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ASBMB TODAY

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

THE ODYSSEY OF AUTOPHAGY

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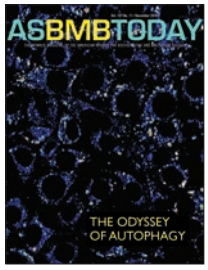

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Note about Nobels

By Rajendrani Mukhopadhyay

It was two weeks after the Nobel Prizes were announced for this year (well, one week, if you include the delayed announcement of the literature prize to Bob Dylan). I was hosting a birthday party for one of my sons at home. This meant I had a herd of elementary-school boys stampeding through my house fueled by cheese pizza and lemonade. I only had to wonder how the noise level would change when the birthday doughnuts were served.

Not only was I responsible for making sure no child lost a limb or an eye, but I also had to host some parents. It was the first time I was meeting these parents, and I was regretting that the social circumstances were not more dignified. But we managed to carry on a conversation while the ceiling trembled over our heads. We began with the obligatory "What do you do?" conversation opener.

I always find these conversations a bit trying, because it takes me a while to explain what I do. When I say I'm a managing editor of a science magazine, people immediately assume it's Scientific American or Popular Science. I then have to say, "No, no, you can't buy this magazine at the grocery store," and, "It's published by a scientific society." Then, inevitably, I get asked the name of the scientific society, and as I rattle off "The American Society for Biochemistry and Molecular Biology" most people's eyes glaze over as they get flashbacks to that one nightmare semester of organic chemistry they took.

It wasn't very different with the parents sitting in my dining room. One was an Air Force pilot. Another was a mental-health therapist. I was the only one steeped in the life-sciences.

At this point of the conversation, I get asked what the magazine covers in its pages. I'm usually ready to talk about the proteomics of breastmilk or the science of catching performance-enhancing drugs in elite sports. But on that day, for a moment, my mind went blank. I can't think clearly when there is a cacophony of yelling and banging of plastic light sabers and wands (Star Wars and Harry Potter are very popular in my household right now). Panicked at causing the conversation to stall, I forced myself to think about what I had edited earlier in the day.

It was John Arnst's feature, which is the cover story for this issue of ASBMB Today. It's about the 2016 Nobel Prize in physiology or medicine to Yoshinori Ohsumi for his work on autophagy.

I turned to the parents and asked, "Did you hear about this year's Nobel Prize to the scientist who described self-eating?" They nodded and eagerly asked me to explain what this year's prize was all about. They had heard the announcement but didn't fully understand what was being recognized by the prize and why it mattered. As I launched into an explanation about autophagy, I sent a mental note of gratitude to Alfred Nobel.

In 1896, the relatives of the Swedish gunpowder magnate Alfred Nobel opened up his will after his death on Dec. 10 and were horrified to discover that the man had bequeathed his wealth in the most unusual way. In his extraordinary will, Nobel stipulated that his wealth would be used to give out prizes in five areas that were of personal interest to him: physics, chemistry, physiology or medicine, literature, and peace. He also stipulated

that there couldn't be more than three winners for each of the prizes.

The Nobel Prizes, like all prizes, are imperfect. In the modern era of multidisciplinary science that involves teams of people, the Nobel Prizes for science can appear anachronistic by choosing a few individuals for fame and glory.

Almost every year, when the Nobel Prizes get announced, there are grumblings about those who lost out on proper recognition. This year's controversial literature prize to Dylan is a perfect example, as many took offense that a songwriter who's already won Grammy Awards got the prestigious prize instead of a writer of literary fiction or a poet.

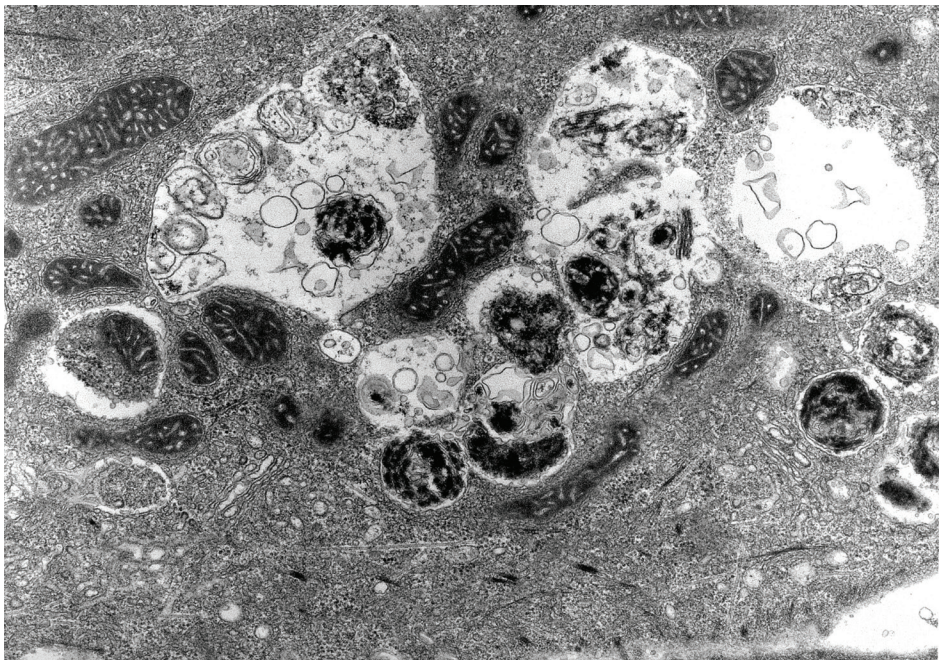

IMAGE PROVIDED BY SHARON TOOZE

The electron micrograph shows autophagy, the subject of this year's Nobel Prize in physiology or medicine, in action.

The Nobel Prizes in science have their fair share of complaints. Just take the Nobel Prize in chemistry, which always sparks a lot of soul-searching about what chemistry really is because biologists seem to keep getting the prize. When Roger Kornberg of Stanford University won the 2006 Nobel Prize in chemistry for his work on RNA transcription, a Nature News story questioned whether the work even was bona fide chemistry. The same thing happened last year. The 2015 Nobel Prize in chemistry was given to Tomas Lindahl at the Francis Crick Institute and Clare Hall Laboratory in the U.K.; Paul Modrich at the Howard Hughes Medical Institute and Duke University School of Medicine; and Aziz Sancar at the University of North Carolina, Chapel Hill. When the announcment was made that the discoveries of DNA repair mechanisms were being recognized, the response was much like that of 2006: "Is this truly chemistry?"

This year, wisecracks swept through Twitter when the chemistry prize was announced to go to Jean-Pierre Sauvage at University of Strasbourg, France; Sir J. Fraser Stoddart at Northwestern University; and Bernard L. Feringa at the University of Groningen, the Netherlands, for developing molecular machines. An NPR editor, Geoff Brumfiel, tweeted, tongue-in-cheek, "But wait, I'm confused. They seem to have given the chemistry prize to actual chemists... For doing chemistry... #NobelPrizeInBiochem"

And then there is the issue over the ones who were ignored. I used to be a reporter for the journal Analytical Chemistry. Controversy broke out in the field of analytical chemistry over the 2002 Nobel Prize in chemistry. Part of that prize went to John Fenn at the Virginia Commonwealth University and Koichi Tanaka at Shimadzu Corp for developing a mass spectrometric technique. No one disputed that Fenn deserved the prize, but many felt, in light of Tanaka's work, that Franz Hillenkamp at the University of Münster in Germany and Fred McLafferty of Cornell University were left out unfairly. Rosalind Franklin's name still comes up in the context of the 1962 Nobel Prize in physiology or medicine to James Watson, Francis Crick and Maurice Wilkins, because of her contributions to the discovery of the DNA double helical structure.

But imperfect as they are, there is one thing that the Nobel Prizes do exceedingly well. Every October, without fail, the prizes turn the world's attention to science. All major media outlets run a mention of the prizes, even if it's just a 30-second clip about who won.

The prizes give us an opportunity to talk about seemingly esoteric niches of science and describe their wonders to people who normally are not plugged into science. I couldn't help but appreciate this fact at my son's birthday party. It's not every day that I get asked by a pilot and a therapist to describe autophagy and all the different facets it affects in cell biology. We only stopped talking about autophagy when we heard a light saber go "Whack!" and a child began to cry.

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Election rattles biomedical research community

By Benjamin Corb

I write this in the wake of the 2016 election results. Donald Trump was announced as president-elect only hours ago. Already, the tension from the research community is palpable. The reality is that there is a lot unknown about what a Trump administration will mean for the scientific community, specifically for biomedical research community. Broadly, statements made during the Trump campaign on issues like vaccines and climate change give me pause. The sentiments are in stark contrast to those of President Obama, who is inarguably pro-science.

What do we know at this moment? We know that the U.S. Congress will remain in the control of the Republican Party. A Republican-controlled Congress has been the norm for the past two years and will continue to be so for the next two. The Congress of the last two years provided a $2 billion increase to the National Institutes of Health last year and proposed sizeable increases again for fiscal year 2017 from both the House and the Senate.

We also saw introduction of the House passage of the 21st Century Cures Act, a legislative proposal that, while not perfect, serves as proof of bipartisan support of the research community. Many of the congressional leaders who led these efforts remain in their posts, including the chair of the Senate Labor, Health and Human Services Appropriations Subcommittee, Senator Roy Blunt, who won re-election last night.

The concern I have for the next Congress is if it will be emboldened by election results and double down on legislative proposals that cap or cut domestic spending. The specter of sequester being a long-term problem is now very real. We have already heard grumblings from Republican lawmakers about the need to cut non-defense discretionary spending, out of which biomedical research is funded. The mystery will be how policy makers "square the circle." How can bipartisan support for increasing investments in biomedical research be juxtaposed with a conservative agenda that wants to cut government spending?

What don't we know? We don't know who will be asked to lead science funding agencies like the NIH and the National Science Foundation. We don't know who will lead the Office of Science and Technology Policy, or how closely the OSTP will be folded into the new administration. President Obama and President George W. Bush had widely different roles for the OSTP, and we don't know how President-elect Trump will view the position.

Additionally, we do not know the impact the harsh dialogue regarding immigration will have on our community. Is immigration reform possible in the new political setting, and will the new administration recognize the important role immigrants play in the scientific enterprise? Will the tone regarding immigration serve as a disincentive to scientists globally who always had viewed America as a beacon for science? This is an issue we'll watch closely.

Finally, we know that there will be challenges for the community and that throughout those challenges, the Public Affairs Advisory Committee at the American Society for Biochemistry and Molecular Biology and other advocates nationwide will continue to work hard to ensure the needs of our membership are met in the years to come.

Benjamin Corb (bcorb@asbmb.org) is the director of public affairs at the ASBMB. Follow him on Twitter at twitter.com/bwcorb.

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Felsenfeld wins Horwitz Prize


FELSENFELD

Columbia University announced that its top honor for achievement in biological and biochemical research, the Louisa Gross Horwitz Prize, this year went to Gary Felsenfeld of the National Institutes of Health. Felsenfeld won the recognition along with Howard Cedar and Aharon Razin of the Hebrew University for their work dissecting the molecular mechanisms of regulation of DNA structure and function. These discoveries are central to the understanding of cellular and embryonic development and epigenetic regulation. Felsenfeld showed how DNA and individual histones interact to form complexes. These complexes regulate gene expression either by tightly packing themselves to make the DNA inaccessible or by leaving exposed regulatory regions of the DNA so that other proteins can bind and modulate gene activity.

— By Mariana Figuera

Hunt and Bertozzi receive ACS National Awards


HUNT


BERTOZZI

Donald F. Hunt, professor of chemistry and pathology at the University of Virginia, and Carolyn R. Bertozzi, the Anne T. and Robert M. Bass professor of chemistry and professor of chemical and systems biology and radiology at Stanford University, are two of the American Chemical Society's 2017 National Award recipients.

Hunt received the ACS Award in Analytical Chemistry, sponsored by the Battelle Memorial Institute. Through his research, Hunt seeks to develop novel methods and instrumentation to identify and characterize the structure of proteins.

Bertozzi received the Arthur C. Cope Award, sponsored by the Arthur C. Cope Fund. Bertozzi's research lies at the interface between chemistry and biology, with a specific interest in studies on cell-surface glycosylation related to disease states.

The ACS National Awards program recognizes outstanding contributions to chemistry, supports research in chemical science and promotes the careers of influential chemical scientists.

O'Shea wins Milstein award


O'SHEA

John O'Shea, scientific director at the National Institute of Arthritis, Musculoskeletal and Skin Diseases, won the Seymour and Vivian Milstein Award for excellence in interferon and cytokine research from the International Cytokine and Interferon Society. The award recognizes scientists who have made significant contributions toward advancing interferon and cytokine research. O'Shea was honored, along with two other recipients, at the annual ICIS annual meeting, held in October.

A leading researcher in the study of cytokines, the society recognized O'Shea for exploring how cytokines "transmit signals to the cell interior of T cells and innate lymphocytes so as to evoke and direct subsequent immune responses," according to the press release from the society. Insights from O'Shea's research have led to the development of pharmacological Jak inhibitors as a new class of immunomodulatory drug.

O'Shea previously won the U.S. Public Health Service Physician Researcher of the Year Award and the Paul Bunn Award in infectious disease.

Two members named Faculty Scholars


KARBSTEIN


SMOGORZEWSKA

The Howard Hughes Medical Institute, the Simons Foundation, and the Bill & Melinda Gates Foundation have selected Katrin Karbstein, associate professor at The Scripps Research Institute in Jupiter, Florida, and Agata Smogorzewska, associate professor at The Rockefeller University, as the 2016 Faculty Scholars. Karbstein and Smogorsewska are among the 84 scientists recognized by the organizations as Faculty Scholars this year. The Faculty Scholars Program recognizes early-career scientists who demonstrate the potential greatly to impact their field of study. The program's sponsors have pledged $83 million over five years to support their awardees' research.

Karbstein's research centers on ribosomes, exploring the assembly factors that allow ribosomes to become fully functional. She previously received the University of Michigan's Biological Sciences Scholar award and the National Science Foundation CAREER award.

As head of the Laboratory of Genome Maintenance, Smogorzewska researches the mechanism of DNA interstrand crosslink repair, seeking to understand the cellular and organismal impact of deficiencies in this type of repair. Among her many honors, Smogorsewska has received the Pershing Square Sohn Prize and the Doris Duke Charitable Foundation Clinical Scientist Development Award.

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Bassler wins Greengard prize


BASSLER

The Rockefeller University has selected Bonnie Bassler as the 2016 recipient of the Pearl Meister Greengard Prize. Founded in 2004 by Nobel laureate Paul Greengard at Rockefeller, the prize recognizes outstanding achievements of women in the science community. The prize carries a $100,000 honorarium.

The Pearl Meister Greengard Prize is another honor for Bassler for her discoveries related to quorum sensing, a process by which bacteria communicate with each other via chemical signaling molecules. She received the Max Planck Research Award for her research earlier this year.

Bassler is the Squibb Professor in molecular biology at Princeton University and an investigator at the Howard Hughes Medical Institute.

Morrissey and Tajkhorshid co-winners of NIH award


MORRISSEY


TAJKHORSHID

James H. Morrissey, the Roy and Eva Hong Professor of molecular and cellular biology, and Emad Tajkhorshid, J. W. Hastings Professor of biochemistry, biophysics and computational biology, at the University of Illinois at Urbana–Champaign, are two recipients of a 2016 Transformative Research Award from the National Institutes of Health. Morrissey and Tajkhorshid, along with Chad Rienstra of UIUC, received their award to develop novel methodology to investigate the effect of lipids on membrane protein function at the atomic level.

Established in 2009, the Transformative Research Awards recognize scientists who contribute groundbreaking, interdisciplinary scientific research that shows the potential to create or change fundamental paradigms. The Transformative Research Awards are part of the High-Risk, High-Reward Research Program, which honors scientists who formulate innovative solutions to challenges in biomedical research.

ASBMB member Morrissey is being recognized for his research on "biochemical mechanisms that regulate the blood clotting system in normal hemostasis and thrombotic disease," according to the NIH press release. ASBMB member Tajkhorshid's research explores the structure-function relationship of membrane proteins through simulation and computational methodologies.

Shadel awarded professorship


SHADEL

Gerald Shadel, professor of pathology and genetics and director at the Yale Center for Research on Aging, has been named as the Joseph A. and Lucille K. Madri professor of experimental pathology at Yale University. After serving as an assistant professor of biochemistry at Emory University, Shadel joined the Yale School of Medicine in 2004.

Shadel's research focuses on the role of mitochondria in disease, aging and the immune system. He and his team have made significant contributions to comprehending mitochondrial gene regulation and mitochondrial DNA metabolism.

The American Society for Investigative Pathology honored Shadel for his research with the Amgen Outstanding Investigator Award from the American Society for Investigative Pathology in 2007 and the Glenn Award for Research in Biological Mechanisms of Aging from the Glen Foundation for Medical Research in 2011.

Dohlman named department head


DOHLMAN

Henrik Dohlman, professor of biochemistry and biophysics at the University of North Carolina, has been named the chair of the department of pharmacology.

As chair, Dohlman will seek to maintain the department as a leader in pharmacological research and education. Gary L. Johnson directed the department for 13 years before stepping down in October 2015.

Dohlman and his team study G proteins and G-protein–coupled receptors. Dohlman previously served on the faculty at Yale University before joining UNC in 2001. Since 2013, Dohlman has served as an associate editor at the Journal of Biological Chemistry.

Collins and Hurley selected as Bakar Fellows


COLLINS


HURLEY

University of California, Berkeley, professors Kathleen Collins and James Hurley have been selected as 2016–2017 fellows for the Bakar Fellows Program.

The Bakar Fellows Program supports faculty at UC Berkeley who are pursuing innovative scientific research that shows commercial promise. Bakar Fellows receive a discretionary research fund of $75,000 per year for a maximum of five years to fund

and help develop groundbreaking scientific research and bring their ideas to market.

The program selected Collins as a fellow for her development of reverse transcriptase technologies. Through her research, Collins has developed new tools that can aid diagnosis in the health care industry. Collins is the Walter and Ruth Schubert Family Chair and professor of biochemistry, biophysics and structural biology in the department of molecular and cell biology. She is also a member of the Berkeley Stem Cell Center.

The program selected Hurley as a fellow for his research on autophagy to combat neurodegeneration. His work shows potential for the development of effective therapies to treat neurodegenerative disease. He is the Judy C. Webb Chair and professor of biochemistry, biophysics and structural biology in the department of molecular and cell biology.

—By Erik Chaulk

Patton wins funding for neural regeneration work

PATTON

A team made up of ASBMB member James G. Patton, Edward M. Levine and David J. Calkins from Vanderbilt University School of Medicine has received funding from the National Institutes of Health to study neural regeneration. The three-year project, which is one of the six funded by the NIH in a $12.4-million award, will identify biological factors that affect neural regeneration in the retina. The six projects are part of the National Eye Institute's Audacious Goal Initiative, which aims to restore vision by regenerating neurons and their connections in the eye and visual system.

The project spearheaded by Patton, Levine and Calkins focuses on the reprogramming of supportive cells in the retina called Muller glia. Their goal is to promote the growth of new photoreceptor cells after retinal injury. The investigators plan to test whether they can reprogram these cells in zebrafish and mice using pharmacological agents and genetic manipulation techniques. They also intend to study the role of exosomes in promoting retinal regeneration.

—By Adriana Bankston

Howard K. Schachman (1918 – 2016)

By Jack Kirsch

Howard K. Schachman died at age 97 in the presence of family members at Kaiser Foundation Hospital in Oakland, California, on Aug. 5. Only about 0.3 percent of the population attain that age landmark. By all measures, Schachman optimized his long stay on Earth. He will be remembered as a pioneering scientist and as a leader in the formulation of science policy. He was often effective as a member of the small cadre of principled individuals who challenged indefensible edicts visited by the University of California administration upon students and faculty. And he will be treasured as a friend and mentor to several young faculty who struggled to navigate the viscous waters of a beginning academic career.

Howard Schachman

Born in Philadelphia to Morris and Rose Schachman, he graduated from Massachusetts Institute of Technology with a B.S. in chemical engineering in 1939. His further education, interrupted by the war years, was spent as a research assistant at the Princeton branch of The Rockefeller Institute for Medical Research, where he worked with Max Lauffer, and later at Princeton University with Walter Kauzmann. After receiving his Ph.D. from Princeton in 1948, Howard accepted Wendell Stanley's invitation to join him as a junior faculty member at his newly established virus research laboratory at the University of California, Berkeley.

Howard's early research capitalized on his doctoral experience with the ultracentrifuge. Together with his first student, William Harrington, he explored the subunit structure of tobacco mosaic virus and, in the process, helped to develop the synthetic boundary cell. The synthetic boundary cell was a new type of ultracentrifuge cell in which one solution was layered over another, denser solution while the ultracentrifuge was in operation to create a sharp, stable boundary; it allowed researchers to measure the hydrodynamic volumes of macromolecules, for example.

Further important developments from the lab included the reintroduction of ultraviolet absorption optics to largely supplant the less sensitive schlieren detection method. The refinements afforded by the addition of the single-beam followed by the double-beam monochronometer enabled the analyses of component mixtures with different absorption maxima. These and other technical developments greatly facilitated the penetration of ultracentrifuge applications into physical biochemistry investigations. However, the instruments were expensive and required substantial laboratory space and considerable skill in both operation and data analysis. Unsurprisingly, this set of circumstances led to a variety of fruitful collaborations including the discovery of the 30S and 50S bacterial ribosomes with Roger Stanier and Arthur Pardee and on DNA with future Nobel laureate Arthur Kornberg. Schachman was recognized widely as the world's expert on the ultracentrifuge in biochemistry to the extent that Jeremy Knowles once suggested that he made the cross-country road trip from Berkeley to a New Hampshire Gordon Conference with his family in his Model E centrifuge.

His 1959 book on the subject was a staple on the shelves of those of the biochemical community interested in macromolecular characterization for nearly 20 years until the instrument gradually was displaced by newer and more accessible technologies, such as gel electrophoresis and high-resolution mass spectrometry.

Ultimately, the most important of the Schachman collaborations was that initiated in 1964 with his junior colleague John Gerhart on aspartate transcarbamylase, or ATCase, the committed enzyme in pyrimidine biosynthesis. They quickly discovered that the enzyme could be resolved

Schachman and Bill Brinkley of Baylor College of Medicine, who was chair of the ASBMB PAAC at the time, presented Mary Woolley of Research!America with the 2007 Howard Schachman Public Service Award.

Schachman's commitment to service

Howard K. Schachman won numerous awards and honors and election to the American Academy of Arts and Sciences and the National Academy of Sciences. Outside of his significant contributions to understanding protein biochemistry, Schachman tirelessly worked in public policy. Between 1995 and 1998, Schachman was on the Public Affairs Advisory Committee at the Federation of American Societies for Experimental Biology, the coalition of 30 scientific societies. In 1987, Schachman became president of the American Society for Biochemistry and Molecular Biology, a FASEB society. In 1998, Schachman served as the president of FASEB. He also served as chair of the ASBMB's PAAC from 1989 to 2000.

As a leader in public policy, Schachman was a vocal critic of politically targeted research funding and excessive indirect costs charged by universities. Schachman also was outspoken against overzealous regulation of science and advocated research integrity.

In 2001, the ASBMB instituted the Howard Schachman Public Service Award. This award recognizes an individual chosen by the ASBMB's PAAC who best demonstrates dedication to public service in support of biomedical science.

into a mixture of two subunits, one of which was responsible for the catalytic activity and the other associated with the regulatory factors ATP, an activator, and CTP, an inhibitor of the enzymatic activity. This important finding launched the duo into the forefront of the then-burgeoning field of allosteric regulation of enzyme activity. The excitement was sustained for several years due in part to the erudite and often witty rhetoric exchanged at meetings and in print by notable luminaries including extant and future Nobel laureates Jacques Monod and William Lipscomb. Monod's original description of an allosteric model

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required that all subunits in a regulated protein change conformation in a concerted fashion, while the more general model formulated by Dan Koshland allowed for intermediate forms. Howard, in a breach of campus solidarity, sided with the Monod view. The ATCase projects sustained the bulk of the Schachman research effort until he closed his laboratory.

Howard's contributions to science as described briefly above would have sufficed to place him among the elite of research biochemists, but it was his willingness and ability to reach beyond the normally proscribed boundaries of scientific endeavor to engage seriously with matters involving politics, scientific ethics and inappropriate intrusion of the government on scientific conduct that put him in a special place in our profession. The first such excursion involved his joining the 200 Berkeley faculty members who opposed the required signing of the UC Regents-mandated loyalty oath, which was aimed at purging communists and their sympathizers from the faculty. Howard painfully watched the 200 dwindle to a few stout souls as some left the university voluntarily and others were fired. Faced with having to support a young family and with few other job prospects, he ultimately signed. In this, he learned a good lesson that he later communicated to me. I don't recall his exact words, but the essence of them was this: "Pick your battles carefully. There are more good causes than you will have the time or stamina to pursue."

The Free Speech Movement erupted in Berkeley early in the fall semester of 1964. The campus quickly divided into two hostile camps: one in support of the student demands to assemble and freely express political views on campus and the other taking the side of the administration and politicians wishing to emaciate such actions to the point of impotence. The first group included mainly younger faculty, humanists, physicists, and social and biological scientists, while the second was largely made up of the professional school faculty (engineering and business), older individuals, and organic, but not physical, chemists. Normally staid and boring academic senate meetings typically attended by the bare minimum needed for a quorum now overflowed the largest auditorium on campus. It is fair to state that the research and teaching activities of the campus were diverted substantially to activities related to the Free Speech Movement for that academic semester. Howard became one of the leaders of the self-constituted committee of 800 faculty who strove to find a sensible resolution to the seemingly impassible conflict. A few of these met regularly at his home. Finally, on Dec. 8, an overwhelming majority passed a resolution substantially supporting the student demands. Further negotiations dealing principally with time, place and manner issues resulted in the resumption of near normal academic activities on campus.

Howard's style as a leader of the Free Speech Movement and in other controversial issues eschewed direct confrontation and inflammatory rhetoric. Rather, his method was to find common ground and support from extant law or custom and to be a voice of reason where others were often irrationally emotional.

Schachman's later years largely were occupied by issues involving scientific fraud and other ethical matters. In every year, including his last, he presented a series of five to six lectures required for training-grant-supported graduate students. As the substance of the subject matter evolves slowly, some instructors might have been tempted to reuse lectures from the previous year. Howard, on the other hand, was so involved in the subject that he spent the majority of his time searching for new examples or interpretations. Well into the last year of his life, he devotedly read the New York Times, the Chronicle of Higher Education and other publications that had occasional reports of scientific misconduct. His lectures were given on Tuesday evenings to about 75 students. I often would stop by his office on Monday afternoons, and he on many occasions would acquaint me with a relevant article from the current issue of a publication that he had just read and was planning to add to his lecture for the next evening. This was a man who, at the age of 97 and with declining eyesight and a steady loss in manual dexterity, could still make his own PowerPoint slides.

Howard met Ethel Lazarus while they were both undergraduates in the Boston area. They married in 1945 and had two sons, Marc and David. Ethel had worked for the Emergency Committee of Atomic Scientists and in that capacity often had acted as a courier to Albert Einstein. On occasion she and Howard provided transportation in their car for him. Although not a scientist, Ethel was well versed in the social sciences, politics, music and art. Howard explored the consequences of all of his important nonscientific activities with her in advance and frequently told me of how often her insights led him to change his intended course of action. They traveled widely together and enjoyed the friendship of many internationally prominent figures including Ephraim Katzir, who was Howard's house guest on the evening when it was learned that he had been named the next president of Israel. Ethel died in 2012. She and Howard enjoyed 67 years of productive happiness and fulfillment together. Their departure leaves a deep hole in the Berkeley scientific environment.

Jack Kirsch (jfkirsch@berkeley.edu) is a professor of the graduate school division of biochemistry, biophysics and structural biology at the University of California, Berkeley.

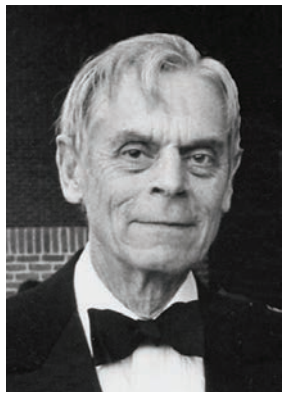
Charles Rawlinson 'Rollo' Park (1916 – 2016)

By Jackie Corbin

Charles Rawlinson "Rollo" Park was a close colleague of mine for 56 years, beginning as my graduate school adviser at Vanderbilt University during the 1960s. Rollo was a gentle man with a very high level of scholarly sophistication. He spoke slowly, and it seemed that every word he uttered was carefully thought through. Most of my conversations with him were about our specific scientific projects, but we often discussed broader scientific subjects in biology, astronomy and physics. Nonscientific subjects included politics, sports, outdoor activities and anything humorous. I was fascinated by the breadth of his knowledge. He had a very positive attitude and a marvelous sense of humor; his slow, deep laugh could be heard far down the hallways.

Rollo was born in 1916 in Baltimore. He received his undergraduate degree from Harvard University in 1937. He received his medical degree and internship experience at Johns Hopkins University Medical School, where his father was a chairman of pediatrics. After that, Rollo served as chief resident at Peter Bent Brigham Hospital in Boston. He did his first research project as a medical student, studying the role of para-aminobenzoic acid as a growth factor for bacteria. After his residency, he was exposed further to a research career by his investigations of body-temperature regulation while serving in the Army at Fort Knox during World War II.

In 1946, Rollo joined the laboratory of Carl Cori at Washington University in St. Louis to do postdoctoral research involving glucose and glycogen metabolism. The following year, Carl, along with his wife and fellow scientist Gerty, would be awarded the Nobel Prize in physiology or medicine. While in the Cori laboratory, Rollo mainly studied the mechanism of insulin action on the uptake of glucose by rat diaphragm muscle. With his collaborators, he made the far-reaching finding that insulin stimulated the transport of glucose into the muscle rather than the intracellular phosphorylation of glucose by hexokinase, a theory favored by the Coris.



Rollo Park

In 1952, Rollo made a leap from being a postdoctoral fellow in the Cori group to being the chairman of the department of physiology at Vanderbilt University Medical School. At that time, the department held only two active faculty members and had very meager facilities. Under his leadership, the department grew in international prominence during the 1960s, 1970s and 1980s. He paved the way for it to be ranked as the number one physiology department in the nation for total National Institutes of Health grant support. Among his faculty recruits was Jane "Janey" Harting from the Cori laboratory, whom he married soon after her arrival at Vanderbilt. Rollo trained or recruited many eminent scientists. He told me that he recruited the eventual Nobel laureate Earl Sutherland to the department in 1963 by convincing him of the good bass fishing in Middle Tennessee lakes. Earl said that he returned Rollo's favor by getting his best scientific thoughts while sitting in a fishing boat on Center Hill Lake.

While at Vanderbilt, Rollo continued his work on glucose metabolism and insulin action with many collaborators. In several classic papers in the early 1960s, he and his colleagues established that insulin stimulated glucose transport rather than glucose phosphorylation. They also found that the non-glucose-transport effects of insulin on inhibiting liver glycogen breakdown and gluconeogenesis, as well as its inhibitory effect on lipid breakdown in adipose tissue, were mediated largely by lowering of the cellular cyclic AMP level.

Rollo's ability in research, organization, training, recruitment and inspiration all played significant roles in these accomplishments and ultimately led to him receiving many awards over the years, including the American Diabetes Association Banting Medal and election into the National Academy of Sciences. In addition, he was a founding member of the board of the Howard Hughes Medical Institute, and he was involved in establishing the nation's first diabetes and endocrinology research center at Vanderbilt. Rollo retired as the physiology department chairman in 1984 after serving for 32 years.

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Rollo stressed seminar attendance. He had a large number of international colleagues who often would drop by Vanderbilt as guest seminar speakers. Almost all of our seminars focused on hormone signaling, which was engendered by Rollo's influence. The seminars were accompanied by arguments, inappropriate interruptions, shouting, rude questions and other forms of impolite behavior, which were a bit shocking to me as a young student. In those days, experimental results were less objective and scientists more open to criticism. Moreover, monetary support for science was more generous, such that peers in the audience or the speaker himself did not fear so much that one of them could be a reviewer of their grants or papers. Rollo asked some of the best seminar questions even when he was well into his 80s.

Although he did his duty to organize the basic physiology course for medical and graduate students, it was not a high priority for him. As a lecturer, he usually did not receive high ratings from the students. Even so, I feel like he was quite effective, and the students would be spellbound by his thundering voice. His pace was slow and deliberate, and he had a knack for presenting the big picture. Rollo undertook the task of protecting the faculty against burdensome lecture and committee assignments. He often ignored his own administrative duties; I heard him say more than once that he was "a bit lazy." He did not request increased laboratory space and other benefits for the department aggressively. He told me that some "crowdedness" in the laboratories was a good thing because it forced people to interact and brought about more discussions and collaborations.

I attended numerous dinners at Rollo and Janey's home. They were elegantly presented and were often assisted by their longtime friend, Lily. Their son Edwards, who is presently on the faculty of the University of Tennessee Medical School, often attended these dinners as well. Edwards was also the given name of Rollo's father, which was in turn taken from Rollo's earlier ancestor, the famous fire and brimstone New England preacher of the 18th century, Jonathan Edwards. Rollo was proud to show me a portrait of his father that was done by Andrew Wyeth, as well as an Albrecht Dürer woodcut. Rollo led the dinner conversations, which considerably shaped the lives of many young scientists and their guests. On many occasions Rollo would invite young departmental scientists to accompany him and other senior faculty members for lunch in a campus cafeteria. This was also a wonderful experience in camaraderie and educational conversation.

Rollo was a modern Renaissance man. He possessed appreciation of the arts, and he enjoyed playing the recorder in a chamber music group. He had a particular interest in attending Nashville Symphony Orchestra performances. Once he invited me to accompany him. I was stunned upon arrival to learn that his season seats were in the middle of the front row, which he explained to me offered him optimum vision and sound for the performances. He used the same logic for attending other types of performances, including seminars.

Rollo was a modern Renaissance man. He possessed appreciation of the arts, and he enjoyed playing the recorder in a chamber music group. He had a particular interest in attending Nashville Symphony Orchestra performances. Once he invited me to accompany him. I was stunned upon arrival to learn that his season seats were in the middle of the front row, which he explained to me offered him optimum vision and sound for the performances. He used the same logic for attending other types of performances, including seminars.

Rollo was a tall, strong man. He participated in many outdoor activities, especially canoeing, kayaking, hiking, fishing and camping. I often accompanied him. He used his swimming pool to practice rolling in his kayak. When I was a student, I once joined him for an overnight tandem canoe trip down a very remote Tennessee river. On the first day, I was paddling in front when he instructed me from the back to "avoid submerged rocks." Although I had some success, at one point I failed to notice one directly in front of the canoe. The canoe bashed into it head-on, and the sudden stop caused Rollo to lunge forward and bang his left lower leg against the middle seat. After a few minutes, his leg was dreadfully swollen. I became very worried, although Rollo assured me that his leg was not broken and that he was not in pain. We paddled onward until dark. I noticed that Rollo did not have a sleeping bag. He pulled a small space blanket from his pack, curled up in it on a sandy bank, and slept soundly through the night. The next morning, we continued our trip down the river, and he never once complained to me then, or in the future, about my blunder.

At the time of his death in 2016, Rollo was 100 years old. He was a giant in every respect.

Jackie Corbin (jackie.corbin@vanderbilt.edu) is an emeritus professor of molecular physiology and biophysics at Vanderbilt University.

Studer wins Tabor award for enzyme catalysis

By Lee D. Gibbs

Sabine Studer, a doctoral candidate in Donald Hilvert's laboratory at ETH Zurich, was named the recipient of a **Journal of Biological Chemistry/Herbert Tabor Young Investigator Award**. Studer got the award for her work in understanding enzyme catalysis by creating de novo catalysts for unnatural substrates and reactions. "We are using a small, artificial metalloprotein, originally designed by Brian Kuhlman and colleagues, as a starting point for the laboratory evolution of proficient metalloenzymes for diverse chemical transformations," says Studer. "Through biophysical and structural characterization of selected intermediates along the evolutionary pathway, we seek to understand how a simple metal-binding protein can be transformed into a proficient biocatalyst."

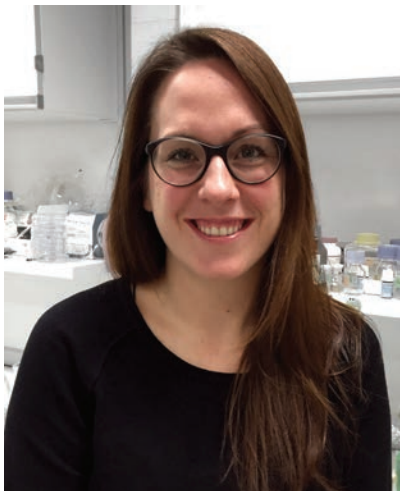

PHOTO PROVIDED BY SABINE STUDER

Sabine Studer

The scientific editor at the JBC, Catherine Goodman, presented Studer with the award at the EMBO conference on chemical biology in September.

Studer grew up in Visperterminen, a small town in the Swiss Alps. Her passion for biology and chemistry led her to ETH Zurich, where she completed a master's degree in 2012. After receiving her master's degree, Studer interned in the area of genomic engineering at the company BASF. Following her internship, she continued her studies at ETH Zurich and currently is completing her doctoral degree. In her spare time, Studer enjoys running and skiing as well as helping out in the family vineyard.

Lee D. Gibbs (Lee.Gibbs@live.unthsc.edu) is a doctoral candidate at the University of North Texas Health Science in the department of molecular and medical genetics.

Upcoming ASBMB events and deadlines

DEC

Dec. 3–7: American Society for Cell Biology annual meeting, booth #835, San Francisco
Dec. 8: Student Chapters renewal deadline
Dec. 8: DEUEL Conference on Lipids early registration deadline

JAN

Jan. 13: Student Chapters annual meeting travel awards deadline
Jan. 31: DEUEL Conference on Lipids abstract and registration deadline

FEB

Feb. 8: ASBMB annual meeting Outstanding Student Chapters Award deadline
Feb. 23: ASBMB annual meeting early registration deadline

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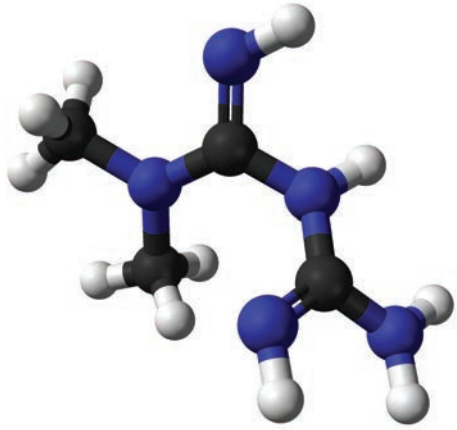
Metformin reverses metabolic memory in a diabetes model

By Christine Lee

According to the Centers for Disease Control and Prevention, type 2 diabetes affects 29 million Americans with complications resulting in, among other things, kidney disease. Many factors, such as reduced physical activity, diet and genetics, place individuals at greater risk for diabetes. Long-term, high-fat diets can induce genetic changes or generate "metabolic memory" even after normal glycemic control is achieved. A recent Paper of the Week published in the **Journal of Biological Chemistry** examines how cells recovering from damage induced by a high-fat diet can be treated with a drug for type 2 diabetes called metformin to reverse the effects of metabolic memory.

Patients with diabetes struggle to maintain a normal balance of glucose levels. Complications emerge when there is an excess of blood glucose or when insulin is not responsive to elevated blood glucose levels. While improved diet and increased physical activity have been proved to mitigate disease onset and symptoms in those already diagnosed with the disease, the effects of prolonged periods of mismanaged glycemic control can be more challenging to reverse at a cellular level in the kidneys and liver.

"Metabolic memory" refers to the notion that glucose-sensing cells function as though glucose levels are high even when they are not. Recent evidence from the Diabetes Complications and Control Trial suggested that even after normal glycemic levels are maintained, the liver and kidney cells remain in a sensitized state because of the metabolic memory of glucose-sensing cells. In this JBC paper, Kulbhushan Tikoo and colleagues at the National Institute of Pharmaceutical Education and Research S.A.S. Nagar in India investigated the effects of metformin, a drug used to treat type 2 diabetes, on metabolic memory in conjunction with diet reversal in a rat model for diabetes.



Metformin may combat metabolic memory of persistent hyperglycemia.

The researchers fed rats a normal or high-fat diet for 16 weeks. The high-fat diet simulated prolonged hyperglycemia. The rats on the high-fat diet were then divided into three groups with different diets: a prolonged high-fat diet, a normal diet to simulate diet reversal and a normal diet with metformin treatment. They were kept on their diets for eight weeks. Tikoo and colleagues then measured body weight of the rats as well as their biomarkers such as glucose levels, lipid profile and kidney function at the eight- and 16-week time points and at the end of the study at 24 weeks.

The authors concluded that the 16-week high-fat diet rendered the rats insulin resistant, a hallmark of type 2 diabetes. After the 16-week high-fat diet, the animals undergoing diet reversal had indications of metabolic memory. However, the rats undergoing diet reversal with metformin treatment had improved outcomes compared to the animals on diet reversal alone. This suggests that metformin treatment can mitigate the negative effects of metabolic memory associated with diabetes.

The authors also investigated the effects of metformin treatment on pathways underlying renal dysfunction and metabolic memory. Activation of the AMP-activated protein kinase pathway, a key regulator in metabolic function, is critical for management of inflammatory markers such as COX-2 and IL-beta. In rats treated with metformin, these renal biomarkers for inflammation were significantly reduced compared with those in rats undergoing diet reversal alone. Histological kidney sections also revealed reductions in fibrotic markers, such as collagen and fibronectin, in metformin-treated rats, indicating that drug treatment also can ameliorate the long-term damage induced by conditions leading to diabetes. In addition to the demonstrated benefits of metformin treatment to combat renal damage and metabolic memory induced by persistent hyperglycemia, this work provides detailed biochemical analysis that can help guide the progress and recovery of the millions of individuals managing type 2 diabetes.

Christine Lee (clee217@jhu.edu) is a Ph.D. candidate in the Department of Biochemistry and Molecular Biology at the Johns Hopkins Bloomberg School of Public Health.

The lives of plant-dwelling bacteria

By John Arnst

You can find hordes of bacteria on the surfaces of a plant's leaves, stems, flowers and fruits. These bacteria range from beneficial to benign, with the occasional bad actor. If you examined Arabidopsis thaliana, you likely would find two bacteria called Sphingomonas melonis and Methylobacterium extorquens inhabiting the entire above-ground plant surface.

To understand better the interactions and adaptations that allow these bacteria and many others to call the plant home, researchers recently performed proteomic analyses of these two organisms. By applying a technique known as SWATH MS, the researchers identified a set of shared proteins, which indicates common mechanisms that underlie successful leaf colonization. They described their work in a paper published in the journal **Molecular & Cellular Proteomics**.

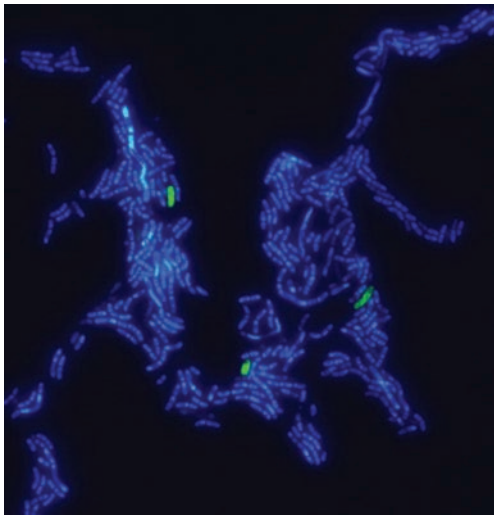


IMAGE PROVIDED BY DANIEL MÜLLER

S. melonis (blue) and M. extorquens (green) share a leafy habitat.

"Historically, people have only looked at the roots," says Daniel Müller at the ETH Zurich's Institute of Microbiology. This is largely because of the role symbiotic root bacteria play in providing the host with nutrients. How the bacteria interact with the part of the plant that is above the ground has been looked into only recently, says Müller. "It became increasingly obvious that the leaves and the phyllosphere in general — all the above-ground parts of plants — are also colonized, and they have an impact on the host cells too," he adds. Müller is a postdoctoral researcher in the lab of Julia Vorholt, the lead author on the MCP paper.

Despite their shared phylogenetic class of Alphaproteobacteria, S. melonis and M. extorquens have evolved to occupy different ecological niches on plants. S. melonis has adapted to a diet of amino acids and hydrocarbon compounds; M. extorquens subsists primarily on methanol, oxalate and alkanesulfonates and also carries out anoxygenic photosynthesis. Additionally, S. melonis has been demonstrated to confer protection against a common leaf pathogen. Researchers believe that the bacteria might provide other symbiotic benefits to the host.

"We are lacking a lot of functional information," says Müller. "This proteomics approach was one of the first steps towards providing such insights. We know what is present in terms of bacterial taxa, but we need to understand what they are actually doing there and how they might influence each other."

To examine which of their proteins S. melonis and M. extorquens activate when occupying the phyllosphere, Müller and colleagues inoculated surface-sterilized seeds of A. thaliana with samples of each strain. They collected the bacteria from the growing plants after 28 days and subjected them to an analysis by shotgun proteomics. From the shotgun proteomics data, the investigators constructed a database containing mass-spectrometric information about every protein of interest. The libraries the researchers generated contained information for about 71 percent of the total proteome of both S. melonis and M. extorquens.

Next, to quantify the bacterial proteomes, Müller and colleagues ionized and fragmented the proteins expressed by the bacteria by tandem mass spectrometry. This allowed them to record the mass-to-charge ratios of all fragment ions, along with other characteristics that helped match the fragments to the database.

The researchers then analyzed this quantitative information with special software. They identified 635 candidate proteins for M. extorquens that were regulated significantly on leaf surfaces compared with minimal media and 545 candidate proteins that were regulated significantly on leaf surfaces for S. melonis. Between the two bacteria, there was a shared subset of 17 proteins.

This means that "despite different modes of metabolism, common adaptive strategies seem to exist, such as acquiring limiting macroelements such as sulfur or phosphorus," says Müller. "Among the shared proteins are some of unknown function, potentially indicating that new functions are essential for leaf colonization."

Future work for Müller and colleagues will include examining the differences in the protein repertoires of different, co-existing bacteria to understand better how they manage to share a plant between them.

John Arnst (jarnst@asbmb.org) is ASBMB Today's science writer. Follow him on Twitter at twitter.com/arnstjohn.

Fats as biomarkers for a pregnancy complication

By Hailey Gahlon

Chorioamnionitis, one of the most common inflammatory conditions, is associated with approximately 1 percent to 4 percent of births in the U.S. Researchers know that lipids can trigger inflammation due to injury or stress and also can help to initiate labor during pregnancy. In a recent report in the **Journal of Lipid Research**, researchers set out to find the composition of fats in amniotic fluid that could be linked to chorioamnionitis. Knowing the fats linked to the disease could help doctors better to diagnose and treat it.

Mothers with chorioamnionitis suffer from symptoms such as uterine tenderness, fever and rapid heart rate. Babies born prematurely to mothers with chorioamnionitis are at a higher risk for developing long-term health problems that can include cerebral palsy, growth retardation and cognitive impairment.

One complication of this condition is that 50 percent of the cases are due to microbial infection while the remaining 50 percent are not associated with infection. Unfortunately, in the cases without infection, both mother and baby are exposed unnecessarily to antibiotics, which contributes to the problem of antibiotic resistance. Krishna Rao Maddipati at Wayne State University points out that another issue, besides antibiotic resistance, is that "we don't know what causes chorioamnionitis in the absence of infection."

Maddipati says he and his co-workers hypothesized that "an imbalance in the composition of lipids in amniotic fluid could be a telltale sign of infection that results in chorioamnionitis." Maddipati and co-workers also hypothesized that there could be a link between key lipid levels and chorioamnionitis in cases where there is no infection.

A paper by Maddipati and colleagues in the FASEB Journal earlier this year described how there are certain fats linked to patients with chorioamnionitis with infection. These included leukotriene B4 and 5-hydroxyicosatetraenoic acid, known as 5-HETE, which were found in higher concentrations in mothers with microbial infection. The answer to whether fat compositions are altered in cases of chorioamnionitis without infection remained elusive.

In the new JLR study, Maddipati and colleagues found a distinct profile of fats that are associated with chorioamnionitis in pregnant women without detectable microbial infection. The investigators collected samples from pregnant women without chorioamnionitis and those with chorioamnionitis both with and without microbial infection. To analyze the samples, they used mass spectrometry to determine the composition of fats within the patients' amniotic fluid.

The researchers did not observe any significant differences in a type of lipids called prostaglandins that normally are present in amniotic fluid in mothers without chorioamnionitis compared with those with and without infection in chorioamnionitis. However, what they did discover was that epoxy fatty acids, another type of lipids found in mothers with normal pregnancies, were appreciably lower or completely absent in mothers with chorioamnionitis without infection. This is the first report to show a difference in fat profiles among patients who have chorioamnionitis without microbial infection.

This study provides insights into what causes chorioamnionitis without infection. Epoxy fatty acids play a role in reducing inflammation. The fact that they are lowered or, in some cases, absent in mothers with chorioamnionitis without infection suggests that there are insufficient fats present to keep inflammation in check. Future work to better understand what causes the reduction in these anti-inflammatory fats could help provide treatment options for patients who have chorioamnionitis without infection.

Hailey Gahlon (h.gahlon@imperial.ac.uk) is a Marie Curie postdoctoral research fellow at Imperial College London. She received her master's degree in chemistry at the University of Minnesota and her Ph.D. at ETH Zurich.

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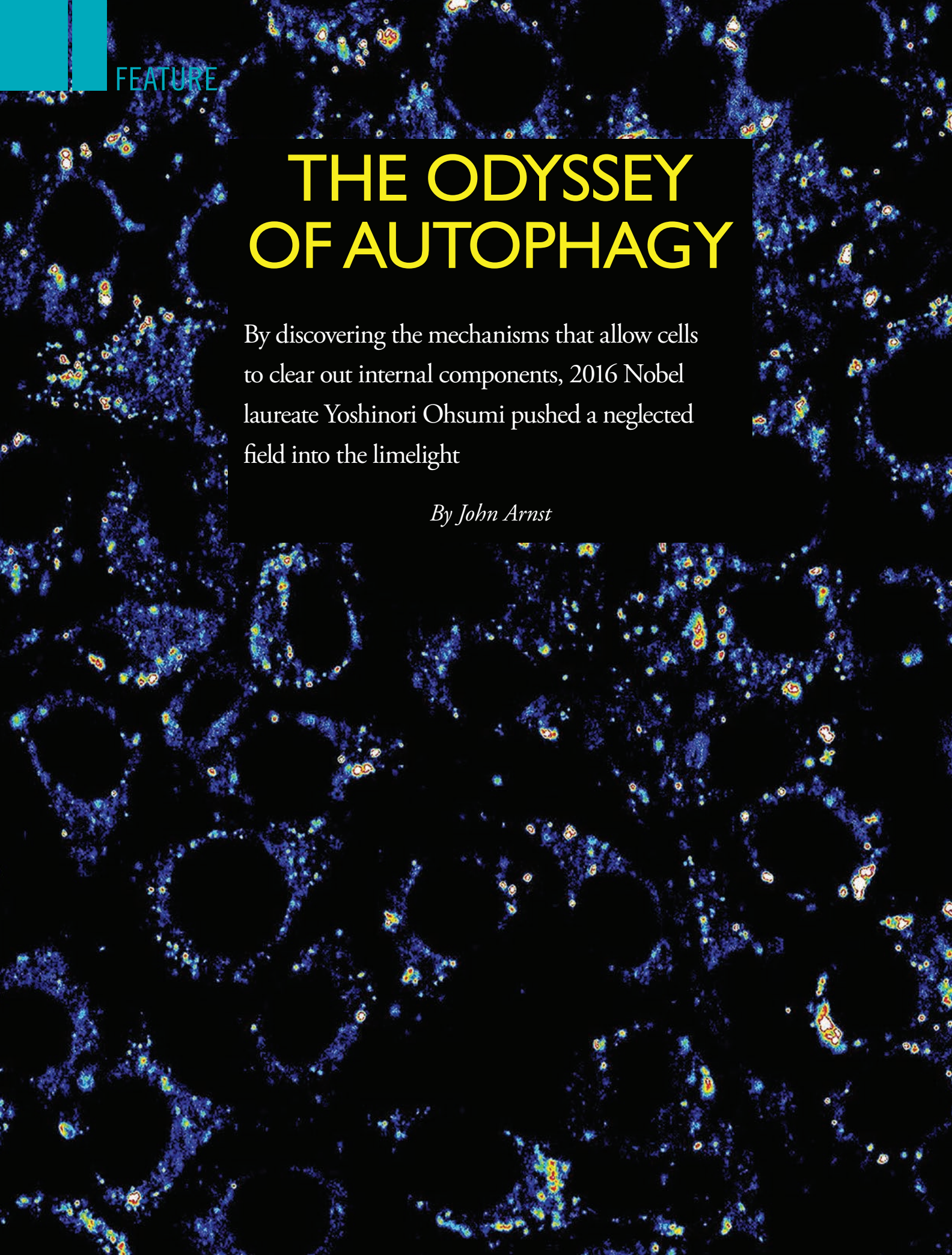

THE ODYSSEY OF AUTOPHAGY

By discovering the mechanisms that allow cells to clear out internal components, 2016 Nobel laureate Yoshinori Ohsumi pushed a neglected field into the limelight

By John Arnst

If you're a problematic protein, pathogen or plaque-precursor peptide, the encroaching of a Pac-Man-like autophagosome is the beginning of the end. Signaled by stress or a scarcity of nutrients, a double-layered membrane begins to form in a cell's cytoplasm. After expanding, this autophagosome surrounds the undesirable cellular component, closes it off and joins membranes with a destructive sack of enzymes known as the lysosome. Once the undesirable component has been broken down, the lysosome opens up, releasing the constituent amino acids, lipids and other cellular building blocks back into the cytoplasm for reuse.

As crucial as this process is for cell survival, it wasn't well understood until 1993, when an associate professor at the University of Tokyo identified the genes responsible for inducing autophagy in yeast cells. The professor's discovery reverberated through nearly all domains of cell biology over the coming decades and revolutionized biomedical research.

This October, the Nobel Committee for physiology or medicine honored that researcher, Yoshinori Ohsumi at the Tokyo Institute of Technology's Frontier Research Center, for his pioneering work in discovering the molecular mechanisms for autophagy.

Ohsumi's "discoveries opened the path to understanding the fundamental importance of autophagy in many physiological processes," said the Nobel Assembly at Karolinska Institutet in Sweden in a press release.

Nobel laureate Randy Schekman at the University of California, Berkeley, says, "This pathway, as we know in mammalian cells, now touches every corner of the cell in terms of metabolism, regulation, control of viral and bacterial infection, and even the tumor potential of transformed cells," adding that the recognition of Ohsumi's work was well-deserved. Ohsumi is a member of the American Society for Biochemistry and Molecular Biology, which publishes ASBMB Today.

Rediscovery

The word "autophagy," which means "self-eating" based on its Greek roots, was coined by the Nobel laureate Christian de Duve of The Rockefeller University and Université Catholique de Louvain in Belgium. After reading a paper by Thomas Ashford and Keith Porter about the presence of membranous sacs containing degraded cellular components in mouse kidney cells, de Duve began investigating the structures.

As it turns out, Porter and Ashford had misidentified the autophagosomes as nascent lysosomes rather than as transient organelles that fused with the lysosomes. De Duve had helped discover lysosomes in the 1950s. After several years of investigation in which de Duve found that autophagosomes increased in number as cellular degeneration increased, he named the process autophagy at a symposium on lysosomes in 1963.

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Yoshinori Ohsumi

The image on the opposite page, which is the same one on the cover, shows how lipids accumulate in cells when autophagy fails. Low lipid levels are seen in blue; high lipid levels are in red. The image was done by Susmita Kaushik at the Albert Einstein College of Medicine.

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However, for the next three decades, the study of autophagy was almost entirely observational and quite difficult. Unlike many other cellular components, the autophagosomes are short-lived, only existing for 10 to 20 minutes at a time. For comparison, the lysosomes with which autophagosomes fuse exist in the cytoplasm for several hours.

Enter Ohsumi. Ohsumi was born in 1945 in Fukuoka, Japan. After earning a bachelor's degree from the University of Tokyo in 1967 and a Ph.D. from the same institution in 1974, Ohsumi began exploring cellular processes in yeast as a postdoctoral fellow at The Rockefeller University in New York City. At Rockefeller, Ohsumi, who was working with mice for his experiments on fertilization, got into working with yeast as a model organism (see "Fortuitous yeast").

In 1977, Ohsumi returned to the University of Tokyo as a junior professor in the laboratory of Yasuhiro Anraku and began exploring the functions of yeast vacuoles, organelles that are homologous to human lysosomes.

Ohsumi continued investigating the vacuoles' active transport systems and lytic functions for the next 11 years, opening his own small laboratory at the University of Tokyo in 1988. Five years later, Ohsumi reported in the journal FEBS Letters the discovery of 15 genes responsible for autophagy in yeast, which would come to be known as the ATG genes.

By growing yeast mutants that lacked vacuolar proteases on a nutrient-restricted medium, Ohsumi created a system in which autophagic bodies accumulated in the vacuole. After subjecting these yeast mutants to a process that generated random genetic mutations, he eventually found a mutant in which the autophagic bodies didn't accumulate. The gene he'd knocked out, soon to be deemed "autophagy-related gene 1," or ATG1, was essential to their formation.

"Yoshinori is really one of the founders of the autophagy field as we know it," says Matthias Peter at the Swiss Federal Institute of Technology in Zurich. Peter says that Ohsumi's significant contribution was that he didn't just observe the pathway by microscopy but also "used an elegant genetic screen to identify molecular components that are required for autophagy. He laid down the genetic foundation of this pathway."

Ohsumi and his laboratory members identified the critical genes

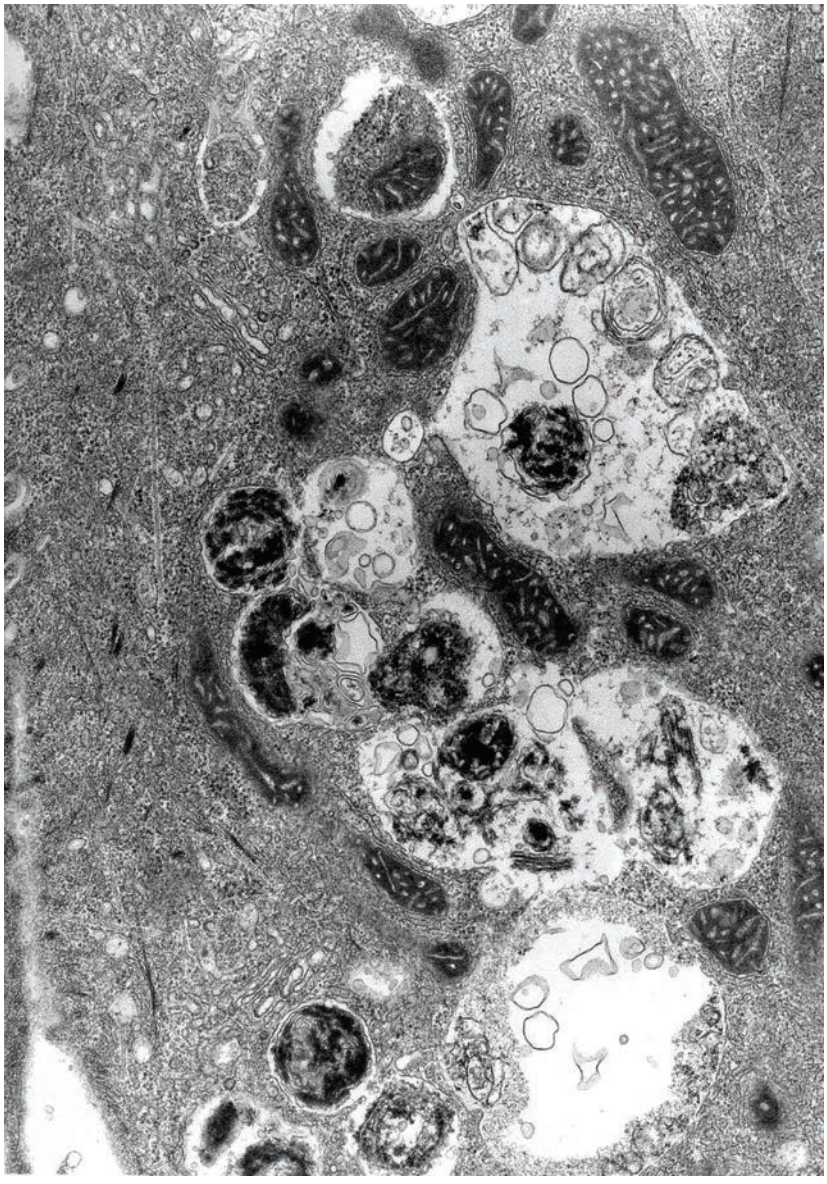

IMAGE PROVIDED BY SHARON TOOZE

Electron micrograph shows mature autophagosomes engulfing intracellular components.

responsible for each step of the autophagy pathway. Those discoveries allowed for the full role of autophagosomes to be mapped through the use of genetic screens. This would allow Ohsumi's laboratory and others to investigate the ramifications of each step in the clearance pathway at the biochemical level.

After the breakthrough in 1993, when Ohsumi and colleagues published the FEBS Letters paper describing all 15 ATG genes, Ohsumi's laboratory members set out to characterize the functions of each step of the pathway. Noboru Mizushuma was a postdoctoral researcher in Ohsumi's laboratory who discovered that the Atg12 protein formed an essential trimolecular complex with Atg5 and Atg16. This complex promotes the conjugation of the protein Atg8 to the phospholipid phosphatidylethanolamine. The conjugated phospholipid then drives the coalescing autophagosomal membrane to elongate around intercellular components targeted for degradation and to fuse together, sealing the target off on its way to the vacuole. Linking these pieces together allowed Ohsumi's team to present the entire pathway in several papers, including two papers in Nature in 1998 and 2000.

Working with Ohsumi "undoubtedly broadened my scientific view," says Mizushima, who is currently at the University of Tokyo. "The most important lesson I learned during my time in Dr. Ohsumi's lab is that researchers should have the courage and determination to pursue research directions and answer questions that they believe to be important irrespective of current trends and apparent usefulness."

In a few years, Ohsumi and colleagues identified the mammalian homologues of the yeast ATG genes, resulting in a cascade of applications throughout cell biology.

"This long-anticipated and extremely well-deserved prize reminds us that the best way to make important discoveries is often to ask a simple question about an interesting phenomenon, pick the right model organism in which that question can be approached genetically and biochemically, and let the grand unity of biology do the rest," says Gregory Petsko at Cornell University, a former ASBMB president.

Another former ASBMB president, Suzanne Pfeffer at Stanford University, agrees. "Dr. Ohsumi is a wonderful choice for this award," she says. "He is a dear and humble man who used the power of yeast genetics combined with microscopy and biochemistry to work out the entire, unexpected pathway of autophagy that is highly conserved from yeast to humans."

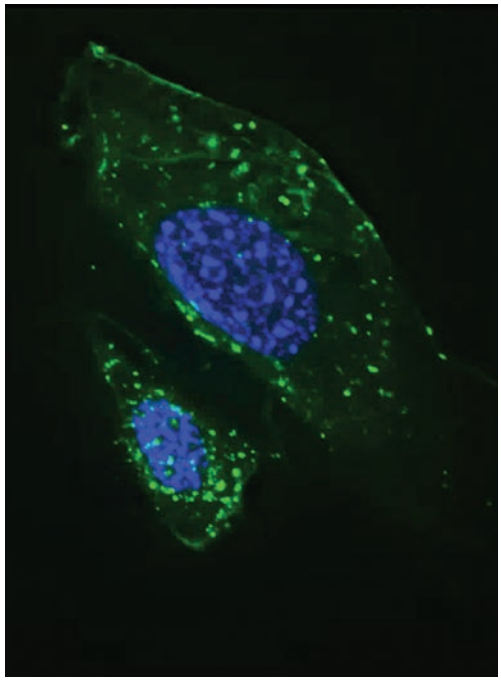

IMAGE PROVIDED BY JAN PETRASEK AND BETH LEVINE

Autophagosomes (green) become activated in starved cells.

Autophagy's many facets

Autophagy has been observed in many life forms, not just yeast and humans. According to Beth Levine at the University of Texas Southwestern Medical Center at Dallas, autophagy's ubiquity across eukaryotes might be due to its early evolutionary role in facilitating eukaryotic cells' ability to tolerate a variety of environments.

"If an organism can degrade and recycle its internal contents to survive short-term periods of starvation, this has tremendous advantages for evolution. The organism can now migrate to other environments and undergo selective mutations that permit it to adapt to other environments," says Levine. "This facilitates evolutionary diversity."

As a self-eating process, autophagy plays a significant role in intercellular nutrient regulation and homeostasis. "Autophagy is fundamental for nutrient homeostasis, sensing amino acid levels and nitrogen levels in both yeast

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and mammals," says Sharon Tooze at the Francis Crick Institute in the U.K. "It's not just a pathway for getting rid of garbage. It's also a pathway that keeps cells in a nutrient-stable condition."

Iron regulation, says Tooze, is one of the most essential pathways that autophagy recently has been found to control. The autophagy protein WIPI4 is involved in the turnover of ferritin, a protein that stores iron in a nontoxic form. When defects arise in WIPI4, iron can accumulate toxically in the brain, causing a condition called "neurodegeneration with brain iron accumulation disorder."

Neurodegeneration from iron accumulation isn't the only effect autophagy has on physiology when it goes awry. Researchers working with neurodegenerative disorders say one of the frontiers in autophagy is the ability to modulate the process selectively in certain parts of the body.

"Normally you activate autophagy every day, in all the cells in your body," says Ana Maria Cuervo at the Institute for Aging Research of the Albert Einstein College of Medicine. "But the level of activation changes with age. In some organs, it cannot reactivate properly."

Within Parkinson's, Alzheimer's and Huntington's diseases, says Cuervo, there is a primary defect in autophagy. "Autophagy usually contributes to eliminate (excess) proteins. That's why you don't see Alzheimer's patients who are 20 years old," says Cuervo.

As autophagy starts declining with age, Cuervo explains, dysfunctional proteins such as beta-amyloid peptides or alpha-synuclein oligomers start accumulating and clogging the autophagy system, creating a vicious circle. "I think that the challenge right now is to try to understand in which diseases the changes in autophagy are the cause of the disease, and in which ones these changes that we see in autophagy are reactive to the disease itself," she says.

While it would be ideal in these instances to ramp up autophagy in neurons, "something that we still don't have is a drug that can very selectively only modulate autophagy," says Cuervo.

Beyond self-eating, another crucial role of autophagy is its ability to remove intercellular pathogens, which include viruses, bacteria and parasites.

Fortuitous yeast

The research that ended up transforming so much of modern cell biology was born out of a period of isolation in Ohsumi's career. While investigating the in vitro fertilization of mouse eggs as a postdoctoral researcher at The Rockefeller University in 1975, Ohsumi crossed paths with Michal Jazwinski, an incoming postdoctoral researcher.

According to Jazwinski, Ohsumi's initial work in the lab of Gerald Edelman involved studying the processes involved in the chromatin decondensation of sperm cells.

"It was a fairly large laboratory, dealing with signals at the cell surface and interactions between cells," says Jazwinski, now at Tulane University. While Ohsumi's work involved cell–cell interactions, "it was a project that was off on the periphery. He was the only one that was looking at that phenomenon."

As Jazwinski's own research with signal transduction in lymphocytes began steering him toward investigating cell division in yeast, he says, he found himself venturing away from the rest of the laboratory.

"We were both isolated, which led to us gravitating toward each other," says Jazwinski, who describes Ohsumi as an easygoing person. This led to Ohsumi beginning to work with Jazwinski on studying DNA duplication within the yeast cells. "We started interacting more. It was fun, because we had a way of being able to exchange ideas about very basic concepts in biology and practical things with experiments."

Jazwinski started using yeast for his experiments. Ohsumi, recalls Jazwinski, "observed what I was doing and became interested in what I was doing." That seed of interest, it seems, grew into a lifelong love of the intricacies of yeasts that Ohsumi still is pursuing to this day.

This aspect of autophagy is known as xenophagy. One of the many research foci of Levine's laboratory is understanding how the cell's self-eating pathway can be used to degrade foreign material.

Disabling the autophagosome's ability to identify foreign objects is a common pathogenic strategy. One example is herpes simplex virus, which generates viral virulence proteins that block the function of the Beclin-1 autophagy protein in neurons. This action causes significant cell damage, ultimately resulting in fatal encephalitis in mice.

By binding to the Beclin-1 protein in neurons, herpes simplex virus can block the cells' autophagy function. Such is the strategy of herpes simplex virus as well as other viruses that target the central nervous system.

For a bacterium like Salmonella, says Levine, "the ability of the autophagic machinery to degrade the microbe basically determines whether the bacterium is or is not an intercellular pathogen." In humans, Salmonella are capable of invading epithelial cells but usually are caught and destroyed by autophagosomes.

In roundworms, Salmonella typically replicates in the lumen of the intestine rather than the epithelium. When the autophagy machinery is knocked out in worms, Salmonella spreads through the epithelium unchecked, killing the worms.

Since 2004, there have been numerous studies from labs worldwide demonstrating that in higher eukaryotic organisms both the autophagy pathway and autophagy proteins play a crucial role in many different aspects of immunity, says Levine.

Dramatic change

From cellular garbage can to nutrient-recycling, plaque-and-pathogen-punishing Roomba, the view of the autophagosomes' role in cellular functions has changed dramatically since Ohsumi's landmark discovery more than two decades ago. By teasing out the function of a pathway that most of his peers had ignored, Ohsumi gave cell biologists the tools they needed to explore deeply the mechanisms behind what is swallowed and what is spared.

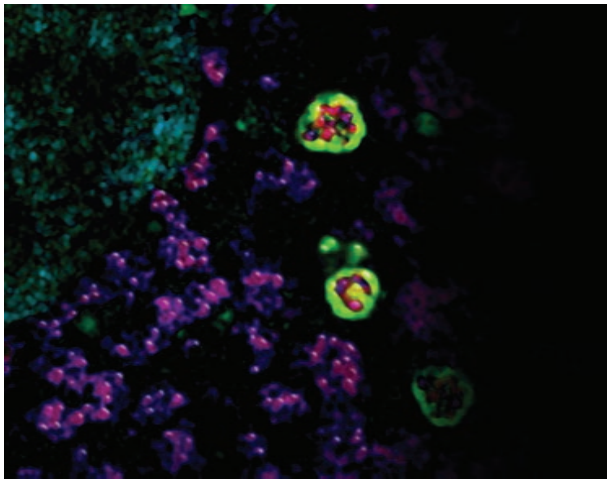

IMAGE PROVIDED BY RHEA SUMPTER AND BETH LEVINE

Autophagosomes (green) surround mitochondria (red).

Experts are excited about the future of this once-obscure niche of cell biology. "There are still many questions regarding regulation from these autophagosomes," says Cuervo. "From the point of view of cell biology, that is the beauty of such a fundamental process."

Ohsumi too marvels at the beauty of autophagy but pays tribute to the hard work of his fellow scientists. "As a scientist, there is no greater satisfaction that having your work recognized, and as the highest scientific honor, the Nobel Prize is very significant," says Ohsumi. "Our discovery of the basic process of autophagy has opened up whole new areas of research. The selective degradation of organelles, protein aggregates and invading bacteria, for example, are physiologically very important phenomena that are now being rapidly uncovered by pioneering scientists all over the world. It is also becoming clear that the medical applications of our basic research in the treatment of cancers and other diseases are ever closer to realization, which is very exciting. I would therefore like to express my gratitude to researchers from all over the world who have shown interest in our work, made important contributions to the field and joined us on this exciting journey of discovery. The growth of the field would not have been possible without their efforts."

In good company

The Nobel Committee for physiology or medicine cited a 2007 paper from the Journal of Biological Chemistry (*J Biol Chem* **282**, 37298 – 37302) among their reference materials for the prize. In the paper, Ohsumi and his colleagues demonstrated that a conjugate between the Atg12 and Atg5 proteins strongly enhances the formation of another conjugate, Atg8-phosphatidylethanolamine. Both of the ubiquitin-like conjugation systems are essential for autophagosome formation, but their relationship to one another was previously unclear.

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Tips for getting a career-development award

By Li-Shin Huang

I often am asked "How do I get a K99/R00 award?" or "I am no longer eligible for K99/R00. What can I do?"

A K99/R00 is a career-development award entitled "Pathway to Independence." It has been sponsored by the National Institutes of Health since 2007. A K99/R00 award helps a postdoctoral fellow transition from a mentored position into that of an independent investigator.

The K99/R00 is the only NIH-sponsored career-development award that's open to both U.S. and non-U.S. citizens and residents who hold either terminal clinical or research doctorates. The combination of a mentored phase (K99 of one to two years) and an independent phase (R00 of three years) makes the award an effective mechanism for junior investigators to achieve independence, which often is reflected in acquiring research project grants in the form of R01s.

So what can you do to better your chance of getting a K99/R00 grant or any type of career-development award?

For six years before retiring from Columbia University in 2015, I served periodically on a special emphasis panel that reviewed about 50 K99/R00 applications per grant cycle submitted to the National Heart, Lung and Blood Institute. This experience gave me insights into the K99/R00 mechanism. In the past year, I became a program officer in the office of research training and career development in the division of cardiovascular sciences at the NHLBI. I manage a portfolio of grants that includes mentored career-development awards and institutional training grants.

Based on my experience, I have a few tips for those who are seeking an NIH career-development award. But these tips are also applicable to other non-NIH-funded career-development awards.

Start early

No matter what grants you are applying for, your qualifications are critical. Start early to become a highly qualified candidate. Work hard and publish. Both the quality and the quantity of your peer-reviewed publications are taken into consideration. Co-authorships attest to your teamwork capability and are a means to increase your publication numbers. However, you must have first-authored original articles to show your productivity and leadership for a project. Reference letters matter in your candidacy. Ask only referees who know you well enough to give you strong and informative letters of recommendation.

Identify possible grant mechanisms suitable for your career stage and your goals as an independent investigator. For example, apply for a predoctoral fellowship while you are in graduate school or a postdoctoral fellowship at the early stage of your postdoctoral training. Prior records of fellowships strengthen an application. Explore the NIH K Kiosk for career-development awards (1) and check out other non-NIH awards that are available to your field of research. A simplified scheme for a career path in academia with possible NIH funding mechanisms is shown in the figure on page 25.

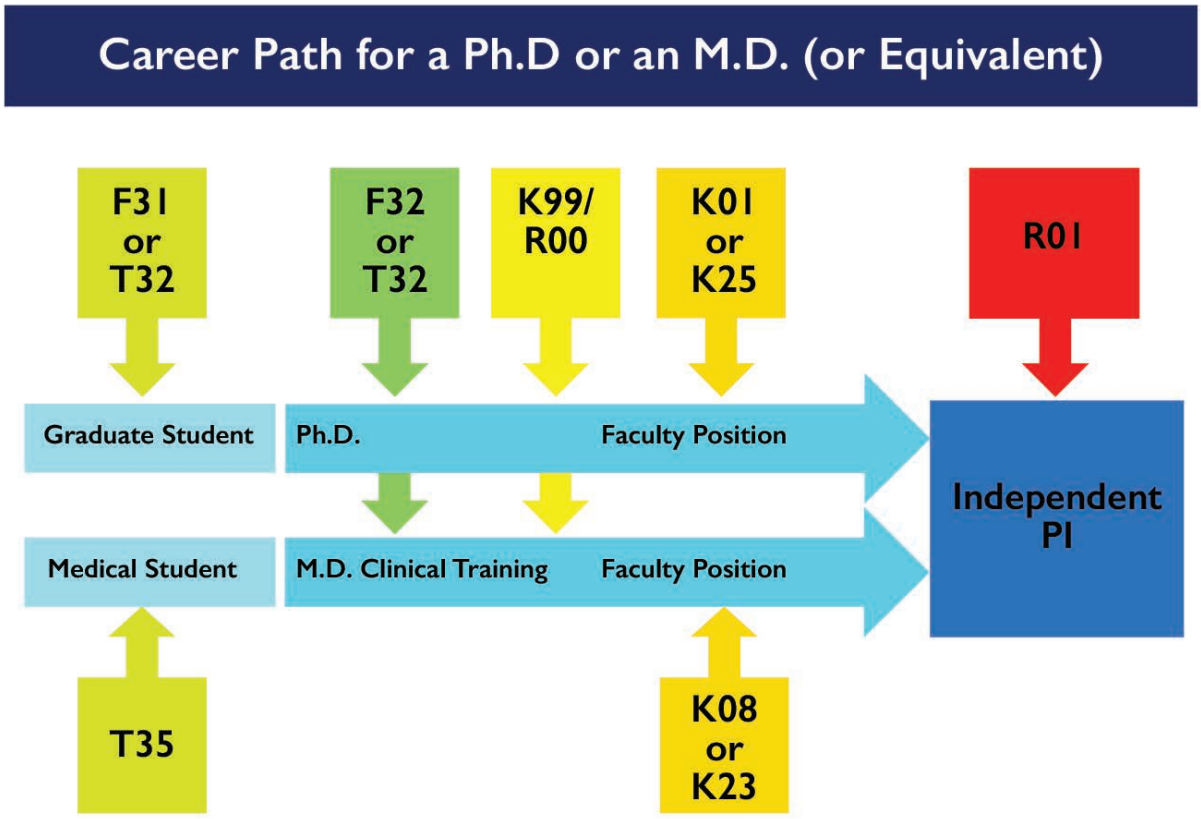

FIGURE PROVIDED BY LI-SHIN HUANG

"T"s stand for institutional research training grants; "F" are for fellowships; "K" are for mentored career development awards. K99/R00s support independent research. R01s are research grants.

Read announcements thoroughly

The basics about an award are found in the grant announcements and NIH web postings. Understanding the information from these resources also will facilitate conversations with NIH staff who can help with any specific concerns or unusual situations. Check out eligibility requirements early in your training. For example, K99/R00 applications are limited to those with four years or less of postdoctoral training at the time of the submission or resubmission deadline. Also, not all NIH institutes and centers offer every kind of K award. Your options will be limited to those grants supported by those institutes and centers with missions that align with your area of research.

Set milestones at the outset of your postdoctoral training, and start working on your proposal at least six months ahead of the application deadline.

Follow instructions carefully

A key to a good proposal lies in your ability to follow the guidelines and recommendations set by the funding agency. Be sure that you are up to date with policy changes. Font size and page limit are enforced strictly. Don't waste your energy attempting to circumvent these rules. Instead, use the time to make it a concise, well-written and visually pleasing proposal with all the required components.

Propose a research plan that is distinct from your mentor's research.

In general, a research plan is judged for its significance to advancing human health, the innovation of its concepts or approaches, and the feasibility of the proposed studies within the proposed time frame. Strong preliminary data or published papers on the proposed research topics greatly strengthen your proposal. Your plan should hone skills (in the early phase of the K award) that are aligned to your career goals (in the independent phase). The proposed studies should lay the foundation for future R01 submissions.

Understand review criteria and work with your mentor(s)

Information about the "Candidate" and "Research Plan" cover two of the five scored criteria in a K-award application. Other scored criteria include "Career Development Plan/Career Goals & Objectives." The career-

CONTINUED ON PAGE 26

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development plan should be tailored to your needs in training. These may include technical skills, didactic courses and plans for professional development in areas such as grant writing, communication training, and lab management. Set a timeline with milestones for the proposed training, completion of specific aims and manuscript/grant submissions.

Your "Mentor(s), Co-Mentor(s), Consultant(s), Collaborators" are judged by their training records, funding and research expertise. Even if your primary mentor's expertise covers all aspects of your proposed research, it is still valuable to assemble an advisory team to evaluate your scientific and professional progress periodically and to offer suggestions. Importantly, your application should specify the role and importance of each mentor in your plan to become an independent investigator. Their letters of support should make clear their commitment, concurrence and understanding of that plan.

Finally, your application should make clear that the "Environment and Institutional Commitment to the Candidate" are of high quality. Your department chair or division chief must include a letter to assure a minimum of 75 percent protected time for research training during the award. However, strong institutional commitments also include tangible contributions to your development, such as space and resources to do your work, startup or pilot funding for research, or support for a research technician. Recognized potential for a tenure-track appointment is a plus for a K99 application, and an actual tenure-track appointment is considered a strong commitment for most other K awards.

Don't overlook other criteria

The NIH has implemented a new policy that requires applicants to address "Scientific Premises, Scientific Rigor" and consider "Sex and Other Biological Variables" in their research plan. A good research plan always addresses these issues. However, with the new policy, the peer reviewers must assess how well these issues are addressed in your application.

Although not listed in the five scored criteria mentioned earlier, your write-ups on "Protection of Human Subjects," "Inclusion of Women, Minorities and Children," "Vertebrate Animals" and "Biohazards" may affect your overall impact scores, as these are considered as part of your research approaches.

There are additional review considerations that do not affect the scoring. However, concerns in any of these categories will need to be addressed prior to funding. These include "Training in the Responsible Conduct of Research," "Select Agent Research," "Resource Sharing Plan," "Authentication of Key Biological and/or Chemical Resources," and "Budget and Period of Support."

Get critiques from your mentor(s) and colleagues

It is critical to solicit critiques from your mentor(s) and colleagues and then revise the proposal accordingly. You need to give them ample time and then allow enough additional time to incorporate their recommendations. So plan ahead and complete a draft far ahead of the application deadline.

Proofread every section of your proposal prior to submission.

A sloppily written grant application is viewed poorly. Take the time to proofread every section of the proposal before submission. Errors distract reviewers from reading the contents of your proposal.

Be responsive to reviewers' critiques

Don't be discouraged if your application is not funded. Take a little bit time to get over your disappointment. Then read the "Summary Statement" carefully, discuss it with your mentors and advisers, contact your NIH program officer for additional input if needed and make a systematic plan to address all of the critiques raised by the reviewers. Summarize your key responses in the one-page "Introduction" section and make the revisions easily identifiable in the body of the proposal. Responsiveness to critiques is weighed heavily for scoring. Don't resubmit until you are able to address most, if not all, of the concerns.

Additional strategic advice and analysis of career-development awards are publicly available (2–5). In summary, start early from the beginning of your postdoctoral training to build up your qualifications and to formulate a plan so you have sufficient time to prepare a competitive proposal for funding.

Finally, try and try again if you don't succeed the first time.

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Exams and evolution

By Peter J. Kennelly

As a university instructor, I have spent years emphasizing to my students the importance of natural selection in the evolution of the organisms and processes that we biochemists and molecular biologists study every day. Higher organisms have emerged and developed in response to the need to overcome selective pressures imposed on them from their environment. It occurs to me that teaching and learning share a lot in common with evolution.

As in biology, student behavior is shaped by the advantages obtained by accruing the greatest possible benefit (e.g., points, grades or credits) from a given investment in time, resources and energy. This drive toward actual or perceived efficiency is not a character flaw; it is our natural default setting. When you or I go on MapQuest, we almost always opt for the most direct or the fastest route rather than the most culturally enriching or scenic. Those of us who hold tenure-track faculty positions constantly make choices on the basis of whether we think the promotion and tenure committee will reward a particular activity.

All this prompts the question of why so many of us neglect to leverage this ingrained behavior when constructing examinations. I would argue that no matter how much time and effort we invest in developing curricula and learning objectives designed to stimulate the development of analytical reasoning and critical thinking skills, if our examinations are dominated by recall-type questions, we are substantially undermining these efforts. If recall is the most efficient way to garner their desired grade, the majority of our students naturally will engage in memorization and invest the minimum effort possible in developing higher cognitive reasoning skills, no matter how doggedly we try to reinforce them in class. It is not my intent to disparage flipped classrooms, clickers or inquiry-based learning, but rather to encourage better alignment of this cornerstone of the rewards system with these efforts.

Now many of us, especially those working at large schools characterized by large class sizes, could argue that the logistics of scoring hundreds of quizzes and exams on a regular basis restrict us to employing question formats that are machine-gradable. We also can argue that one class is insufficient to convert students who have been fed a continual diet of multiple-choice exams. There are practical limits to what can be done. On the other hand, what if every examination our students took included at least one or two questions that challenged them to engage in analytical or critical reasoning, to synthesize rather than select?

Such a coordinated approach would spread the logistical burden across the faculty, undermine the perception that such questions represent a temporary aberration peculiar to a specific class or instructor, and provide the benefits of continual practice and reinforcement over time. So next time you put together an exam, try exploiting "selective pressure" as a means of stimulating your students to evolve higher cognitive reasoning abilities.

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Bringing enzymes to deaf and hard-of-hearing students

By Austin Gehret

As a faculty member at the National Technical Institute for the Deaf, my job in higher education is unusual. I work exclusively with deaf and hard-of-hearing students.

The NTID, hosted within Rochester Institute of Technology as one of nine colleges on campus, was established as the first institution devoted to the technical and professional postsecondary education of deaf and hard-of-hearing students. The wealth of resources available through the NTID's presence attracts many deaf and hard-of-hearing students to the institute's other colleges as well. I serve as an instructor within the NTID for our associate degree in laboratory science technology but also as a tutor for the baccalaureate-level deaf and hard-of-hearing students in other colleges within the institute. This latter role places me in the unique position of academically supporting deaf and hard-of-hearing students taking classes taught by other nonsigning faculty members. My peers and I serve these support faculty roles to ensure all deaf and hard-of-hearing students at Rochester Institute of Technology achieve equal access to the lecture material presented in their classes.

When I was hired, I needed time to develop my sign-language skills, so I assumed a support role initially to tutor deaf and hard-of-hearing students in biochemistry coursework. When I had developed sufficient sign-language skills, I then had the opportunity to teach the basics of enzyme catalysis in my own biotechnology class at the NTID.

Foundational concepts in biochemistry have been shown to be misconstrued by many students (1, 2). Enzyme kinetics is certainly no exception to this phenomenon (3, 4). Many biochemistry instructors see a noticeable change in students' expressions when enzyme kinetics becomes the topic of discussion. A good number of students weakly retain concepts of kinetics, but, with the wealth of conceptual information presented on top, it is simply too much for them to absorb.

In my role as tutor, I too was presented with some blank stares. But I had the additional challenge of the limited time I had to figure out where my tutees were disconnecting from the material.

To help with comprehension, I developed visual tutorials to supplement what I could not convey effectively through sign language. I wanted students to develop a deeper understanding of this topic beyond memorization of the Michaelis–Menten equation and how to extrapolate kinetic parameters. In doing so, I devoted significant effort to clarifying the simplifying approach of measuring the initial rate (V_0) of enzyme catalysis as well as the steady-state assumption.

As a teacher of deaf and hard-of-hearing students at NTID, direct instruction is not simply an exercise of lecturing in American Sign Language. Our students' communication preferences and academic needs are extremely diverse. Several students in our LST program do not rely on signed communication, so I lecture by speaking and signing at the same time. Presenting scientific material through two different language channels simultaneously introduces its own set of challenges. Because of this, inclusive learning activities become part of my communication strategy.

I was fortunate to have at my disposal a department stockroom that had accumulated over the years a variety of educational resources. When I came upon a Pop-It Beads DNA modeling kit, I was inspired to develop a kinesthetic activity that could supplement my teaching of enzyme catalysis.

Students were presented with two bins, each containing several pairs of connected Pop-It Beads that acted as the substrate. The students would act as enzymes to separate the beads into individual products in one bin (which represented the products of the catalyzed reaction) while leaving the second bin untouched (which represented the uncatalyzed reaction). In performing the activity, the students could quantitate their influence on this reaction by determining and comparing their catalyzed rate to that of the uncatalyzed reaction. To model molecular behavior effectively, students were instructed to avert their eyes from the substrate bins while catalyzing. We didn't use blindfolds because that would have restricted many students' ability to communicate with their partners.

In the few years running this activity, the effect of substrate depletion on catalytic function appears to be its most tangible feature. Most students view the fixed amount of time given to catalyze as a challenge

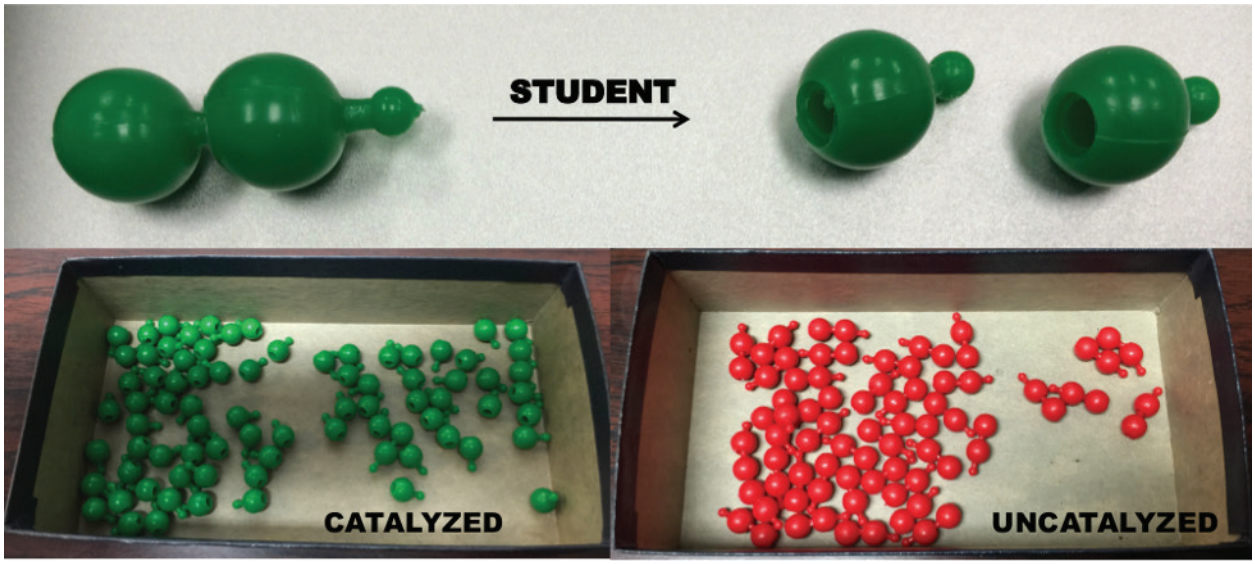

PHOTO PROVIDED BY AUSTIN GEHRET

Pop-It Beads help deaf and hard-of-hearing students understand the fundamentals of enzyme catalysis.

to find and break down all substrates. However, each of them discovers this task becomes increasingly difficult to achieve the longer catalysis continues. Their collective demeanor reflects this struggle. Allowing students to internalize this experience appears to be a more effective way for me to teach substrate depletion effects than to have me lecture about it. Students observe this phenomenon when they quantitate enzyme activity, so it's a nice opportunity for them to see their classroom experience translate to the laboratory.

Kinesthetic approaches have been used before to model Michaelis–Menten kinetics with a variety of objects (5–8). This activity allows students to model basic dynamics of an enzyme-catalyzed reaction that I feel also holds value in its ability to demonstrate the importance of measuring V_0. Based on my tutoring experiences, providing students with opportunities to revisit foundational concepts in novel ways may help them navigate applied topics a little more confidently in their biochemistry courses.

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Sustained funding

By Benjamin Corb

In this series, you've read about steps that the American research community can take in order to build a robust and sustainable biomedical research enterprise. We can begin to shape the biomedical research workforce for the needs of tomorrow through workforce improvements, such as making better use of staff scientists and improving the experiences of postdoctoral trainees. Sadly, one key element of sustainability that is entirely outside of the control of scientists is access to robust federal investments in research.

Since the American Society for Biochemistry and Molecular Biology's Sustainability Summit in February, former ASBMB president and current editor-in-chief of Science Jeremy Berg has done extensive research into modeling the impact of boom-and-bust funding trends for basic biomedical research.

In Berg's Science editorial "Benefits of Steady Growth," which appeared on Aug. 26, he explains the problem. "Such fluctuations have important consequences," he wrote. "Outstanding applications that would have been funded one year go unsupported the next year, so that potentially groundbreaking research may be missed for arbitrary reasons of timing. Low success rates result in scientists spending more time writing and reviewing proposals instead of conducting research. Investigators, particularly those at vulnerable career stages, can become demoralized by the apparently capricious nature of funding decisions."

Berg developed a model that predicts, with a 0.866 correlation coefficient, the impact of funding levels on grant-application success rates at the National Institutes of Health. The model gives us a tool through which we can begin to build a case for sustainable growth. For example, Berg's analysis compared the doubling period of the National Institutes of Health's budget from 1998 through 2002 with a hypothetical sustained-increase model. He found that sustained growth of 7 percent over the same time period, instead of rapid growth followed by a period of flat funding that we have experienced, would have had the potential to provide funding for 35,000 more grants than the number actually funded during that time period.

The impact of fluctuations comes as no surprise to researchers who are at the front lines, whose very existence depend on the success of their latest grant applications. Funding agencies like the NIH are very aware of the impact that unpredictable funding has on their constituencies. We appreciate the hard work done by Berg, because the ASBMB's advocacy efforts now will use the tool to support our arguments to policymakers in Washington that we are served best by robust and sustained investments.

Benjamin Corb (bcorb@asbmb.org) is the director of public affairs at the ASBMB. Follow him on Twitter at twitter.com/bwcorb.

Me and the OpenBiome

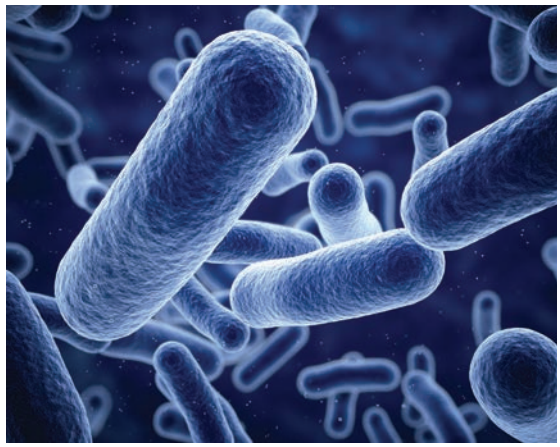
By Garner Soltes

I started my fifth year of graduate school like many Ph.D. students: forging ahead on a timeline with shifting goalposts while weighing future academic and nonacademic careers. I knew that I wanted to pursue a career closely tied to science with strong roots in communication. But much of my future trajectory remained unresolved.

In an effort to broaden my training and explore applications of my degree in molecular biology, I enrolled in science policy courses at Princeton University. During one of these classes, I researched potential biological and policy interventions for the impending antibiotic resistance crisis and came across OpenBiome.

OpenBiome is a nonprofit stool bank and research organization based in Somerville, Massachusetts. OpenBiome provides safe access to fecal microbiota transplantation for patients with severe Clostridium difficile infections and enables microbiome research. Being lighthearted about the scatological material and familiar with the recent advances in microbiome research, I immediately was interested in this organization at the intersection of microbiology, research, health, policy and public outreach. When OpenBiome came to a career fair at Princeton in the fall of 2015, I had to give the organization a shot.

Based on my conversations with colleagues and mentors in life science and health care industries, I worried that there wasn't an opportunity for a Ph.D. scientist in a nonresearch role. In my mind, the academic career pipeline and nonacademic industry routes traditionally selected for marketable scientific skills and publications, placing secondary emphasis on "softer" interpersonal and communication skills. The folks at OpenBiome, though, seemed excited about my interest in complicated science policy issues and science communication. I quickly found that my founding of a science literacy initiative called Science by the Cup, which was seeded by funding from the American Society for Biochemistry and Molecular Biology, was as important as my research interests. In the end, describing the cutting-edge biology of beer brewing to a lay audience is quite similar to communicating research objectives and expectations to clinical partners. But at the time, I didn't appreciate that this was one of the many common threads I would connect from my academic experience to my work with OpenBiome.



After the career fair in late 2015, I coordinated with the OpenBiome team members for a six-week summer placement, working on the organization's external affairs. Within a month of my placement, I created internal educational resources to inform new team members about the microbiome, developed pitches for fundraising, and crafted communications materials to jump-start clinical and basic-science microbiome research.

As expected, I have developed further my ability to communicate science clearly and hear the viewpoints of disparate audiences. However, jumping headlong into a new field and a smaller organization for a brief period of time also has required me to work efficiently and often independently, which is familiar from tight research presentation deadlines and late-night experiment-planning sessions. Combing through clinical research is not unlike studying for qualifying exams. And confident presentation skills developed at countless lab meetings and science outreach events have been essential in my professional life.

My time at OpenBiome has strengthened my belief that there is true value in a Ph.D.'s capacity to distill and communicate scientific information, regardless of his or her field of training. This unique competitive advantage, reinforced by the informal facets of a Ph.D., is invaluable in pursuing a career. Now, if I find myself again at the edge of the professional abyss, I will know to reflect on these skills, identify others I would like to develop and then search for opportunities that enable this growth.

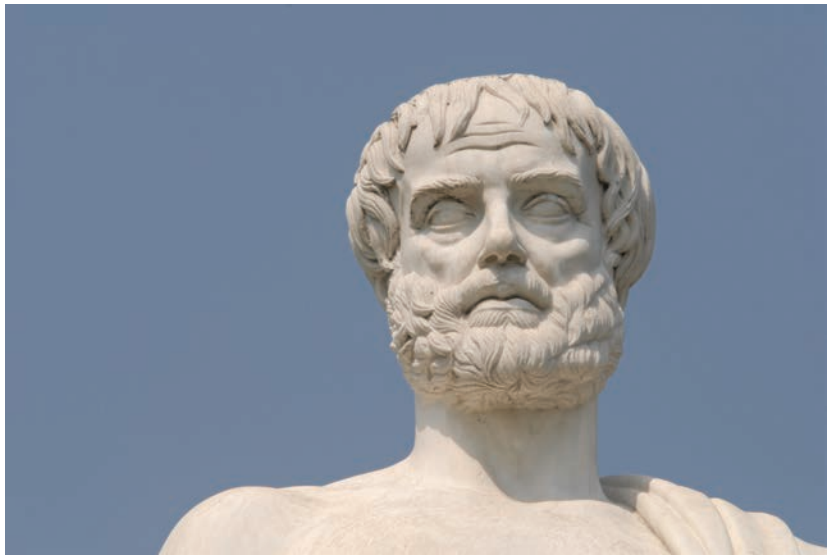
Garner Soltes (gsoltes1@gmail.com) is a recent Princeton University graduate with a Ph.D. in molecular biology. He is the founder of Science by the Cup, a Princeton University adult science literacy initiative.

How chemistry defies philosophy of science

By Ashutosh Jogalekar

Hypothesis generation and falsification lie at the heart of the scientific method. Whether it's investigating the forces governing the motion of planets or galaxies, testing factors influencing the feeding behavior of birds, or constructing molecular models of drugs interacting with proteins, hypothesis testing and falsification are such a ubiquitous part of scientific research that many scientists take them for granted. When you look at the larger landscape of science, however, a more complex view of applying the scientific method emerges, one in which doing science does not depend only on constructing or falsifying specific hypotheses. In fact, non-hypothesis-driven science has been an integral part of scientific progress for a very long time. This fact is exemplified best by the science and art of chemistry.

At first sight, the lack of hypothesis-driven science poses a conundrum. If you don't have a hypothesis, how would you know what experiment to perform or what quantity to calculate? Yet when chemists synthesize new molecules, they seldom have a hypothesis in mind. The hypothesis may lie in the application of those molecules; for example, one may be making a molecule to test a hypothesis about the workings of a particular biochemical pathway or about the quantum yield of a particular solar cell. But the synthesis itself is not really in the domain of hypothesis testing. The oft-quoted comparison between chemistry and architecture thus is not without merit from this viewpoint: When you are laying down plans for



a new bridge, what hypothesis exactly are you generating?

The same goes for another pillar of science — namely, falsification. When a chemist is synthesizing a new molecule, she is not expressly trying to falsify a hypothesis except in the trivial sense of trying to falsify the basic laws of chemistry. As the chemist and Nobel laureate Roald Hoffmann of Cornell University elegantly put it in an essay collection called "Roald Hoffmann on the Philosophy, Art, and Science of Chemistry":

"What theories are being tested (or falsified, for that matter) in a beautiful paper on synthesis? None, really, except that such and such a molecule can be constructed. The theory building in that is about as informative as the statement that an Archie Ammons poem tests a theory that the English language can be used to construct novel and perceptive insights into the way the world and our minds interact. The power of that tiny poem, the cleverness of the molecular surgery that a synthetic chemist performs in creating a molecule, just sashay around any analytical theory-testing."

Chemistry is largely a creative activity, trying to come up with novel ways of deciphering the structure of molecules and of making them. Synthesis always has been the unique element at the heart of chemistry. Chemists synthesizing molecules are like termites building an intricate nest; the humans who make molecules are no more trying to falsify molecule building than termites are trying to falsify termite-mound building. The goal is to create novelty, not to falsify existing ideas.

This principle applies to a wide range of fields in chemistry. For instance, consider two pillars of tool-driven revolutions in biochemistry: X-ray crystallography and nuclear magnetic resonance spectroscopy.

The goal of both techniques is to determine the structure of complex molecules like proteins. Sometimes the goal may be to test specific hypotheses regarding the function of these molecules, but equally often it's simply to figure out their structures for their own sake. Today there are literally hundreds of thousands of proteins whose structures have been determined, but structure determination by itself is as much art as science. It's simply being driven by the pleasure of finding things out.

Sometimes the goal is also esthetic. Cartoon models of proteins adorn biochemistry textbooks in the manner of paintings adorning national galleries. Their contours and three-dimensional structures are as much works of visual pleasure as examples of hypothesis testing. The same goes for the study of countless biochemical and genetic pathways in living organisms. Scientists who perform this painstaking detective work are not always testing or falsifying hypotheses; they simply are trying to find out unique biochemical features of living systems.

The fact that much of chemistry and biochemistry defy both hypothesis testing and falsification highlights the limitations of the traditional philosophy of science as it's currently taught. One of the reasons this is so is that the philosophy of science traditionally has been created, taught and proselytized by people with a background in physics. Many of the big names in the philosophy of science — Aristotle, David Hume, Karl Popper and Thomas Kuhn, to name some of the most prominent — were trained in physics, thought mostly about physics, lived during a time of great upheavals in physics or were influenced by physicists. Kuhn and Popper especially came of age in the heyday of physics. Kuhn, who was a physicist himself, had written extensively about the Copernican revolution and other topics in physics and astronomy before he published his seminal work "The Structure of Scientific Revolutions."

The principles laid out by these philosophers of science were not incorrect. But they illuminated only one aspect of scientists' daily work, and incompletely at that. For example, falsification is almost never on the minds of everyday scientists working on their everyday problems. What's on their minds is confirmation. Neither do most scientists throw away their theories when a few experiments threaten to falsify them; if they did this every time, the progress of science would be much slower than it is.

Even in physics, there are now subfields like the physics of emergent systems in which hypothesis generation and falsification are not the most important activities. Isaac Newton was not wedded to hypotheses. In one passage of his famed "Principia," he remarked, "Hypotheses, whether metaphysical or physical, or based on occult qualities, or mechanical, have no place in experimental philosophy." The problem with much of philosophy of science, then, is not that it's invalid; it's that it's biased by the backgrounds of the philosophers who preach it and the existing fashions of the time. As Hoffmann says, the philosophy of science might have looked very different if it had been taught by chemists, emphasizing synthesis and exploration instead of hypothesis generation and falsification.

Every science shares some facets of the traditional philosophy of science, but it also has its own explanatory devices that render its philosophy unique. Chemistry is a model example of why as science changes its philosophy must change and adapt, retaining the most cogent of the old principles but nimbly incorporating new ones.

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Hit the road

By Emilia (Emily) Arturo

As I write this, I am enrolled as a fifth-year Ph.D. student in the biochemistry program at Drexel University College of Medicine in Philadelphia. Between the spring of 2003, when I received an undergraduate degree in applied mathematics and biology from the New Jersey Institute of Technology, and 2012, when I started this Ph.D. program, there were two mortgaged homes and three apartments across six different states, one marriage, two children, one year spent as a laboratory technician in a genetics sequencing facility, five months unemployed, nine months as a mathematics tutor and substitute teacher, four months as an analytical chemistry technician, and three years as a stay-at-home mom. And during all this, I began three Ph.D. programs — one in biophysics, one in chemistry and one in biochemistry.

Soon after I'd finished my undergraduate degree, I moved to Massachusetts to begin a Ph.D. program in biophysics at Brandeis University. The department accepted me on the basis of my mathematical training and my desire to apply mathematics to the modeling of neuronal networks. Within the first year, due to personnel changes that were out of my control, I had no lab in which to pursue the training for which I had applied. Nevertheless, I decided to stay and learn what to do at the bench.

Unfortunately, before my first research rotation, I had never once used a micropipette. I didn't know any molecular biology-related rules: how to store purified protein, make stock solutions, order primers or pour a gel. Bench work, in and of itself, can be stressful, but for me it soon became demoralizing when one of my major difficulties turned out to be, of all things, mental math! Things like unit conversions suddenly churned my math-y brain into a pathetic scramble. I felt completely ill-prepared, and I panicked. After I was asked to retake my preliminary exam, I left the program weeping.

I was newly married then. My spouse graduated with a Ph.D. shortly after I left Brandeis. Neither of us could find a "real" job. To help support us financially, I worked as a temp-to-hire technician in a genome sequencing facility. I found this job after months of searching, living on sporadic tutoring gigs, remaining wedding cash and reduced-cost meals from the pub where my spouse had a relatively lucrative interim career as a waiter.

I was full of questions, but as a technician, asking questions was not in my job description. My job was to be focused and efficient and to follow protocols. So I began applying to graduate schools. Shortly thereafter, my spouse secured a postdoctoral position, and we decided to move to Missouri. Expecting that his position would last on the order of three years, I joined a Ph.D. program in chemistry there to be near to him. A year later, he was recruited by a large chemical company for a "real job" that required him to relocate to Michigan. Deciding whether to stay or to leave was one of the most grueling decisions of my life to date. I chose to move to Michigan to be with my husband. Within three months, I was employed part-time as a tutor and substitute teacher but felt aimless and isolated while he moved temporarily 1,300 miles away on a research rotation.

By the spring, I was pregnant with our first child, and we relocated to Texas. Four months after my daughter was born, I cheerily returned to the bench as a technician analyzing gasoline samples. Working full time meant a need for reliable childcare, which, in that particular town, was hard to come by. I did find tolerable daycare, but pumping for breast milk in the ladies' room on a tattered sofa at lunchtime and at 5 o'clock each morning at home depressed me and quickly dried me up. Within six months, I left my job to stay home with my daughter. Two months later, I was pregnant with my son. He was born just before my 30th birthday in the spring of 2010.

For the next two years, I stayed home full time with my two children. During this time, my husband's employer purchased a company near Philadelphia. I begged for relocation, because unlike our location in Texas, Philadelphia was rich in excellent graduate programs. After three years in Texas, we relocated to Pennsylvania. I spent a few months preparing to retake the GRE, and by the fall of 2012 I was matriculated in my current Ph.D. program.

When I think about the decisions I've made en route to where I am now, I often think of Robert Frost's poem "The Road Not Taken." The poem's

most famous lines are these: "Two roads diverged in a wood, and I — I took the one less traveled by/And that has made all the difference." These lines have become the battle cry of the masses who want to believe that blazing one's own trail, over taking the conventional route, is what makes one truly happy and successful.

The message of the poem, in my opinion, however, is more subtle and powerful. Whereas the speaker of the poem claims at the end of the poem that he "took the one less traveled by," he actually saw both roads as indistinguishable from one another; the other one was "just as fair" and "as for that the passing there/Had worn them really about the same." He knew that he would retell the events "with a sigh/Somewhere ages and ages hence," and in doing so he demonstrates the brilliant foresight he had to realize that he would one day rewrite his story, making it more intriguing or perhaps just more tolerable. Therefore, it's not that the best road to take is the one less traveled by. The best road to have taken is the one that you took.

I don't wholeheartedly recommend the road I've taken. I do, however, appreciate the irreplaceable role it has had in forming me into who I am today. Unlike my 23-year-old self, I am focused, bold and resilient. I have been relatively successful as a graduate student this time round, almost entirely because of the expansive support group I have assembled over the years. This group is made up of family and friends as well as numerous sympathetic and brilliant collaborators and mentors I collected along the way. In particular, I am fortunate to have an extraordinarily supportive Ph.D. adviser, Eileen K. Jaffe.

Despite how well things are going now, I can only hope that future employers (and my children!) will find my decisions tolerable, if not desirable, but I can't know for sure. As I approach graduation, I have more big decisions I will make. For example, I consider whether I might move abroad with my children to pursue postdoctoral training. My main professional goal is to develop continually my skills and knowledge as a scientist, but I also want to explore the world (and show it to my children).

What I do recommend wholeheartedly is to consider all viable options. Whatever the road is, no matter the precedence or lack of one, it is each one of your decisions, and what you personally learn from them collectively, that will make all the difference.

PHOTO PROVIDED BY EMILY ARTURO

Arturo with her children earlier this year.

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Living at 43.4742 N, 70.4461 W

By Scott Arthur Scarneo

43.4742 N, 70.4461 W is where I found myself as a graduate student studying neurobiology. I can't say the cold state of Maine was my first choice of graduate school location. However, the never-ending pursuit of knowledge swayed me enough to relocate.

Most graduate students are less interested in the location of the school than in the promise and advancement of our skills and intelligence. I mean, for most of the week, we hardly have any time to enjoy our new location.

PHOTO PROVIDED BY SCOTT SCARNEO

Scarneo and his dog, Koda, in a wild blueberry field in Maine.

I know this may not be popular advice with some principal investigators, but I'll say it: Graduate students, make the time to get out of the lab. I mean it. Don't be that kid who is cooped up in the lab 24/7 worrying if his or her PCR will be perfect. Don't get me wrong: I am partial to a nice PCR, but the point is to get out and enjoy your local area even if, like me, it isn't your first choice of dwelling.

When I arrived in the state of Maine, I was happy to find out I had my fair share of work to occupy me in the lab. I worked all day and went home when the sun was setting, in a mental state too useless to get out and explore.

However, I found that getting out of my comfort zone and making time to immerse myself in the local culture became essential to my success in the program. I know this may sound silly, and I'm worried even to write it here, but in getting to know the local area better, I made a checklist of things I wanted to complete while living in Maine:

1) Eat a lobster roll. I guess this one is self-explanatory. They sell lobsters at most gas stations in the state.

2) Go whitewater rafting and camping. Why not get adventurous?

3) See a moose. I'm not talking about one in a zoo. More like a full-on moose crossing the road or in a bog somewhere.

A little more than seven months later, I am proud to say I have done the first two out of the three items on my list. The moose have eluded me so far. I will admit that after, and only after, I pushed myself to explore the state, I truly became comfortable and began to enjoy my stay in my new home.

My advice to any graduate student out there who is in a new location is to make the time to push yourself and explore your new surroundings. You never know what you may find!

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