine. Though ant colonies are rare in medical school labs, the deans at NYU and Penn, like the HHMI, understood the potential impacts this research could have on human health. The deans provided Reinberg and Berger with the financial support to build temperature-controlled ant rooms capable of housing dozens of ant colonies in clear plastic boxes.

Two intrepid postdocs agreed to lead the labs' first studies in carpenter and jumping ants: molecular biologist Roberto Bonasio in Reinberg's lab and computational biologist Daniel Simola in Berger's lab. Bonasio and Simola learned to use each species' unique reproductive strategy to maintain the colonies. They also learned how to conduct and interpret assays that quantify foraging, scouting and other social behaviors for later use in epigenetics research.

"The two of them really were the reason we got this going so beautifully in our two labs," Berger said of Bonasio and Simola. "We struck it rich in getting two really brilliant trainees."

The two labs clean the nests in their ant colonies once a week and feed the ants multiple times per week. The carpenter ants get sugar-water, mealworms and protein supplements; the jumping ants get live crickets. To meet U.S. Department of Agriculture requirements, the ants live in escape-proof containers with slippery walls in a sealed containment facility filled with oil traps.

When worker ants determined to forage for food manage break to out of their nest, they cannot reproduce and do not survive for long, especially if they encounter hostile workers from a different colony.

Using the genomics technology available at the time, it took the team two years to sequence, annotate and compare the carpenter and jumping ant genomes and transcriptomes. They discovered that the two types of ants had two common epigenetic tags (DNA methylation and histone acetylation) and enzymatic machinery to add and remove them.

Interspecies and intercaste differences in epigenetic tag prevalence and the expression of acetylating and methylating enzymes suggested that epigenetics plays a role in the social structure of each species. The scientists hypothesized that changing epigenetic tags could change behavior. Liebig's lab began feeding carpenter ants epigenetic drugs in their water. This strategy made the foragers more active but did not change the soldiers' behavior.

As in other animals, the brains of young ants are more plastic than those of adults; they are still developing and easier to change with drugs and other interventions. The researchers decided to switch from feeding adult ants drugs to injecting the drugs into the brains of young ants. When they injected newly hatched carpenter ant soldiers with inhibitors of deacetylation enzymes, the ants behaved like foragers instead of soldiers. The behavioral switch happened after injection with drugs that blocked several epigenetic enzymes and with RNA molecules that blocked specific enzymes.

"Although the drugs are very short-lived (lasting only a few hours), we could get a long-lasting epigenetic switch of behavior that could last 50 days," Berger said. "The soldiers would now forage as long as we could assay them."

"There was only a very small window in development in which we could change the phenotype," Reinberg said. "Once the

COURTESY OF ROBERTO BONASIO



Molecular biologist Roberto Bonasio, now an independent investigator at the University of Pennsylvania, led the Reinberg lab's studies of jumping ants when he was a postdoc.

COURTESY OF SHELLEY BERGER



As a postdoc, computational biologist Daniel Simola, now an investigator with GlaxoSmithKline, led the Berger lab's first studies in carpenter ants.



Two carpenter ants on a sleepy hibiscus bud at Juno Beach, Florida.

ant acquired the change, it was stable. That immediately told us that, yes, epigenetics is important.”

Armed with their knowledge of ant genetics and gene expression, Reinberg, Berger, Liebig and their collaborators turned to the gold standard in establishing a model organism: generating a heritable genetic mutation. In the fruit fly and other insects, the olfactory co-receptor Orco is required for olfactory function but not for survival. The team therefore decided to target Orco to generate adult mutant jumping ants that could demonstrate the role of Orco in social behaviors.

The ability to produce reproductive pseudoqueens from mutant jumping ant workers would make it possible to establish

colonies of mutant ants without relying on limited numbers of true queens. Learning to inject jumping ant embryos with the CRISPR-Cas9 machinery necessary to remove the Orco gene and then raise the resulting larvae to healthy, reproducing adults took years of trial and error. The researchers had to make tough decisions about which strategies to pursue.

“A lab is a company with one mission to accomplish,” Reinberg said. “We needed to abort some projects to make sure we could accomplish the mission. It was a very step-by-step learning experience.”

Finally, postdoc Hua Yan, grad student Comzit Opachaloemphan and NYU professor and fruit fly expert Claude Desplan estab-

JÜRGEN LIEBIG



A Harpegnathos worker next to a cocoon and a larva.

lished a successful CRISPR-Cas9 protocol. Jumping ants missing the Orco gene had reduced sensitivity to odorant chemicals and loss of brain regions responsible for processing olfactory signals. The mutant ants also displayed impaired social interactions with other ants, wandering outside the nest but not foraging for food and less able to mate, reproduce and care for their young. This study paved the way for future work on the role of olfaction in eusocial behavior and established the jumping ant as a genetic model organism.

The future of ant epigenetics

Reinberg and Berger continue to build on their decade of experience in ant epigenetics. After the HHMI Collaborative Innovation Award program ended in 2016, they secured traditional National Institutes of Health funding from the National Institute on Aging to apply their genetic and epigenetic tools in aging research.

Their labs are working to define gene expression changes behind caste development, behavior and aging, especially in the brain. Led by postdoc Karl Glastad, they are defining epigenetic pathways that change the brain to control caste identity. They hope to find epigenetic tags that persist as an ant transitions from one caste to another and continue to affect the ant's behavior, anatomy and/or longevity. In the future, they hope to expand the genetic toolkit of carpenter and jumping ants to rival that of more established model organisms, such as the fruit fly.

Reinberg, Berger and Liebig are proud of the work their teams have done to establish new model systems to study epigenetics.

"Each of us had to leave their comfort zone and engage in something new," Liebig said. "This allowed cross-fertilization from genetics, epigenetics and behavioral ecology and led to a boost in both areas. Ants have now become a new model system in genetics."

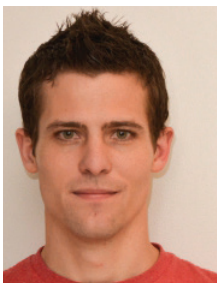
"I was hoping that the brain was going to be plastic enough that we could manipulate it and change the behavior," Berger said, "but I've been amazed that we can alter the brain using these methods. I think we'll be able to accomplish the same thing in aging as well."

"There is nothing impossible in science if you are persistent and passionate," Reinberg said. "Now I have to convince the entire scientific community that it was a success."

A lot has changed since that long cab ride in Mexico City. Reinberg and Berger, with the help of their collaborators and trainees, moved epigenetics research out of the test tube and into a complex model organism. Roberto Bonasio and Hua Yan are now independent investigators; together with Reinberg, Berger, Liebig and Desplan, they will carry ant epigenetics research decades into the future.

"With every model system we have used over the years," Reinberg said, "we have learned a lot from each of them that can be applied to humans. I do not know what exactly we are going to learn, but I know that we will learn at least two or three important things."

COURTESY OF SHELLEY BERGER



Postdoc Karl Glastad was first author on a recent paper out of Shelley Berger's lab on epigenetic pathways that change the brain to control social behavior in ants.

Alyson Smith

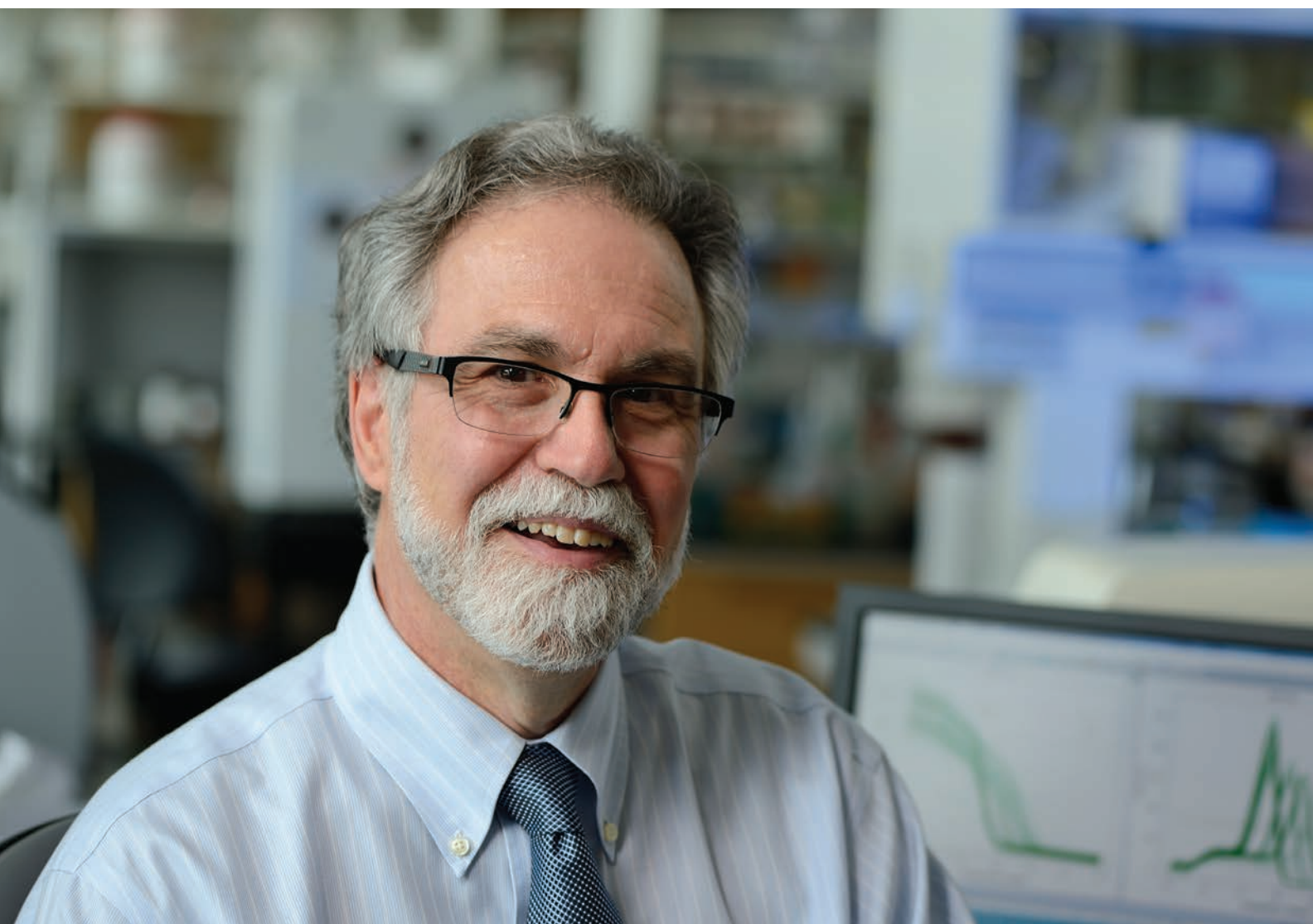
(alysonscsmith@gmail.com) is a scientist and scientific writer at Vala Sciences Inc. in San Diego, California. Follow her on Twitter @cellbionerd.





A jumping ant carries a flower for nest entrance decoration in Wynaad, India.

OXYGEN SENSING AND ADAPTING TO ALTITUDE



Gregg L. Semenza is one of three physician–scientists awarded the 2019 Nobel Prize for physiology or medicine.

Semenza shares 2019 Nobel Prize in physiology or medicine

By John Arnst

All cells of the human body, even cancerous ones, live or die by their access to oxygen. When that gaseous molecule is in short supply, the body responds by upregulating the hormone erythropoietin, or EPO, to pump out more red blood cells, as well as proteins that affect wound healing, metabolism, embryonic development and altitude adjustment. This response also plays a role in anemia, stroke, infection, myocardial infarction and cancer.

This year, the Nobel committee awarded its prize for physiology or medicine to a trio of physician-scientists — Gregg L. Semenza at Johns Hopkins University, William G. Kaelin Jr. at the Dana-Farber Cancer Institute and Peter J. Ratcliffe at Oxford University — for their roles in discovering how cells sense and adapt to oxygen availability.

In 1993, Semenza characterized the protein complex hypoxia-inducible factor, or HIF, which controls the production of EPO and other proteins made in response to hypoxia, or reduced oxygen levels. In 1995, he identified the genes that encode the two subunits of HIF. During that time, his lab and Ratcliffe's lab independently found that the oxygen-sensing mechanism is present in all bodily tissues rather than only in the kidney, where EPO is produced. Kaelin and his lab then found that the protein VHL, named after the inherited syndrome von Hippel-Lindau's disease, was involved in controlling responses to hypoxia. Ratcliffe's group subsequently found that VHL interacts with one of the two subunits of HIF, HIF-1 alpha, and tags it with ubiquitin for degradation at

normal oxygen levels.

Semenza and his lab since have probed the role that HIF-1 and a related protein, HIF-2, play in sites across the body, including the breast cancer tumor microenvironment. He also has taken an interest in how variants in HIF pathway proteins have been selected over millennia in populations in Tibet that have adapted to living at high altitudes.

"We started with a really specific goal," Semenza said. "We wanted to understand expression of one gene and how that gene responded to changes in oxygen in particular cells. And then, as we went on, the role of the HIFs just continued to expand and expand."

Like many laureates before him, Semenza missed the first early-morning phone call from the Nobel committee in October.

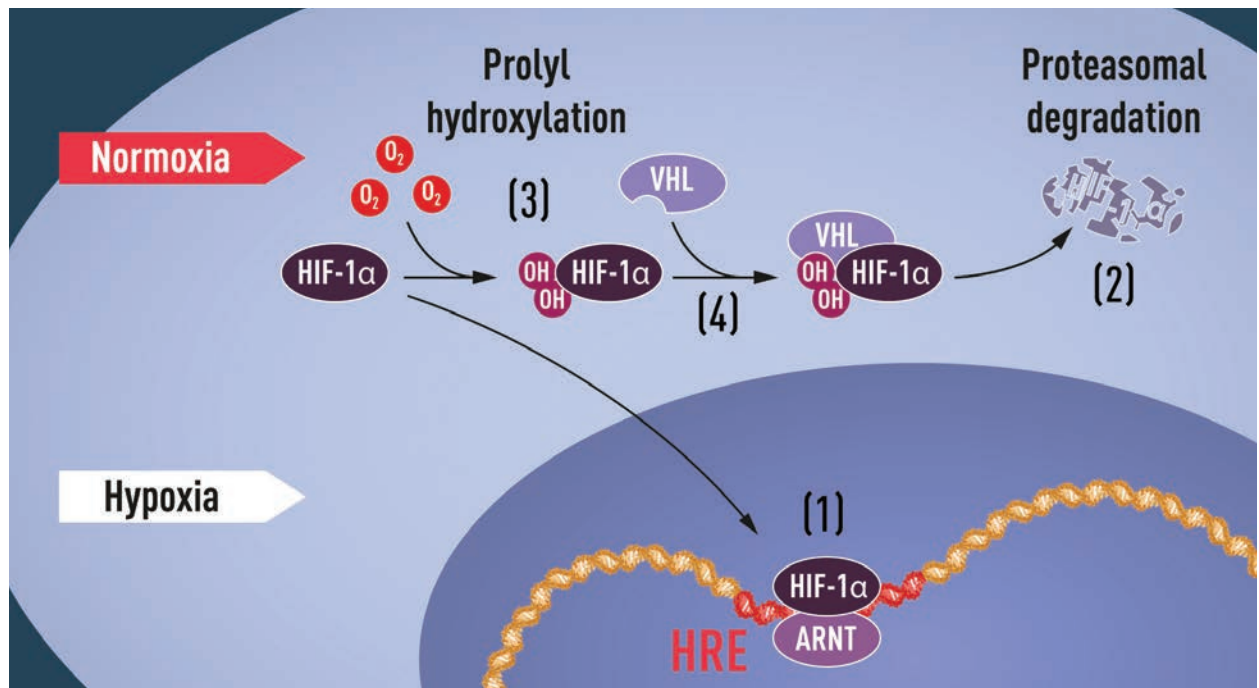
"I was so sound asleep that, by the time I got to the phone, it had stopped ringing. So I went back to sleep," he said. "It was actually quite some time later that the second call came and I thought 'I better be quicker this time.'"

The news was an exceptionally welcome bright spot in 2019. "It was a pretty bad year up until a few weeks ago," Semenza said during a mid-October interview in his lab at Hopkins.

In May, he fell down a flight of stairs and broke his neck. Hopkins was, by his account, a good place to be for that injury, from which he has recovered and has few complications. "Fortunately, we have an excellent neurosurgery department," he said.

Winning the Nobel was exciting, but for Semenza, ever since he decided as an undergrad to study genetics,

COURTESY KAROLINSKA INSTITUTE



When oxygen levels are low (hypoxia), HIF-1 alpha is protected from degradation and accumulates in the nucleus, where it associates with ARNT and binds to specific DNA sequences (HRE) in hypoxia-regulated genes (1). At normal oxygen levels, HIF-1 alpha is degraded rapidly by the proteasome (2). Oxygen regulates the degradation process by the addition of hydroxyl groups (OH) to HIF-1 alpha (3). The VHL protein then can recognize and form a complex with HIF-1 alpha, leading to its degradation in an oxygen-dependent manner (4).

FINDING EPO

The French physician Paul Carnot and his graduate student Clotilde-Camille Deflandre proposed hormonal regulation of red blood cell production in 1906 after investigating the effects of bloodletting on red blood cell concentration in rabbits. In 1948, Finnish scientists Eva Bonsdorff and Eeva Jalavisto named the hormone erythropoietin for the erythrocyte blood precursors found in bone marrow.

Eugene Goldwasser's lab at the University of Chicago purified EPO in 1977. In collaboration with the biopharmaceutical company anemia in people with kidney disease. The U.S. Food and Drug Administration approved the drug, sold as Epogen, in 1989. Amgen, Goldwasser then isolated the EPO gene and expressed it in an epithelial cell line. This paved the way for the drug epoetin alfa, developed to treat anemia in people with kidney disease. The U.S. Food and Drug Administration approved the drug, sold as Epogen, in 1989.

the focus always has been on how his research might affect patients' well-being.

"One of the benefits of being trained as a physician is that that also gives you a certain perspective ... and you see what patients and their families go through," Semenza said. "Then an experiment that doesn't work is not such an end-of-the-world thing."

Semenza and his wife waited a few hours to tell their adult children about the Nobel committee's call. In the meantime, he headed to his lab for an early-morning champagne toast.

Homing in on HIF

After graduating from Harvard University in 1978, Semenza enrolled in an M.D.–Ph.D. program at the University of Pennsylvania. When he arrived at Hopkins in 1986 for a postdoctoral fellowship — fresh off a pediatrics residency at Duke University Medical Center — he intended to continue studying his thesis topic, the molecular basis of the hemoglobin deficiency disorder beta-thalassemia in transgenic mice. However, Semenza's mentor at Hopkins, Haig Kazazian, and his colleague Stylianos Antonarakis had shifted to studying mutations in the factor VIII gene,

which is essential to blood clotting.

Semenza decided to focus on EPO expression (see box: Finding EPO); at the time, the hormone was believed to be expressed in the liver during early development but only in the kidney during adulthood.

The research team took advantage of the EPO gene's small size by inserting a fragment containing the whole gene and small flanking sequences, for a total of about 4 kilobases of DNA, into transgenic mice. As hoped for, this yielded expression of EPO in the liver of adult specimens.

Due to the presence of both the human and mice EPO genes, the mice produced too many red blood cells, a condition called polycythemia.

"But the gene was not expressed in a regulated way in the kidney," Semenza said. "And it was expressed in a lot of places where we thought it shouldn't be expressed, including the brain."

The researchers then inserted a larger piece of DNA, which curtailed some of the extraneous EPO expression. When they inserted an even larger fragment, which included important flanking sequences, they found that the protein was expressed exclusively in the fibroblast kidney cells where endogenous EPO is expressed.

"It was only then, after we had done all those experiments, that I began to think about the mechanisms for regulating the gene according to oxygen tension," Semenza said.

The researchers soon found that a short DNA sequence downstream of the EPO gene, which they named the hypoxia-response element, controlled the increase of EPO gene transcription in response to hypoxia. Over the following years, Semenza and his postdoc Guang Wang identified, characterized and purified a protein that bound to the HRE, which Semenza named HIF-1, and identified the sequence of its two subunits, designated as HIF-1 alpha and HIF-1 beta. The papers in which they characterized and purified HIF-1 were published in the *Journal of Biological Chemistry* in 1993 and 1995, respectively.

At low oxygen levels, HIF-1 alpha accumulates in the nucleus, where it and HIF-1 beta, which is identical to the protein ARNT, bind to and upregulate the EPO gene, stimulating production of hemoglobin. However, at normal oxygen levels, HIF-1 alpha rapidly is degraded by proteasomes, which target the protein once it has been

KAELIN, RATCLIFFE AND VHL

William Kaelin, who shared the Nobel Prize with Gregg Semenza and Peter Ratcliffe, discovered the von Hippel-Lindau, or VHL, protein — named for a genetic disease — when he was investigating its effects in families who had inherited a mutated form of it and, as a consequence, suffered dramatically increased risk of certain cancers. He found that cancer cells that did not express VHL expressed high levels of genes normally regulated by hypoxia, such as those related to angiogenesis, and thus tumor growth.

However, the oxygen-dependent mechanisms that told VHL when to tag HIF-1 alpha with ubiquitin remained a mystery until 2001, when Kaelin and Ratcliffe simultaneously found that, at normal oxygen levels, oxygen-sensitive enzymes called prolyl-hydroxylases modify HIF-1 alpha with hydroxyl groups that interact with VHL, bringing the entire mechanism into focus.

tagged with ubiquitin by the von Hippel-Lindau protein (see box: Kaelin, Ratcliffe and VHL).

Adaptations to altitude

Since puzzling out how HIF allows cells to sense oxygen levels, Semenza has wanted to know how that system adapts to the reduced oxygen in high-altitude environments such as Tibet and the Bolivian Andes. When someone whose family has lived for generations at low elevation rapidly ascends to altitudes above 8,000 feet, they can develop symptoms of acute mountain sickness, such as headaches, dizziness, nausea and exhaustion. Over time, this can develop into chronic mountain sickness, which is characterized by polycythemia and increased blood pressure; in severe cases, this becomes high-altitude pulmonary edema.

"As the red blood cell count goes up, the blood becomes more viscous and may be more likely to cause complications, particularly in pregnancy," Semenza said.

JOSEF PRCHAL



Gregg L. Semenza, left, and Josef Prchal, right, have been collaborators for over 30 years. In 2017, they visited a Mongolian nomad settlement on the Tibetan Plateau in China's Qinghai Province with Ge Ri-Li, director of the Research Center for High Altitude Medicine at Quigai University, and high-altitude anthropologist Cynthia M. Beall.

“When you think about it, the problem is not too few red blood cells, it’s too little oxygen.”

In 2014, Semenza and his collaborator Josef Prchal sequenced the HIF-containing genomic regions of 26 people from Tibet. To the researchers’ surprise, they found that hemoglobin levels don’t spike in the Tibetans and that a mutation was responsible for a lower oxygen threshold for HIF to signal EPO production.

“It was basically gain of function in Tibetans of negative regulators of HIFs,” Prchal said. “So in hypoxia, the Tibetans downregulated HIF.”

According to Semenza, Prchal was interested in finding mutated HIF variants after noticing that previous studies sequencing the genomes of people in Tibet were all missing a specific sequence.

“He found that that was very difficult to sequence, so he developed a protocol for getting it,” Semenza said. “And lo and behold, there was a polymorphism there that affected the amino acids. And remarkably, it occurred on the background of a gene that already had a variant at another site in the protein.”

Were it not for that first mutation, the second one, which was associated with low levels of hemoglobin, would have been impossible to develop.

“He calculated that this second mutation occurred 8,000 years ago on the background of this C-SNP (cysteine single nucleotide polymorphism),” Semenza said.

In a subsequent study, Prchal and colleagues at the University of Copenhagen found that a similar mutation had evolved in populations in the Bolivian Andes.

“Nobody went from Tibet to the Andes and said, ‘I’ve got a few variants you might need,’ right? This occurred independently,” Semenza said.

Independent groups also have found that HIF-2 alpha is mutated in both Tibetan mastiffs and Tibetan sheep.

“This is how you get to the best state under high altitude, right?” Semenza said. “You make a variant right in this gene ... medicine, biology, evolution — it’s amazing.”

Partners and mentors

Prchal, a hematologist at the University of Utah and native of the Czech Republic, has been collaborating with Semenza since the latter was a postdoc at Hopkins.

“He’s an extremely focused and driven person,” Prchal said. “If I need any advice about some very difficult biological puzzle, I don’t think anybody can give me better advice than Gregg.”

In 1995, shortly after Semenza published his seminal work on HIF regulation of EPO expression, he and Prchal collaborated on a paper in the journal *Nature Genetics* about mutations causing familial polycythemia in the Chuvash, a Turkic ethnic group in western Russia.

By Prchal’s account, he is one of a small handful of scientists Semenza has collaborated with continuously over the years, outside of Semenza’s mentors and mentees.

“I’ve been very fortunate to have had really superb mentors at every step of my career,” Semenza said. “I was really inspired by a school biology teacher; her name was Dr. Rose Nelson, and she started me on the way to my career in science.”

While Semenza encourages independence in his trainees, he continues to collaborate with a number of them. One of his former postdocs, Daniele Gilkes, who studies the hypoxic breast tumor microenvironment, started as an assistant professor at Hopkins in 2015.

“Having a mentor that was both a clinician and a scientist was extremely important and impactful for my training,” Gilkes said. “Gregg helped me to focus on



Daniele Gilkes' research at Johns Hopkins University focuses on the genetic alterations that happen under hypoxic conditions and how they can both contribute to tumor progression and be prevented.

research that could make a true impact on improving outcomes.”

Semenza pointed out early in her postdoctoral fellowship that metastasis, rather than the primary tumor, is what kills patients with breast cancer. Gilkes then focused her research efforts on oxygen's role as a critical determinant in the metastatic process.

She noted that even with as many as 15 people in the lab, Semenza always responded quickly to her questions.

“I try to do that for my students, because that was really important to me,” she said. “It made me feel like he

was very interested in the work that I was doing and that it was important to him. But it's difficult to emulate.”

Beyond the lab

In addition to their value as basic research, Semenza, Ratcliffe and Kaelin's discoveries about oxygen sensing have helped pave the way for drugs, now in advanced clinical trials, that could kill cancer cells by starving them of oxygen through inhibiting the prolyl hydroxylases that modify HIF or inhibiting HIF-1 alpha outright. While some have been approved in China, the drugs have yet to be marketed.

“I think in the U.S., we'll probably have an answer in one to two years from these trials,” Semenza said.

“We're doing those experiments because we hope that we're going to be able to do something that'll impact on public health. We haven't gotten there yet, so we'll just keep going.”

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



IN MEMORIAM: Paul Greengard

As we celebrate Gregg Semenza's Nobel prize, we look back on laureates Paul Greengard and Sydney Brenner who died earlier this year. A retrospective of Brenner is on page 14.

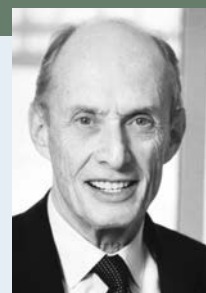
Neuroscientist Paul Greengard, who won the Nobel Prize in physiology or medicine in 2000 for discovering how brain cells react to dopamine, died April 13 at the age of 93.

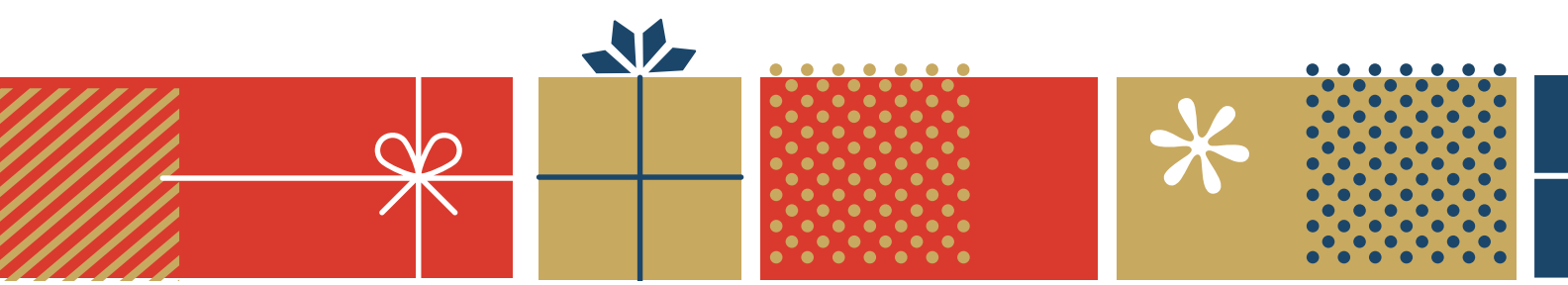
Greengard was born in Brooklyn on Dec. 11, 1925. After graduating from high school, he enlisted in the Navy, where he became an electronic technician and was assigned to a team at the Massachusetts Institute of Technology that worked on early-warning radar system to protect American ships in World War II. He then went to Hamilton College, where he majored in physics and mathematics. He received his Ph.D. in biophysics from Johns Hopkins University in 1953, and joined the faculty at Yale University in 1968 after years of postdoctoral work and a stint in the pharmaceutical industry.

At Yale, he conducted his then-underappreciated groundbreaking research on neurochemical signal transduction, which went against the prevailing notions that nerve cells communicated solely through electrical signals.

He started at The Rockefeller University in 1983, where he served as the founding director of the Fisher Center for Research on Alzheimer's Disease, a topic he researched, along with Parkinson's disease, depression and schizophrenia, until his death.

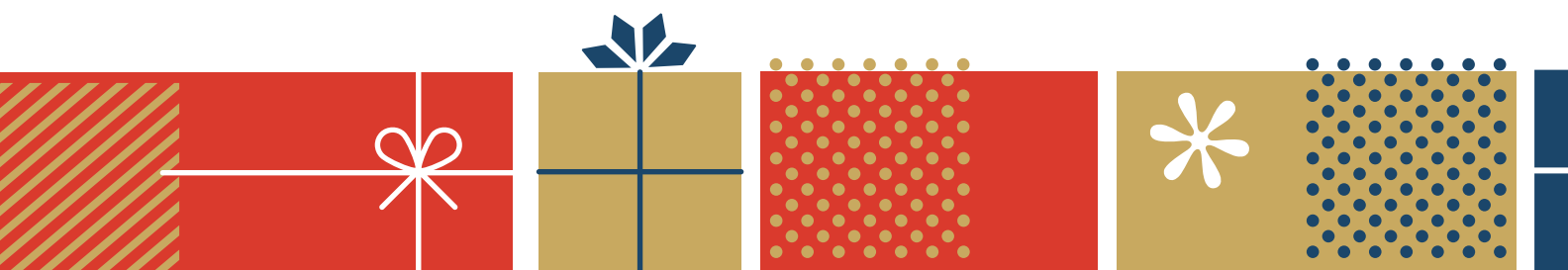
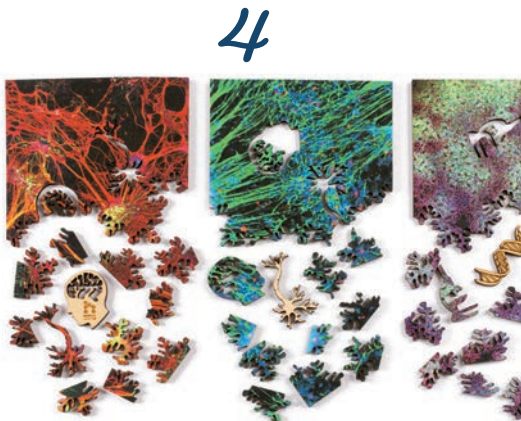
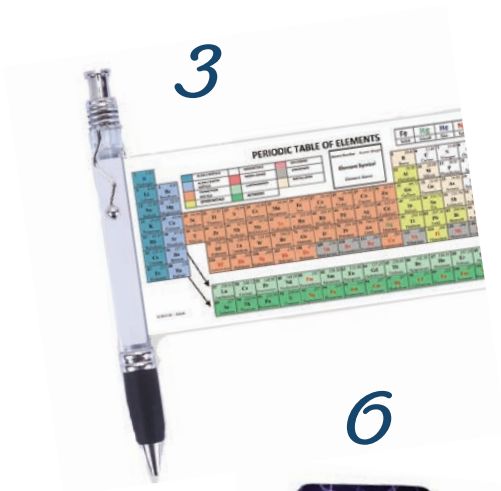
Greengard and his wife Ursula von Rydingsvard used the \$400,000 Nobel award to found an annual prize at Rockefeller University for outstanding female biomedical scientists. The Pearl Meister Greengard Prize, named after Greengard's mother, who died giving birth to him, has been awarded since 2004. Greengard is survived by his wife Ursula, sister Linda Greengard, three children and six grandchildren.

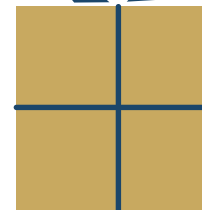




Gift Guide

WE HOPE THESE GIFT RECOMMENDATIONS HELP YOU CHECK SOME OF YOUR FAVORITE SCIENTISTS OFF YOUR HOLIDAY SHOPPING LIST.



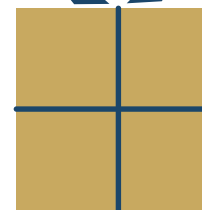


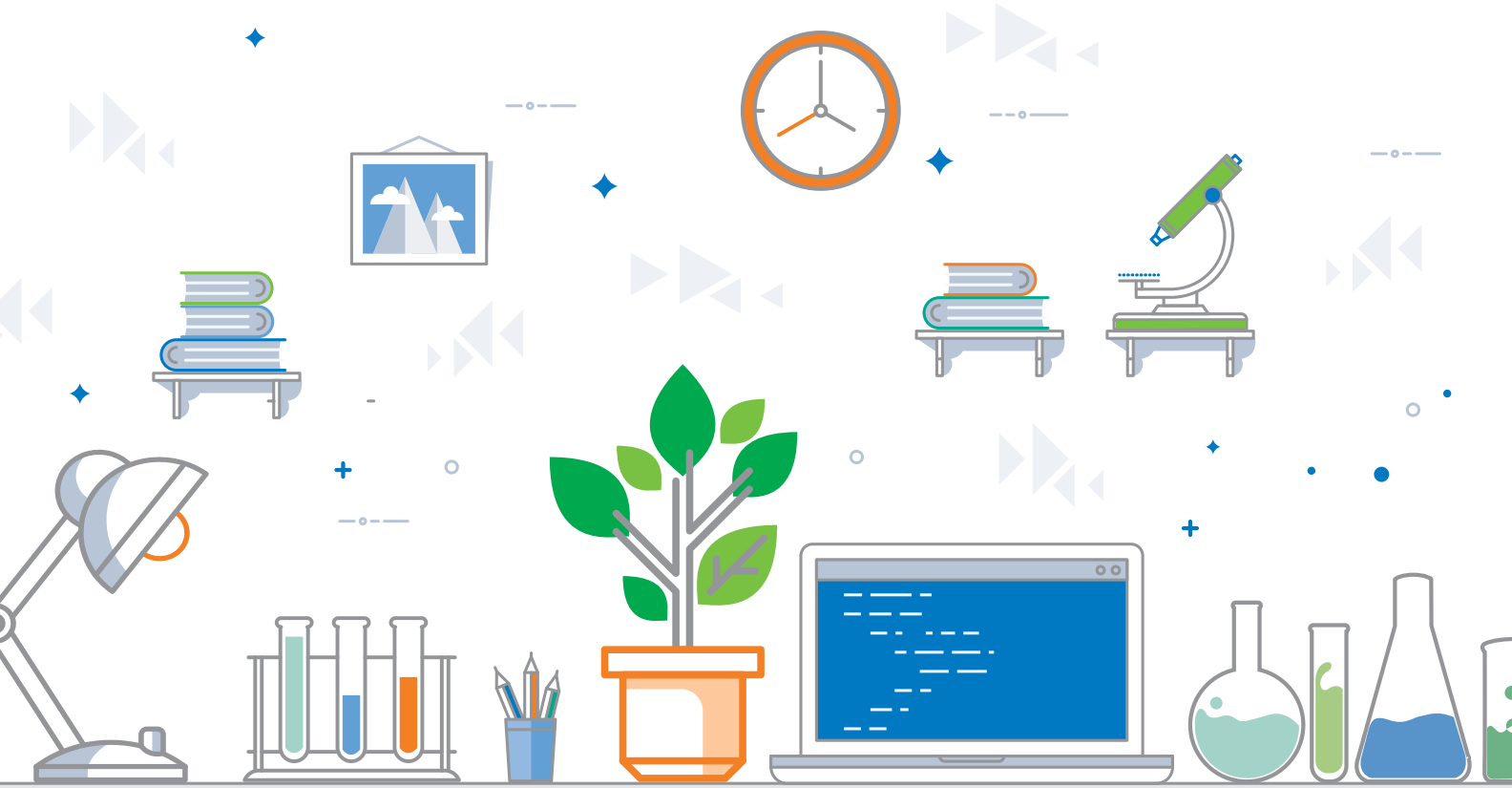
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This D.C.-based summer workshop yields impressive results; 75% of participants end up with successful grants within two years.

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asbmb.org/specialsymposia

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Annual meeting to highlight JLR junior associate editors

By George M. Carman & Robert V. Stahelin

The Journal of Lipid Research recently recruited four outstanding early-career scientists to serve as junior associate editors: Raymond Blind of the Vanderbilt University School of Medicine, Gissette Reyes-Soffer of the Columbia University Irving Medical Center, Brandon Davies of the University of Iowa Carver College of Medicine and Rotonya Carr of the University of Pennsylvania Perelman School of Medicine.

The JLR instituted the junior associate editors program to facilitate development of review skills and associated editorial activities. Since their appointments, these four junior AEs not only have been involved with the review process but also have organized a series of virtual issues highlighting the cutting-edge research published by the journal on lipoprotein clearance, sphingolipids and lipoprotein (a). A fourth virtual issue is due to be published this month.

When the American Society for Biochemistry and Molecular Biology Meetings Committee asked us to organize the JLR session for the upcoming annual meeting in San Diego, it seemed obvious that there was no better way to highlight the journal's commitment to early-career scientists than to have a session centered around our junior AEs. The JLR session, titled "Lipid Diversity and Disease: Spotlight on Journal of Lipid Research Junior Associate Editors," will highlight their lipid-based research ranging from basic to clinical studies.

As co-chairs of this JLR session, we invite you to read in the following pages about our junior AEs and the exciting work they will present on April 7 at the 2020 ASBMB Annual Meeting.

George M. Carman
(gcarman@rutgers.edu) is the founding director of the Rutgers Center for Lipid Research, a Journal of Lipid Research associate editor and co-director of the ASBMB Lipid Research Division.



Robert V. Stahelin
(rstaheli@purdue.edu) is the Retter professor of pharmacy at Purdue University and co-director of the ASBMB Lipid Research Division.



JLR JUNIOR ASSOCIATE EDITOR RAY BLIND

Becoming an active citizen and scientist

By Elizabeth Stivison

One thing becomes apparent quickly when talking to Ray Blind, an assistant professor of medicine, biochemistry and pharmacology at Vanderbilt University and Journal of Lipid Research junior associate editor: He doesn't isolate himself in an ivory tower.

Since he was a grad student at New York University, Blind has reached out to students of all ages and abilities who need a mentor or a teacher, especially those who otherwise might be unable to forge their way into science. He tutored learning-disabled undergraduates, mentored high schoolers and taught evening classes at Berkeley. During his postdoc at the University of California, San Francisco, he worked as a National Institutes of Health institutional research and academic career development, or IRACDA, fellow, teaching at a local college and sharing his insights about higher education. He also took time out of his postdoc work to teach at an understaffed medical school in Tanzania.

"The students who didn't go to private schools, the ones who had to work through college and maybe didn't have all the privileges other students had, I wanted to do whatever I could to help people like that," he said.

Blind sees himself in those students; his mother emigrated from Paraguay as a teenager after working outside her home since age 9, and his father built machine parts for General Motors. Both were curious, adventurous problem solvers,

The many facets of nonmembrane lipids

Ray Blind's lab studies aspects of what nonmembrane phosphoinositide lipids can do in the cell and how they do those things. In particular, the lab is interested in these lipids acting as signaling molecules in the nucleus.

One main arm (among many) of this work takes structural biology approaches, elucidating the structures of lipid-binding nuclear receptors as well as the nuclear lipid signaling enzyme inositol polyphosphate multikinase, or IPMK. This work suggested potential roles for the disordered domains in IPMK that previously had been somewhat mysterious to scientists.

Another branch of the lab's work is looking at the potential role lipid signaling enzymes like IPMK and PTEN have in chromatin remodeling and gene expression. They investigate genomewide binding of these molecules to understand how these proteins, traditionally thought to act only on membrane-bound lipids, may be regulating chromatin and transcription directly.



Ray Blind

important traits for the parents of a future scientist, but they were not part of the elite academic world, so Blind had to make his own way.

He initially thought he'd pursue a teaching career at a smaller liberal arts college but soon realized he wanted to do more research, and he has flourished since starting his lab. He hasn't forgotten his mission of service, though; he is working to establish an IRACDA teaching postdoc program at Vanderbilt.

Blind's mentor at the JLR, George Carman, describes him as

an "outstanding young scientist" as well as a "good citizen to the lipid community." Judging from Blind's career of service, he appears to be a good citizen of the wider science community as well.

Elizabeth Stivison (elizabeth.stivison@gmail.com) is a careers columnist for the ASBMB and a postdoc at Columbia University studying mechanisms of DNA repair.



JLR JUNIOR ASSOCIATE EDITOR ROTONYA CARR

Blending clinical, research perspectives to define early lipid disease

By Courtney Chandler

Rotonya Carr had little research experience before she began her medical residency fellowship at the University of Pennsylvania 11 years ago. After four years in med school and another four as a primary care physician, Carr joined the university's gastroenterology specialization program, which includes emphasis on the liver.

Carr was interested in metabolism and endocrinology, so she elected to work in the lab of Rexford Ahima, who since has moved to Johns Hopkins University. Ahima was starting to focus on diseases related to fatty livers, and Carr dove right in.

"It was the best decision I made in my career," Carr said. "I learned how to do bench science and learned about fatty liver disease from a clinical perspective and from a basic biology perspective too."

Now an assistant professor in the UPenn department of medicine's division of gastroenterology, Carr has made fatty liver disease her career. As a testament to her contributions to the field of lipid biology, she recently was selected as a junior editor for the *Journal of Lipid Research*.

Fatty liver disease, or FLD, is defined by the presence of fat in more than 5% of liver cells. Carr researches the early stages of FLD and wants to understand how dysregulation of lipid metabolism in the liver promotes disease. As a practicing clinician, she works with patients who have the disease she studies.

"My patients have so many

Understanding lipid crosstalk in fatty liver disease

Fatty liver disease, or FLD, is the most common liver disease in the U.S. and is estimated to affect more than 30% of the population. The liver, the body's largest internal organ, has myriad important roles, including converting food to fuel and processing fat. FLD can have alcohol-related and non-alcohol-related origins.

While the disease often is hard to diagnose in the early stages, this is exactly where Rotonya Carr has focused her research. Carr and colleagues have found that crosstalk between lipid droplets, which are lipid-rich cellular organelles, and lipid metabolism in the liver may relate to the development of FLD. She has identified a specific lipid droplet protein called perilipin 2 as a potential therapeutic target in alcoholic FLD and has related it to sphingolipid metabolism. Her lab is one of the only ones to identify ceramides, a specific family of lipid molecules, in lipid droplets.

Carr's talk at the American Society for Biochemistry and Molecular Biology annual meeting will focus on the crosstalk among sphingolipid metabolism, lipid droplets and cellular components and how it relates to FLD.



Rotonya Carr

questions related to the biology of their disease," she said. "I can explain what's going on in their bodies, and once they understand this connection between biology and disease, we see better results with their treatment plans."

Mentorship at the bench is important to Carr; she takes pride in supporting trainees who, like her, may have started with limited lab experience. Her top two pieces of advice are useful for researchers and clinicians alike.

"Have passion about your area of work and surround yourself with supportive colleagues," she said. "Your success will depend on you and your drive."

Courtney Chandler (courtneyec19@gmail.com) is a postdoctoral researcher at Johns Hopkins University and a careers columnist for the ASBMB. Follow her on Twitter @CourtneyEChan.



JLR JUNIOR ASSOCIATE EDITOR BRANDON DAVIES

Unraveling regulation of lipid partitioning

By Isha Dey

Good mentoring along his academic and professional journey helped shape Brandon Davies' career as a research scientist right from the start.

"I had a really good AP Biology teacher in high school who turned me on to science," Davies said.

His older brother Sean, a professor and researcher at Vanderbilt University, was Davies' first career mentor. Watching his brother go through the process of attending graduate school, doing a postdoc and then getting a job showed Davies what it takes to establish a career in science and guided him along his own path.

"I was blessed with excellent mentors during my Ph.D. and postdoc," he said. Though they each had different styles of mentoring and leadership, Davies said, they always wanted him to succeed and genuinely supported his desire to be a career scientist.

After majoring in biology and English as an undergraduate at the University of Utah, Davies earned a Ph.D. from the University of California, Berkeley, where he studied the role of two transcription factors in ergosterol synthesis. As a postdoc in the lab of Stephen Young at the University of California, Los Angeles, he simultaneously worked on two projects: the role of nuclear lamins in health and disease and the function of a protein called GPIHBP1 in the metabolism of triglyceride-rich proteins.

"Brandon was a joy to have in

A protein that regulates lipid partitioning

Lipids in the foods we eat are packaged into chylomicrons for circulation in the blood; from there, they are taken up by many tissues including the heart, skeletal muscle, adipose tissue, and the liver. Improper partitioning of lipids to tissues is associated with conditions such as diabetes, atherosclerosis and obesity.

A protein called lipoprotein lipase, or LPL, is a key determinant of lipid partitioning in the human body; the greater the LPL activity in a particular tissue, the greater the uptake of triglycerides by the same. Davies' lab seeks to understand how a group of proteins called angiopoietinlike proteins, or ANGPTL, regulate LPL activity. One such protein, ANGPTL4, inhibits LPL activity in the adipose tissue and shifts the delivery of fat away from adipose tissue to the heart and muscles, contributing to conditions such as atherosclerosis and muscle insulin resistance.

Davies and his colleagues study the tissue-specific activity of ANGPTL4. They have discovered that knocking out ANGPTL4 in the liver or adipose tissue of mice causes an age-dependent shift in fat partitioning. This is relevant because, with age, chances of developing metabolic disorders such as diabetes increase. This finding, when extrapolated to humans, could help explain the biology behind such metabolic disorders.



Brandon Davies

the group," Young said. "He was calm, diligent, organized, honest and creative."

Now an associate professor of biochemistry at the University of Iowa studying the regulation of lipid partitioning within the body, Davies advises budding researchers not to get discouraged with failure but to learn from their mistakes. "Look for a mentor who looks out for you," he said.

When not in the lab, Davies enjoys mountain biking and spending time with his three children.

Isha Dey (ishaadey@gmail.com) is a scientist at Thermo Fisher Scientific in India.



JLR JUNIOR ASSOCIATE EDITOR GISSETTE REYES-SOFFER

The rich rewards of a steep learning curve

By Pingdewinde Sam

Gisette Reyes-Soffer spent the first four months of her post-doctoral fellowship in Henry N. Ginsberg's lab pipetting lipoproteins by the bubbling method, a technique that is crucial for accurate and consistent results, while Ginsberg watched over her shoulder, making a 20-minute process feel like it was taking hours.

He had reason to be watchful. At the time, Reyes-Soffer had no previous lab experience. After earning an M.D. in the Dominican Republic, her homeland, she moved to the U.S. She joined Ginsberg's lab at the Columbia University Irving Institute for Clinical and Translational Research in 2004. The early stage of her transition to translational research came with a steep learning curve, she recalls. Bench work required persistence, which she had.

Reyes-Soffer is now an assistant professor in the department of medicine in the division of preventive medicine and nutrition with her own lab at the Columbia University Irving Medical Center Vagelos College of Physicians and Surgeons, mostly involved in clinical and translational research. Medical school satisfied the human aspect of her interest in health, while research has given her a solid career path to inquire into disease states and mechanisms that regulate them.

"When an experiment in the lab gives us expected results, we smile big," she said. "When it gives us unexpected results, we smile broader. This means we need to come up

Studying lipid-altering proteins in disease

Gisette Reyes-Soffer's lab uses stable isotopes to examine lipid and lipoprotein metabolic pathways with established and newly developed methodologies of mass spectrometry. The lab has developed key analytical methods to examine lipid-altering proteins that regulate cardiovascular and liver diseases.

Heart disease is the leading cause of death for both men and women in the U.S. Reyes-Soffer and her team have shown the relationship that exists between lipid and lipoprotein metabolism and the most common cause of cardiovascular disease, atherosclerosis. Atherosclerosis, or hardening of arteries, is caused by a buildup of fatty plaques that prevents oxygen-rich blood from flowing normally to organs and tissues, and the condition can lead to heart attack, stroke and death.

The Reyes-Soffer lab also is working to improve the health of the largest organ in the human body, the liver, which in adults is about the size of a football. The liver is involved in food digestion, storing energy and eliminating toxic substances. The lab is enlarging their research to include proteins other than lipoprotein (a) that might be involved in nonalcoholic fatty liver disease and body fat accumulation.



Gisette Reyes-Soffer

with a new hypothesis and find new answers to the problem."

Ginsberg mentored Reyes-Soffer for 15 years, from postdoctoral fellow to R01-funded assistant professor. "What has remained constant is her enthusiasm for research, which is only exceeded by her boundless energy and determination to be a successful, independent investigator," he said. "These characteristics, which are not uncommon in academics, are combined with her concern for

the success of her colleagues and her own trainees and, most importantly, a 'glass is full' love of life that makes working with her a joy."

Pingdewinde Sam
(psam1@jhmi.edu)
is a Ph.D. candidate in the department of cellular and molecular physiology at the Johns Hopkins University School of Medicine and the founder of Teëbo.org. Follow him on Twitter @samestry.



The nightlife of a scientist–mother

By Teisha Rowland

My half-awake mind dismissed the gentle rustling, but the movement persisted. Groggily I remembered the newest member of our family. My hand slipped between the crib bars, trying to soothe my nearly three-month-old son.

Hadn't I just fallen asleep?

A glance at the clock confirmed that once again my mind had deceived me; a couple of hours had passed. These awakenings interrupted my sleep three or four times a night. And every time, it felt like I had just dozed off.

A plaintive crying joined the increasingly frantic flailing inside the crib. My son was hungry. And if I waited much longer, he might wake up the entire household.

Time to move quickly.

I pulled back my warm sheets and, like an automaton, carried out the protocol that, though still new, had become familiar. I sat up, situated him on my lap and reached for my phone. Even on its dimmest setting, the screen seemed bright. Squinting, I navigated to the baby app and started the nursing timer.

My husband remained sound asleep. I'd crawled into bed early, after getting the baby down, while he stayed up entertaining our toddler until her bedtime. I missed the evenings with them, but this was the easiest way for me to accumulate maybe six hours of sleep, combining interrupted chunks plus sleeping in.

My husband didn't have the luxury of sleeping in — while I was on

maternity leave, he was already back at work. As a university professor and department chair, he'd need to be ready for a full day of teaching, mentoring, back-to-back meetings and directing the bucket brigade to put out the usual departmental fires.

Not long ago, I'd stayed up late too. But now I was up at all hours. A quiet, private time with our infant. And the manuscript.

My eyes adjusted while I checked for new emails from my collaborators. A few replies had arrived. They thought the revised figures looked good and the cover letter justified the novelty of our findings. The way we explained that unexpected result in the discussion section would have to be good enough for now; my co-authors agreed that we could wait to do the experiment later, after seeing reviewer responses. I couldn't do experiments now, in any case, and was starting a new job soon after my maternity leave ended. We would aim to submit later in the week. It would be my first paper as a postdoc in the lab. I was thrilled to have created a paper with a Nobel laureate.

I wished I could share the news with my husband, but I dared not disturb him.

I thought back to the frantic months in the lab, all of us racing against the clock to collect the data before my due date. *Were the figures we'd outlined on the whiteboard at that first manuscript meeting still the best way to tell this story? Did the surprising results complement the narrative or*

derail it? What gaps remained? Did we have the time fill them before I left the lab for months? Tick tick tick. If we didn't make this deadline, would we be scooped? If we succeeded, would the reviewers appreciate the significance of the findings in such a niche field? Would they be right not to appreciate them?

Somehow, we'd kept the momentum going, even across multidisciplinary collaborations. Somehow, I'd managed, even with increasing fatigue and new aches and pains, to collect the data before I'd left. It was a crazy plan. Somehow, it worked.

After giving birth, I worked from home to finish writing the paper. I scraped together the free moments of my day — between diapers, laundry, scarfing meals my husband had prepared and trying to soothe a fussy new being. I was grateful to collaborators who continued to wrap up loose ends in the lab and communicate via email. Face-to-face meetings (even virtual ones) were out of the question (I was still trying to teach my newborn what a schedule was; perhaps by the time he went to college he'd get it). Luckily, he was healthy and napped well. I often nursed him at my computer; he'd fall asleep on my lap, and I hardly noticed the hours passing as I focused on the manuscript. I pecked away at the keyboard with one hand. I fought for each spare second. Outlining, writing, editing, rewriting, making figures, tweaking figures, retweaking figures and editing my collaborators' revisions.



Was there an alternative to chasing this manuscript, this obsession? *Motherhood*. I wanted what was best for my baby, to bond with this tiny fascinating life. At the same time, I felt like I was fighting for my identity as a scientist against potentially all-consuming motherhood. It did not surprise me to learn of a recent study published in *Nature* showing that more than 40% of full-time female scientists quit science or became part-time after having their first child (compared to 23% of new fathers). Being a new parent is exhausting. And there's the guilt. Was I still being a good mother? Was my drive to publish diminishing my motherhood? Would my children grow up to resent me because I have a career?

My return to full-time work was also a matter of finances; without my

job, we could not afford our mortgage. One postdoc I knew could not afford full-time daycare and had to juggle taking baby care with their partner. Yet another postdoc said she couldn't have kids because she couldn't afford the childcare on her salary. A female professor once told me that, financially, it was better to wait until landing a tenure-track job before having kids, but with fertility rates dropping in a woman's 30s (more steeply after 35), and most postdocs being 30-34 years old, and most first tenure-track positions being landed at age 33-36, it is definitely tight timing. *Tick tick tick*.

My phone vibrated. "Have fed for 15 minutes," a pop-up told me. The baby was asleep, his lips barely moving. Gently I lifted him, patting him close against my shoulder,

and he let out a satisfying burp. As I was changing his diaper, he woke up. In the dark room, my hands went through the familiar motions. He softly cried, and again I tried to calm him before the wails woke my husband and toddler. He was ready for round two.

Sitting back in bed, I started the timer again.

What would I be doing when I got back to lab? I opened my action items and added a few more bullet-pointed experiments to the long list. I'd have only one week in lab before starting my new job. Five days to wrap it all up. *If I made the cDNA on Monday morning, assuming the RNA was still good, how many qRT-PCR plates could I run? Where would that put me by Wednesday, and then by Friday, assuming I wasn't so sleep-deprived that I*

Suddenly, I heard a gentle rustling, followed by a plaintive cry.

Hadn't I just fallen asleep?

I looked at our clock. No, more than two hours had passed, once again. At least it's easy to fall asleep when one is so sleep deprived.

botched the experiments? I opened my calendar app and blocked out time for the runs.

Then I shifted the times I already had blocked off for running to the lactation room, roughly every 2-3 hours. (*If I spaced the times out more, would there still be enough milk to avoid formula for a while?*) I tried to remember which incubation steps were at least 20 minutes long, allowing for a lactation room visit. Thinking about a recent study showing that the time of day that milk is produced acts as a circadian cue to the infant, I set a reminder to label my bottles when I pumped, and I hoped daycare could follow such labeling instructions too. It would be nice if that helped him sleep through the night.

Keeping busy would at least help distract me from missing him. We liked the day care center but didn't know our baby's caregivers. I hoped he'd be in good hands, that they'd get him to take his bottles well, that if he managed to roll onto his belly during a nap they'd make sure he didn't suffocate. I hoped he wouldn't catch a cold from the onslaught of day care germs, and then I felt guilty as I realized I was worried about how his illness might disrupt my carefully planned experimental schedule.

I'd have more flexibility at my new job as director of a new shared stem cell center. It was focused on my specialty – researching human pluripotent stem cells. I'd be doing

fewer experiments, but I'd have more meetings and teaching obligations, so picking up sick kids still would be a careful dance with my husband and his busy schedule. Having my own office meant I could pump at my desk, with little disruption to my work.

I opened my action items for getting the stem cell center off to a good start. *Move forward with purchasing the specialized tissue culture incubators. Look for a refurbished, used or demo microscope to save funds. Set up the center's website to attract users. Get the word out on the training that will be offered.* I wanted everybody to know about this new resource where people could grow their own cells, do their research and receive hands-on training. I dreamed of it being busy with users conducting world-class research and forging multidisciplinary collaborations. *How would I get there? How long would it take?*

My phone vibrated. "Have fed for 15 minutes." I listened to the baby's rhythmic, peaceful breathing.

I set my phone back on the nightstand. Gently lifting my son to my shoulder, I patted him a few times and he burped. I held him a little longer, feeling his cheek against mine. *Who will you be someday? Will you become a scientist like your parents, try to answer the difficult questions of our time or build tools to help humanity — or wisely run from the profession?*

He settled in his crib, and I settled back into bed. Emails I wanted to send and action items to add to my lists still buzzed through my brain, but I resisted picking the phone back up. Soon, the gentle breathing of my husband and baby lulled me back to sleep.

Suddenly, I heard a gentle rustling, followed by a plaintive cry.

Hadn't I just fallen asleep?

I looked at our clock. No, more than two hours had passed, once again. At least it's easy to fall asleep when one is so sleep deprived.

I placed my baby on my lap and reached for my phone.

Teisha Rowland (Teisha.Rowland@colorado.edu) is director of the Stem Cell Research and Technology Resource Center at the University of Colorado Boulder. She is passionate about science education; Women in Science and Education, or WISE, efforts; helping scientists become better communicators; and being a geek. Rowland was a postdoc in Thomas R. Cech's laboratory while on maternity leave, and the manuscript she writes about was published in PNAS.



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DECEMBER	2–8	National Influenza Vaccination Week
	5	ASBMB–Deuel Conference on Lipids early registration deadline
JANUARY	1–31	National Mentoring Month
	30	Deadline for last-chance abstracts for 2020 annual meeting
	30	Deadline for scientific outreach abstracts for 2020 annual meeting
FEBRUARY	31	Deadline for Student Chapters Honor Society applications
	4	World Cancer Day
	4	Deadline for ASBMB–Deuel Conference on Lipids abstract submission
	14	Deadline for ASBMB Outstanding Chapter Award applications
19	Deadline for ASBMB–Deuel Conference on Lipids registration	
29	Rare Disease Day	



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<http://www.asbmb.org/Careers/Jobs/81990/>

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Candidates should have a Ph.D. in forensic science, molecular biology, analytical chemistry, or other closely related field, a strong commitment to undergraduate education, and demonstrated teaching abilities. Extensive professional work experience working in a forensic science laboratory or in a molecular biology/analytical chemistry laboratory focused on forensic science applications is required.

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Daily morning sessions at the ASBMB annual meeting are divided into eight tracks addressing different topics in biochemistry; stay in your lane or explore other domains.

BIOCHEMISTRY OF LIPIDS AND MEMBRANES

- Novel roles of lipids in health and disease
- How lipids impact the structure and function of membrane proteins
- Membrane biogenesis and trafficking

GLYCOSYLATION AND EXTRACELLULAR MATRIX IN DEVELOPMENT, REPAIR AND DISEASE

- Glycosylation and extracellular matrix in development, repair and cancer
- Glycosylation and extracellular matrix in immunologic, inflammatory and infectious disease
- Glycosylation and extracellular matrix in neurologic and metabolic diseases

MOLECULAR MACHINES – STRUCTURE AND FUNCTION

- Molecular machines: New paradigms in structure, function and engineering
- Molecular motors
- Molecular motors in transport, biosynthesis and energy transduction

MOLECULAR MECHANISMS OF CELL SIGNALING

- Mechanosignaling
- Posttranslational modifications/signaling
- Emerging mechanisms of signaling

NEW DEVELOPMENTS IN METABOLISM

- NAD synthesis, salvage and sirtuins in tissue health
- Control of cell fate by metabolic intermediates
- New insights into control of metabolism by transporters

RNA AND DISEASE

- Noncoding RNAs and disease
- RNA modifications and disease
- RNA binding proteins and control of RNA biogenesis in disease

RE-IMAGINING STEM: WHO WE ARE AND WHAT WE DO

- Who we are: Creating a culture of wellness in science
- What we do: Choosing pedagogy over content

UNDERSTANDING THE RULES OF LIFE

- Cell decision making
- Regulation of gene expression
- Best practices for preventing/managing incidences of harassment in the workplace