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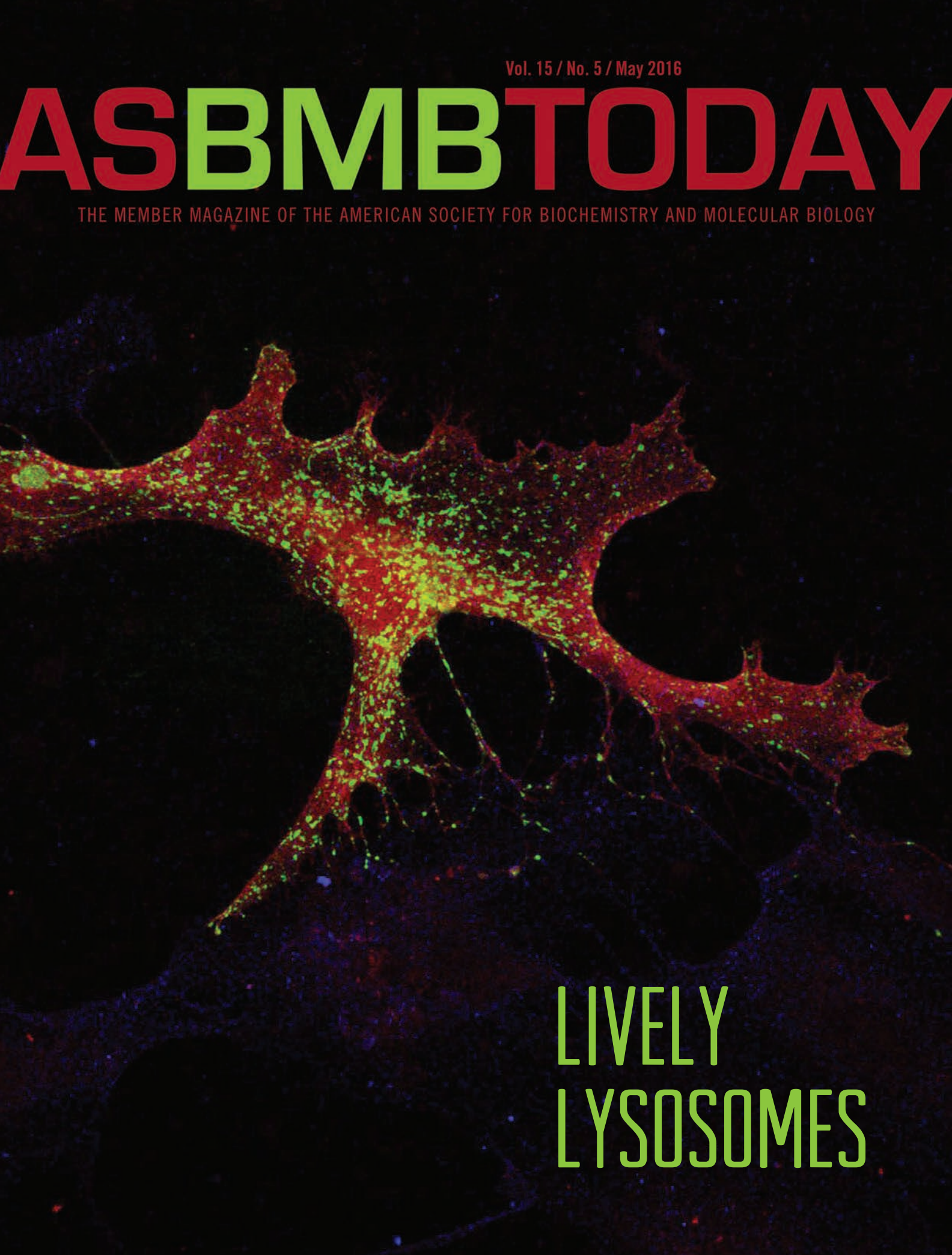
ASBMB TODAY

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



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C	D-Glucosaminic Acid	D-Glucuronic Acid	Chondroitin-6-Sulfate	Mannan	D-Mannose	α-Methyl-D-Mannoside	D-Mannitol	N-Acetyl-β-D-Mannosamine	D-Melezitose	Sucrose	Palatinose	D-Turanose
D	D-Tagatose	L-Sorbose	L-Rhamnose	L-Fucose	D-Fucose	D-Fructose-6-Phosphate	D-Fructose	Stachyose	D-Raffinose	D-Lactitol	Lactulose	α-D-Lactose
E	Melibionic Acid	D-Melibiose	D-Galactose	α-Meth Glactos								
F	Adonitol	L- Arabinose	D-Arabinose	β-Meth Xylopyra								
G	Tricarballylic Acid	D,L-Lactic Acid	Methyl D-lactate	Methyl pyruvat								
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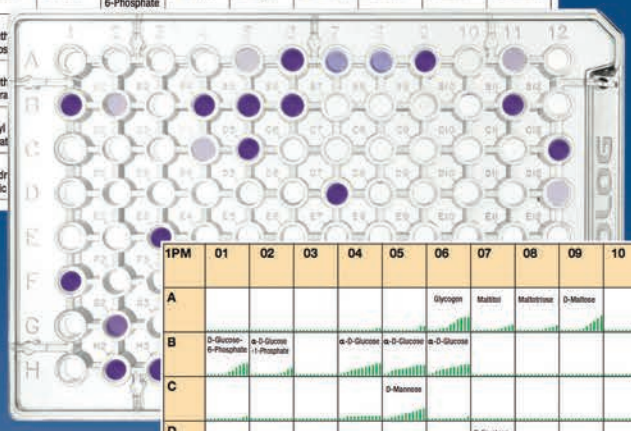

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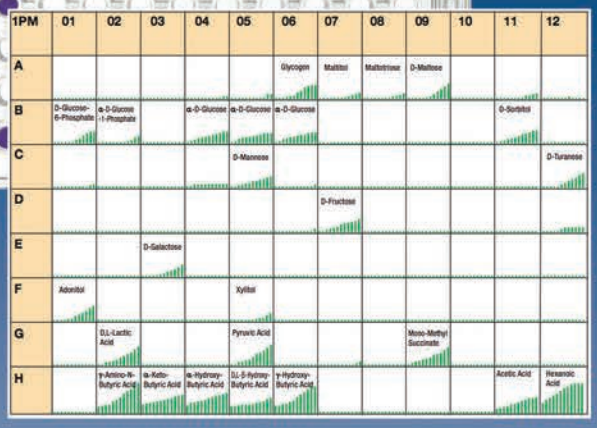

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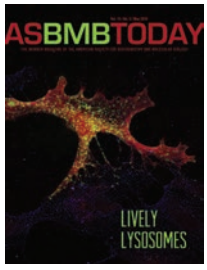
Lysosomes are appreciated to be more than just the cell's trash cans.

IMAGE COURTESY OF DYLAN J. BRITT AND JUAN S. BONIFACINO AT THE NATIONAL INSTITUTES OF HEALTH



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ASBMBTODAY
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Citation corruption

By Steven McKnight

If I understand things right, journals get scored for citation impact via a metric that considers only two years subsequent to the publication of their papers. Papers that get cited after this two-year window do not enhance the impact factor of the journal in which they were published. For journals, this is big business — they live and die by citation impact.

For scientists, this used to be an afterthought. But boy do Bob Dylan's famous words ring true in this instance: "The times, they are a changin'." Whether we know it or not, scientists are judged by the company we keep. If we publish our papers in journals that have high impact factors, the benefit rubs off in many ways. If we publish in journals that have modest citation impact numbers, we suffer.

I see certain flaws in the use of numerical scores to rank the value of a scientist. Some of these flaws have been articulated by other critics of citation impact. Do a simple Google search, and Wikipedia will give you plenty of input regarding the pros and cons of citation impact. Despite obvious flaws, I do not dispute the general thesis that there is a correlative relationship between the value of a paper and the number of times it eventually is cited.

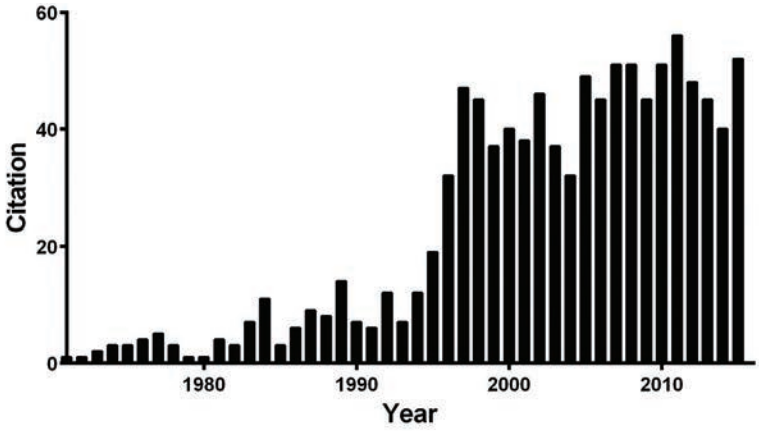
I do choose to critique the two-year time window.

Take the case of a paper published in the Proceedings of the National Academy of Sciences back in 1971 (1). The report was authored by Ronald Konopka and Seymour Benzer and described the results of a forward genetic screen in search of genes that might tell us something about the circadian rhythm of fruit flies. Using ingenious phenotypic assays that allowed timing of both pupal eclosion and locomotor activity, Konopka and Benzer found mutations that lengthened, shortened or eliminated the 24-hour circadian clock of flies. Remarkably, all three categories of mutations mapped to the exact same gene — dubbed by the authors the "Period" gene.

The accompanying figure shows the citation history, according to the Web of Science, of the landmark paper entitled "Clock mutants of Drosophila melanogaster." It was cited once in 1971, once in 1972 and only 24 times in the decade after its publication. Things sped up in the next decade, during which the paper was cited about seven times per year. Over the past two decades, since Michael Rosbash, Jeffrey Hall and Michael Young cloned the Period gene (2) and it became clear that the Konopka and Benzer discovery was of watershed significance, the paper has been cited roughly 40 to 50 times per year.

Few would doubt that the paper by Konopka and Benzer describes one of the most significant discoveries ever achieved in the field of circadian biology. By contrast, citation metrics would have given reward neither to PNAS nor to the authors. Publication of this paper instead would have hurt both the journal and the authors. In the two-year interval subsequent to publication of this paper, it was cited only two times. It is hard to get a worse score than that!

The consequences of the insidious infection of citation impact, at least in its current form, are huge. Both journals and scientists want papers to have immediate impact. After the two-year



The citation history, according to the Web of Science, of the landmark paper "Clock mutants of Drosophila melanogaster"

window, forget it — the stuff is yesterday's news. The corruptive influences of this flawed system are obvious: We are forced to work on what is faddish or trendy.

If anything, I think a paper should be revered if blessed with the unusual feature of having been ignored in the immediate post-publication window but having gained recognition later. The journal that publishes these sorts of papers should be rewarded, not penalized. Likewise, we all know that Konopka and Benzer were sage scientists. They set the trend decades ahead of others. Is this not the testament of greatness?

In its present form, this measure of citation impact conspires heavily in favor of what is trendy and faddish. Journals will die if they publish Konopka/Benzer-like science. Worse yet, scientists — if scored by these measures — will wither professionally if they fail to follow what is in fashion.

It is hard to think of anything worse for our profession than this insidious form of citation corruption. We should desire and create a system that encourages scientists to take risks and work on new horizons. We should reward and encourage Konopka/Benzer-like creativity. What a pathetic mistake of unintended consequences we have created in allowing science to be led around by the lunacy of citation corruption.

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1. http://www.pnas.org/content/68/9/2112.full.pdf
2. http://www.nature.com/nature/journal/v312/n5996/pdf/312752a0.pdf

Steven McKnight (steven.mcknight@utsouthwestern.edu) is president of the American Society for Biochemistry and Molecular Biology and chairman of the biochemistry department at the University of Texas-Southwestern Medical Center at Dallas.

Meeting up in San Diego

Lila Gierasch, incoming editor-in-chief of the Journal of Biological Chemistry, and Fred Guengerich, the journal's interim editor-in-chief, talk with a booth visitor.

University of Georgia Graduate School Dean Suzanne Barbour advises an attendee during ASBMB career hour.

Marketing Director Jennifer Dean holds up a hot sale item in the ASBMB booth.

Plenary lecturer Xiaowei Zhang and opening lecturer Robert G. Roeder

A busy poster presenter describes her work

From left, plenary lecturer Peter Walter, Federation of American Societies for Experiemental Biology President Parker Antin, FASEB Award lecturer Bonnie Bassler, incoming ASBMB President Natalie Ahn and current ASBMB President Steven McKnight

Attendees smiling through poster session time

Experimental Biology attendees goof off.

Better funding to weather public health crises

By Benjamin Corb

Late in 2014, at the height of the Ebola epidemic that took the lives of more than 10,000 people in western Africa, President Barack Obama requested more than $6 billion in emergency funding. The money was for research that would expedite understanding of the virus and help speed approval of an Ebola treatment that could bring the disease under control. A month after the president's request and nine months into the Ebola outbreak, the United States Congress finally took action and earmarked more than $5 billion to the National Institutes of Health, Centers for Disease Control, Food and Drug Administration, and other agencies to fund a U.S.-led effort to combat Ebola that has proven to be a global health success.

I wrote a blog post for the American Society for Biochemistry and Molecular Biology's Policy Blotter in the fall of 2014 expressing my concern that emergency requests for massive infusions of new funding to combat a disease can set a dangerous precedent for biomedical research funding. I argued that funding "disease du jour" research is not sustainable and that the NIH had limited resources and needed to choose areas of research for funding based on national priority. Ebola was already a fairly well-understood disease. In my post I argued that it was also not an existing threat to the American population and that the massive increase in funding to fight the disease might come at the expense of research into other diseases that were less well understood.

This year, one of those other, less understood diseases is in the spotlight. The Zika virus, currently wreaking havoc in Brazil, is predicted to spread to the U.S. mainland within the year. To date, more than 300 American citizens have contracted the virus, and globally more than 4,000 birth defects are blamed on the mosquito-borne illness. Unlike Ebola, not a lot is known about Zika, and at a press conference led by the National Institute of Allergy and Infectious Disease director, Anthony Fauci, U.S. public health officials announced that they are finding the disease more dangerous with every new bit of research they conduct.

Once again, the political response to a public health crisis is to provide a bolus of funding to solve the problem. The White House is requesting $2 billion for Congress to combat Zika, and predictably, Congress is not enthusiastic about releasing the funds. In 2014, it took a month of debate in Washington, D.C., to provide the president with the Ebola funding he requested. Today, Appropriations Committee Chairman Rep. Hal Rogers (R-Ky.) says that funding is likely to come but not for several months.

The reality is the need for these often politically charged funding requests is a symptom of a larger issue. Federal investments in biomedical research at the NIH have not kept pace with research needs for nearly a decade, and as a result, the NIH hasn't had the resources to research a multitude of diseases that are health threats to many, such as heart disease, cancer and Alzheimer's disease. Disease-focused translational research has moved slowly into the spotlight, leaving basic discovery research — the type of research that may benefit those focused on major diseases and minor diseases — a seemingly lower priority. NIH Director Francis Collins published a letter in Science last month reaffirming the NIH's commitment to basic research and the important role it plays, but that he felt a need to write such a letter indicates a recognition that basic researchers are feeling heavy pressures resulting from a decade of flat funding.

Understanding how specific cancers metastasize, figuring out how the brain works, and investigating the underlying mechanistic makeup of flaviviruses like Zika are all equally important areas of research, and only when the biomedical research enterprise is funded appropriately can we truly be prepared to respond to tomorrow's unexpected public health crises.

Benjamin Corb (bcorb@asbmb.org) is director of public affairs at ASBMB.

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Grossenbacher wins NCAA scholarship


GROSSENBACHER

Max Grossenbacher, a biochemistry major at Colorado College, has received a National Collegiate Athletic Association postgraduate scholarship for academic and athletic excellence. NCAA postgraduate scholarships are awarded to student athletes who have performed with distinction on the playing field, are good citizens, possess a grade-point average of at least 3.2 and intend to continue their education.

A senior and a midfielder on Colorado College's Division III men's soccer team, Grossenbacher will receive $7,500 from the NCAA. He plans to attend medical school in 2017.

NCAA awards are bestowed three times a year, corresponding to the sports seasons of fall, winter and spring. Grossenbacher is one of only 29 male and 29 female students to receive the award during soccer season.

Grossenbacher is the Southern Collegiate Athletic Conference offensive player of the year, leading the conference with 27 points and nine assists. Additionally, he was one of 34 men's soccer players to receive Academic All-America honors from the College Sports Information Directors of America in November and only the third player in the history of his college to be named a Scholar All-American by the National Soccer Coaches Association of America.

Written by Erik Chaulk

Charpentier and Doudna share Alpert Prize


CHARPENTIER


DOUDNA

Emmanuel Charpentier at Umeå University in Sweden and Jennifer Doudna at the University of California, Berkeley, have won the 2016 Warren Alpert Foundation Prize. Charpentier and Doudna share the prize with three others. All five recipients are being recognized for their contributions to the understanding of the CRISPR system and its potential for genome editing.

Established in 1987 by philanthropist Warren Alpert and awarded in association with Harvard Medical School, the $500,000 prize recognizes scientists and physicians whose research holds great promise in the prevention, treatment or cure of a human disease or disorder.

Charpentier and Doudna won for establishing that the CRISPR bacterial immune system could be used to alter or replace targeted DNA in a broad array of organisms, including humans. They share the award with Rodolphe Barrangou at North Carolina State University, Philippe Horvath at duPont and Virginijus Siksnys at the Institute of Biotechnology of Vilnius University in Lithuania.

Charpentier and Doudna's work on CRISPR has been lauded widely. In addition to their many individual honors, the two share the 2015 Breakthrough Prize in the Life Sciences, the Paul Janssen Award for Biomedical Research, the Gruber Prize in Genetics, the Massry Prize and the L'Oreal-UNESCO International Prize for Women in Science.

Written by Lee D. Gibbs

Cantley and Kahn win Wolf Prize


CANTLEY


KAHN

Lewis Cantley at the Sandra and Edward Meyer Cancer Center at Weill Cornell Medical College, and C. Ronald Kahn at Joslin Diabetes Center and Harvard Medical School, have won the 2016 Wolf Prize in Medicine.

Wolf Prizes, considered the Nobel Prizes of Israel, are bestowed annually by the Wolf Foundation, a nonprofit organization founded in 1976 by former Cuban ambassador to Israel Ricardo Wolf. The prizes recognize achievements in the fields of agriculture, chemistry, mathematics, medicine, physics and the arts. Cantley is being honored for his discovery of the enzyme phosphoinositide-3 kinase and its link to cancer and other diseases. Kahn is being honored for his work on insulin signaling and its contribution to the understanding of type 2 diabetes. The two winners will divide a $100,000 monetary award.

Cantley and Kahn have received many of the highest honors in their fields and both been elected to the National Academy of Sciences and the Institute of Medicine.

Written by Erik Chaulk

Garcia receives Protein Science award


GARCIA

Benjamin Garcia, presidential associate professor of biochemistry and biophysics at the University of Pennsylvania Perelman School of Medicine, has won the 2016 Protein Science Young Investigator Award.

The award comes from the Protein Society and recognizes scientists in the first eight years of an independent career who have contributed

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significantly to the study of proteins. Garcia was chosen for developing and applying novel mass spectrometry approaches to better study post-translational modifications of proteins, especially those involved in epigenetics, such as histones. His work on the development of analytical and computational tools to understand better the importance of simultaneously occurring histone modifications also was noted.

Garcia already has received the Presidential Early Career Award, the National Science Foundation Early Career Award and the National Institutes of Health Director's New Innovator Award.

Written by Sarah Elkin

DAVID B. KNAFF (1941 – 2016)

KNAFF

David Barry Knaff, an expert on redox reactions in plant photosynthesis and professor at Texas Tech University, died in January in Lubbock, Texas. He was 74.

Knaff led Texas Tech's biotechnology and genomics department and was a former editor-in-chief of the journal Photosynthesis Research. His research focused on the mechanistic details of redox reactions in plant photosynthesis with an emphasis on nitrate and sulfate assimilation and the redox regulation of carbon metabolism.

Born June 5, 1941, in the Bronx, N.Y., Knaff attended the Bronx High School of Science before completing a bachelor's degree in chemistry at the Massachusetts Institute of Technology. He received his master's and Ph.D. in chemistry from Yale University, where he was a National Science Foundation predoctoral fellow.

After his formal education, Knaff transitioned to plant biochemistry — a field he committed to for the next 50 years. He served as a National Institutes of Health postdoctoral fellow at the University of California, Berkeley, from 1964 to 1968 and stayed at UC Berkeley as a staff scientist in cell physiology from 1968 to 1976.

Knaff joined the Chemistry Department at Texas Tech in 1976 and in 1987 received the university's highest faculty rank, the Paul Whitfield Horn professorship. During his tenure, Knaff chaired the school's chemistry and biochemistry department, co-established and served as director of the Center of Biotechnology and Genomics, and led efforts to create a biotechnology master's program and dual degree M.S./J.D. program with the Texas Tech University School of Law.

Along with the consecutive funding he received from federal agencies and private foundations for 43 years and his more than 220 refereed journal articles, Knaff's accolades included Texas Tech's President's Academic Achievement Award, the Barnie E. Rushing Jr. Faculty Distinguished Research Award and the Texas Academic Reward for College Scholars Scientist of the Year award.

Knaff leaves behind a wife, Joyce R. Kobb, a daughter and a granddaughter.

Written by Jennifer A. Codding-Bui

Upcoming ASBMB events and deadlines

MAY **May 16:** Application deadline for the Marion B. Sewer Distinguished Scholarship for Undergraduates

JUL **July 14 – 16:** ASBMB Grant Writing Workshop, Washington, D.C.

AUG **Aug. 1:** Abstract and registration deadline for the ASBMB Transcriptional Regulation by Chromatin and RNA Polymerase II symposium

OCT **Oct. 6 – 9:** ASBMB Special Symposia: Transcriptional Regulation by Chromatin and RNA Polymerase II, Snowbird, Utah

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Osamu Hayaishi (1920 – 2015)

By Shuh Narumiya

Osamu Hayaishi, emeritus professor of Kyoto University, died in December at the age of 95. A leading international figure in biochemistry, Hayaishi discovered oxygenase, ADP-ribosylation and the sleep-inducing action of prostaglandin D_2.

Hayaishi was born on Jan 7, 1920, in Stockton, Calif., where his Japanese father, who had studied medicine in the U.S., ran a clinic. The family moved from California to Germany and then settled in Osaka, Japan, where Hayaishi grew up. He graduated from Osaka University Medical School in 1942, served as a medical officer in the Japanese navy during the war and joined the lab of microbiologist and virologist Tenji Taniguchi at Osaka University.

Living conditions in severely damaged, postwar Osaka were miserable, and the university's laboratory facilities were hopeless. Hayaishi spent much of his time in Taniguchi's employ reading scientific literature until the day he received an unexpected visit from Yashiro Kotake, a biochemist known for his study of tryptophan metabolism in mammals. Kotake gave Hayaishi a bottle of tryptophan purified from casein lysates — a precious gift at the time. Hayaishi had read about an enrichment culture technique to isolate soil bacillus with adapted enzymes for added organic compounds and began culturing soil samples with tryptophan. He enriched a strain of pseudomonas, which degrades tryptophan completely to carbon dioxide, water and ammonia via kynurenine, anthranilic acid and catechol. He prepared bacterial extracts and found in them an enzyme that catalyzed conversion of catechol to cis,cis-muconic acid as the reaction product. He named it pyrocatechase. Using Warburg's manometer, Hayaishi found a concomitant consumption of equimolar molecular oxygen with the conversion. At this point he suspected that consumed molecular oxygen was incorporated directly to the substrate, but experimental proof of his assumption was years away.

Hayaishi published his findings in 1949, attracting the attention of David Green at the University of Wisconsin. Green invited Hayaishi to be a postdoctoral fellow, and Hayaishi crossed the Pacific to join him in Madison. Hayaishi spent eight months with Green before moving to the laboratory of Roger Stanier at the University of California, Berkeley. Stanier also studied tryptophan metabolism in pseudomonas, and the two men struggled together in vain to extract tryptophan-metabolizing enzymes. One rainy evening in Berkeley, Hayaishi met National Medal of Science winner H. A. Barker, who advised him to use alumina to grind the bacteria. It worked. Hayaishi was able to extract enzymatic activities that reconstituted metabolism of tryptophan to catechol and consumed molecular oxygen concomitantly. After four months with Stanier, Hayaishi joined the lab of Nobel Prize-winner Arthur Kornberg. Kornberg, whom Hayaishi had first heard speak at a Federation of American Societies for Experimental Biology meeting, had offered him a position before Hayaishi moved to Berkeley. Hayaishi worked with Kornberg at the National Institutes of Health as a postdoctoral fellow and later at Washington University as an assistant professor.

Appointed chief of the toxicology section of the National Institute of Arthritis and Metabolic Diseases in 1954, Hayaishi led a team that tested his long-held hypothesis on pyrocatechase. Using O-18 isotopes, he found that oxygen atoms incorporated in the product came entirely from O_2 and not at all from H_2O. His discovery and a concurrent independent discovery by Howard Mason at the University of Oregon Medical School of incorporation of an atom of molecular oxygen into a substrate by mushroom phenolase were milestones in the understanding of how oxygen is utilized in biological systems. Until then, scientists believed that biological oxidation occurred exclusively through the dehydrogenation process that German Nobelist Henrich Wieland had discovered decades earlier. Hayaishi named the group of enzymes catalyzing incorporation of molecular oxygen into organic substrates "oxygenases."

In 1958, Hayaishi returned to Japan and became a professor and chairman of the Department of Medical Chemistry at Kyoto University Faculty of Medicine. He said of the move, "My salary in Kyoto was one-thirteenth of that (at) NIH. More(over), the experimental facilities were miserably shabby."

As Hayaishi got to work reconstructing the department, a flood of young people eager to learn modern biochemistry joined him. Hayaishi was as gifted a mentor as he was a scientist. He organized a lunchtime seminar where all members in the laboratory gathered and critically discussed papers. Hayaishi called the seminar a dojo and trained those in attendance through serious discussion. He still loved being close to the bench and made a daily round in his labora-

tory. When writing a paper, Hayaishi invited the authors to his office and carried out several rounds of review by examining the paper's findings and logical flow and correcting his researchers' English word by word.

Hayaishi inspired and trained several hundred people during his 25-year tenure in Kyoto and his several years of joint-appointments at Osaka University and the University of Tokyo. More than 130 of them became university professors or department heads.

TAKAO SHIMIZO

Osamu Hayaishi gives a lecture at the University of Tokyo in 2012.

Hayaishi and his researchers extensively studied structures and properties of oxygenases and came to a conclusion about the presence of the enzymatically activated form of oxygen in the ternary complex of the enzyme heme—oxygen—substrate. The study of oxygenase initiated by Hayaishi has developed enormously, and we now know that oxygenases are involved in the formation of various bioactive substances, cytochrome P450-catalyzed xenobiotic disposition, and the sensing of oxygen tension.

Hayaishi's study on oxygenase also led him to create new fields of research, including work on ADP-ribose, a discovery derived from his study on the oxygenase-driven tryptophan metabolism to nicotinamide adenine dinucleotide, or NAD, and made in parallel with Paul Mandel at the University of Strasbourg and Takashi Sugimura at the National Cancer Center of Japan. Hayaishi also discovered the diphtheria toxin-catalyzed ADP-ribosylation of aminoacyl transferase 2 and thus clarified the toxin's action mechanism. He was the first to demonstrate that the bacterial toxin is an enzyme. Hayaishi also discovered indoleamine 2, 3-dioxygenase and its induction by interferon, which is now known as one of the major immunosuppression mechanisms.

The last area of Hayaishi's research, sleep induction by PGD_2, began a few years before his retirement from Kyoto University. By characterizing enzymes in PG biosynthesis, Hayaishi found that PGD synthase and PGD_2 are enriched in the brain. He unexpectedly found that intracerebroventricular injection of PGD_2 induced sleep in animals. His subsequent works revealed that PGD_2 acts on its receptor in the leptomeninges surrounding the brain and transmits its signal from there to the sleep-regulation center in the hypothalamus. This mechanism of sleep induction by PGD_2 fascinated Hayaishi. He maintained an active group to pursue the topic and enjoyed discussing it with the lab members up until two years ago, when he fell ill.

Hayaishi retired from Kyoto University in 1983 and founded the Osaka Bioscience Institute. Hayaishi served as the president of the International Union of Biochemistry from 1973 to 1976, received numerous awards and prizes and was a member of several academies, including the U.S. National Academy of Sciences.

The principles discovered by Hayaishi are known now to operate in many physiologically important processes, and the science he created has influenced nearly all areas of bioscience and medicine.

A man of great charm, Hayaishi leaves behind his wife of 69 years, Takiko; their daughter, Mariko; two grandsons and six great-grandchildren. The academic community, his friends, colleagues and students, have lost an inspiring scientist who embodied the spirit of the field.

Shuh Narumiya (snaru@mfour.med.kyoto-u.ac.jp) is a professor and the director of Medical Innovation Center of Kyoto University School of Medicine.

Large donations fund new immunotherapy institutes

By Bree Yanagisawa

Two sizeable donations to fund the creation of immunotherapy centers for cancer research were announced within weeks of each other in March and April. Both centers aim to encourage collaboration to speed up the generation of new cancer therapies.

First, Vice President Joe Biden and former New York City Mayor Michael Bloomberg announced $125 million in funding to the Johns Hopkins University for the Bloomberg–Kimmel Institute for Cancer Immunotherapy. Financed largely by Bloomberg and the philanthropist Sidney Kimmel, with support from more than a dozen others, the institute aligns with the goals of the Obama administration's Moonshot Initiative to cure cancer. Biden, who lost a son to brain cancer last year, is spearheading the initiative.

BLOOMBERG

KIMMEL

Second, Sean Parker, co-founder of the music-sharing site Napster and former president of Facebook, announced that he will be putting $250 million behind the Parker Institute for Cancer Immunotherapy. Parker's institute will be led by Jeffrey Bluestone, an immune system researcher at the University of California, San Francisco, School of Medicine, and is intended to bridge research between six major institutions: the University of Pennsylvania; Memorial Sloan Kettering Cancer Center; Stanford University; the University of Texas MD Anderson Cancer Center; UCSF; and the University of California, Los Angeles.

PARKER

Both institutes will put an emphasis on collaboration. The Bloomberg–Kimmel Institute wants to improve relationships between industry and academic scientists. The Parker Institute will manage separately the patenting and licensing of any discoveries among its six involved institutions to streamline the therapeutic development process.

Immunotherapy is a promising approach to cancer treatment, and research in the area is increasing. Immunotherapies can help boost the body's immune system and train it to seek out and attack cancerous cells.

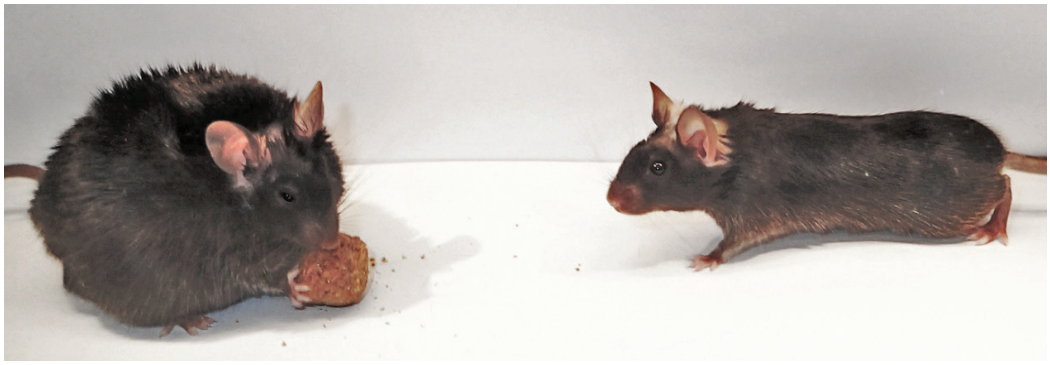
In a news release from UCSF, Parker expressed hope that his donation will give the promising field the push it needs to be successful for more patients. "We believe that the creation of a new funding and research model can overcome many of the obstacles that currently prevent research breakthroughs," he said.

"Ending all cancer would rank among humanity's greatest achievements, and immunotherapy is bringing that dream within reach," said Bloomberg in a Johns Hopkins press release. He added that the Bloomberg–Kimmel Institute "will build on the pioneering work that doctors and researchers at Johns Hopkins have done in immunotherapy and help fuel new advances and discoveries."

Bree Yanagisawa (byanagisawa@asbmb.org) is a science writing intern at ASBMB Today and a Ph.D. candidate in pathobiology at the Johns Hopkins School of Medicine.

Fat mice lead researchers to new feeding control pathway

By Rajendrani Mukhopadhyay



OLOF LAGERLOF

Researchers injected littermates with either a control virus or a virus that knocked out OGT in a part of the brain. The mouse missing OGT (left) ate twice as much as its normal sibling. The photo was taken about five weeks after the virus injection.

When their lab mice unexpectedly packed on weight, Richard Huganir at the Johns Hopkins School of Medicine and his colleagues had to figure out why the mice suddenly turned obese. In a paper in the March 11 issue of the journal Science, the investigators describe their discovery of a protein-modification pathway in the brain that plays a surprising role in feeding control and satiety.

"This was a serendipitous discovery," says Huganir, a neuroscientist and member of the American Society for Biochemistry and Molecular Biology. "We had to learn a whole new area of biology — feeding control, metabolism and obesity. Luckily, we had great collaborators at Hopkins who had the expertise to help us figure out what was going on. We eventually found out that the mice had impaired satiety and ate larger meals."

The investigators originally were working on deciphering the role of an enzyme called O-GlcNac transferase, known as OGT, in regulating synaptic transmission and plasticity in the brain as well as its potential role in learning and memory. OGT catalyzes the attachment of a short sugar molecule to proteins; the sugar molecule then influences the function of the proteins.

As part of their project, Huganir and colleagues genetically modified the brains of mice so that the researchers could turn off the expression of OGT in the forebrain and hippocampus. These two regions of the brain are important for learning and memory.

"Much to our surprise, a couple of weeks after we knocked out OGT, the mice got very, very fat," says Huganir. "We stopped studying learning and started studying feeding control."

The parts of the brain the investigators had targeted in their mice usually are not associated with feeding control. But the hypothalamus is.

When the investigators looked at the hypothalamus, they discovered that they inadvertently had removed OGT in specific cells in a region of the hypothalamus called the paraventricular nucleus.

To make sure that OGT in the paraventricular nucleus cells was what was influencing the feeding and satiety of the mice, Huganir and colleagues created another set of genetically modified mice. These mice had OGT missing only in the paraventricular nucleus cells. "Knocking out OGT in only these cells inhibited their activity and produced the same overeating phenotype," says Huganir.

The investigators now know that OGT plays an important role in the paraventricular nucleus cells in feeding control, but the molecular details are still unknown. For one, the investigators don't know what substrates OGT acts on in the paraventricular nucleus cells to regulate their activity.

And, as with any work done on mice, the implications for humans have to be worked out. "This work in mice does suggest similar mechanisms are important in human satiety," says Huganir. "However, much more work is needed to identify potential therapeutic targets to modify this pathway in humans to regulate food intake."

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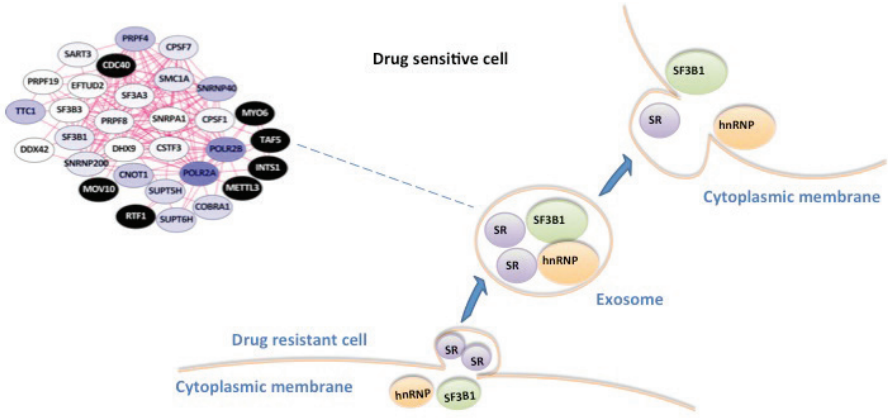
Leukemia cells teach other cells not to self-destruct

By Bree Yanagisawa

In acute myeloid leukemia, or AML, relapses are a major concern. About 65 percent of adult patients with AML go into remission through chemotherapy, but more than half of those patients relapse.

Residual AML cells are thought to cause these relapses. These cells persist in the patient despite chemotherapy and may expand and re-create the cancer. The cells survive chemotherapy using various mechanisms, including avoiding the usual cell-death pathways. In a recent paper published in the journal **Molecular and Cellular Proteomics**, Connie Jimenez at the VUmc Cancer Center Amsterdam and her colleagues Anna Wojtuszkiewicz and Jacqueline Cloos dissect the interplay between these residual AML cells and their surrounding environment.



Acute myeloid leukemia cells use exosomes to transfer resistance to neighboring cells.

When things go wrong inside a cell, apoptotic mechanisms are in place to serve as a self-destruct signal. Cancer cells are capable of avoiding these typical processes, making them harder to kill. In the study, the researchers found that resistance to self-destruction may be passed from AML cells to surrounding cells via secreted exosomes.

The extent to which cancer cells can ignore self-destruct signals fluctuates over the course of the disease. Counter to what one might expect, patients who carry AML cells that are highly resistant to apoptosis at diagnosis can have AML cells with decreased levels of such resistance after chemotherapy. This suggests that the cell death pathways are governed by complex mechanisms.

The researchers collected samples from patients with AML at the beginning of disease and after remission. When they examined the apoptotic profiles of residual AML cells and surrounding normal lymphocytes within the bone marrow, the researchers were surprised to find that the two different cell types shared similar levels of proteins typically involved in apoptosis. In addition, when cultured together, AML cells that were especially resistant to apoptosis were capable of making low-resistance cells more likely to ignore self-destruct signals. These findings suggest the apoptotic profiles of cells are being influenced by external factors.

The authors profiled secreted proteins from AML cells with high and low levels of resistance to apoptosis. Unexpectedly, the most prominent types of proteins identified weren't apoptotic proteins. Many of the identified secreted proteins were those usually involved in gene regulation, hinting at a potential mechanism by which AML cells can influence their surroundings. Furthermore, these secreted proteins are housed in vesicles that originate from the AML cells. Jimenez says that these findings suggest that "by secreting vesicles, leukemic cells may affect the global expression profiles of the recipient cells."

In the future, the authors intend to look into the ways in which these secreted proteins affect surrounding cells.

"Unraveling the mechanisms of communication between leukemic cells, including stem cells, and their microenvironment is crucial to the efficacy of cancer treatment," says Jimenez. "Our work suggests that it is a mutual interaction in which not only the cells of the bone marrow niche can promote survival of leukemic cells but leukemic cells themselves are shedding vesicles, which can influence their neighboring cells."

Bree Yanagisawa (byanagisawa@asbmb.org) is a science writing intern at ASBMB Today and a Ph.D. candidate in pathobiology at the Johns Hopkins School of Medicine.

Predicting pre-eclampsia

By Bree Yanagisawa

Pre-eclampsia affects roughly 3 percent of pregnant women in the U.S. and can lead to a host of complications that can include premature birth and even death for both mother and child. Unfortunately, there is no effective diagnostic test to predict the onset of the disease, which is characterized by high blood pressure that may not appear until the second half of pregnancy.

In a recent paper published in the **Journal of Lipid Research**, Steven Graves of Brigham Young University and colleagues described a set of biomarkers that could help in the early detection of pre-eclampsia.

Although proteins are considered a more conventional class of biomarker, Graves and his colleagues decided to look to lipids in the blood because they tend to be more forgiving subjects than their protein counterparts. According to Graves, lipids "are not particularly heat-sensitive compared to a protein or peptide, and they're not degraded rapidly by proteolytic enzymes, which exist in the serum."

THE NATIONAL INSITUTES OF HEALTH

Pre-eclampsia is a potentially dangerous complication in pregnancy characterized by high blood pressure.

Unlike invasive sampling procedures, which may be risky, serum samples containing the lipids can be collected in the clinic relatively easily with blood draws. The researchers used samples that had been collected for a trial studying the early in utero development of children with Down's syndrome. From the available samples, they selected those taken between 12 and 14 weeks of gestation.

Using mass spectrometry data, the team compared the serum lipid profiles of women who went on to develop pre-eclampsia and those who did not. After an initial analysis and a second confirmatory run in another sample set, the team identified a set of 23 biomarkers in the form of mass spectral profiles that were able to predict those women who would go on to have a pre-eclamptic event.

Any biomarker on its own can't provide sufficient predictive value, but combining the markers together into sets increased predictability. For their sample population, the investigators found that using six biomarkers helped with predicting pre-eclampsia; combining more than six markers failed to show an increase in predictive value. When the lipid test becomes publicly available, Graves advises using all 23 biomarkers together to account better for individual patient factors.

Though the lipid biomarkers are intriguing, Graves is careful to point out these biomarkers aren't ready for the clinic just yet. A lipid-based test will be available only after further study and approval by the U.S. Food and Drug Administration. "What should happen now is one should establish a clear hypothesis that this set of markers would be useful and then carry out studies," he says.

The research may not be of immediate clinical value, but knowledge of the biomarkers could help streamline the research process. Because the disease occurs infrequently, one of the biggest issues with prospective studies for pre-eclampisa is the sheer number of women that need to be enrolled in order to have adequate numbers of pre-eclamptic cases. However, if researchers first can narrow the population using a set of predictive biomarkers such as the one proposed in the paper, fewer women would need to be enrolled. According to Graves, this "could save time and allow for more things to be tested more efficiently."

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The Venus flytrap's major protease

By Indumathi Sridharan

Venus flytraps grow in the nitrogen-poor soil of the southeastern United States. The lack of nutrition in the soil has turned these plants into sophisticated hunters. Two lobes of the flytrap produce sweet sap that lures small insects. If an insect brushes against a few microscopic, hair-like structures on the lobes' surface in quick succession, the lobes spring shut instantaneously to trap the insect. Then the plant secretes a fluid that kills and digests the prey.

The flytrap's digestive fluid is a rich concoction of enzymes including lipases, chitinases and proteases. In a recent paper in the **Journal of Biological Chemistry**, Jan Enghild and a team of researchers at the department of molecular biology and genetics at Aarhus University in Denmark, characterized the function and structure of a 45 kDa cysteine protease, dionain-1, which is found abundantly in the digestive fluid. The protein has a precursor form called pro-dionain-1. Pro-dionain-1 contains an N-linked glycan group, which is required for proper folding of the protein. The researchers used cDNA sequence analysis to demonstrate that pro-dionain-1 is similar to the precursors of other plant cysteine proteases, such as papain.

Further analysis revealed that pro-dionain-1 is also homologous to propapain at the structural level. Despite the sequence and structural similarity, pro-dionain-1's function is better suited to acidic environments than papain. Pro-dionain-1 undergoes autoproteolysis at an acidic pH. The autoproteolysis process leads to loss of the integrity of the prodomain and unravels the active site to produce the functional and mature dionain-1. The authors highlight that, unlike other proteases that require acidic pH only for maturation, dionain-1 must exert its main proteolytic function at the acidic pH of 3.4 to 4.4 found in the digestive sap of Venus flytraps.

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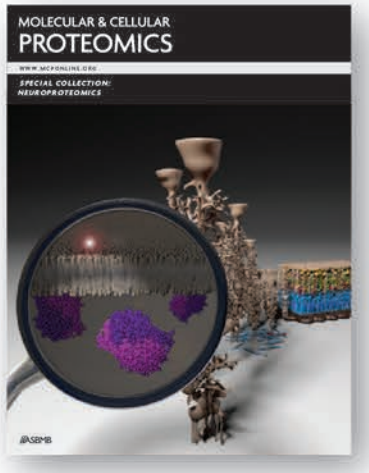
Carnivorous Venus flytrap plants secrete enzyme-rich fluid to mediate nutrient absorption from their prey.

The mature dionain-1 efficiently digests lysine- and arginine-rich muscle proteins to release nitrogen-rich peptides. Thus, the authors conclude that dionain's function is finely tuned to serve the plant's need for nitrogen-rich sources. According to the study's lead author, Michael Risør, dionain's enhanced acid tolerance and its preferential digestion of nitrogen-rich proteins is an important evolutionary adaption that facilitated the flytrap's carnivorous lifestyle.

Enghild, who oversaw the work, says that the research on the digestive fluid offers insight not only into the mechanisms of plant carnivory but also how those mechanisms differ from molecular strategies employed by carnivorous animals. In the future, Enghild and his team plan to investigate other enzymes in the flytrap's digestive fluid.

Indumathi Sridharan (Sridharan.indumathi@gmail.com) earned her bachelor's degree in bioinformatics in India. She holds a Ph.D. in molecular biochemistry from Illinois Institute of Technology, Chicago. She did her postdoctoral work in bionanotechnology at Northwestern University.



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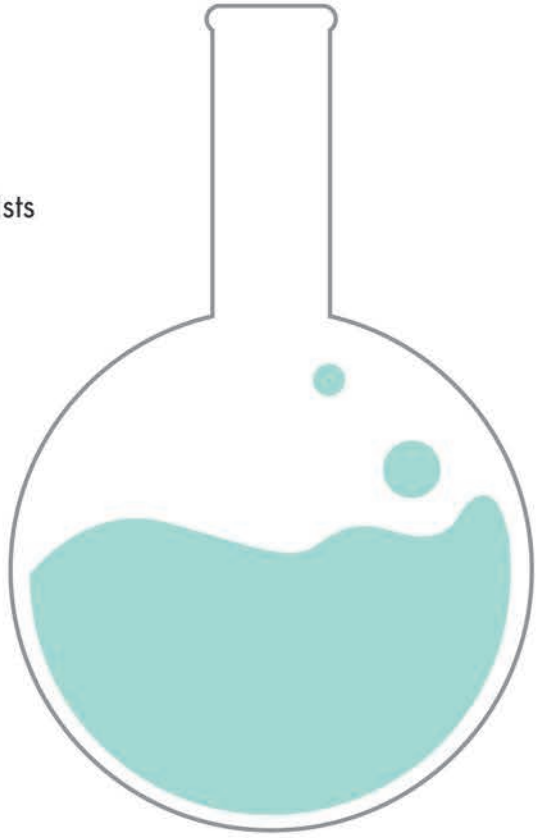

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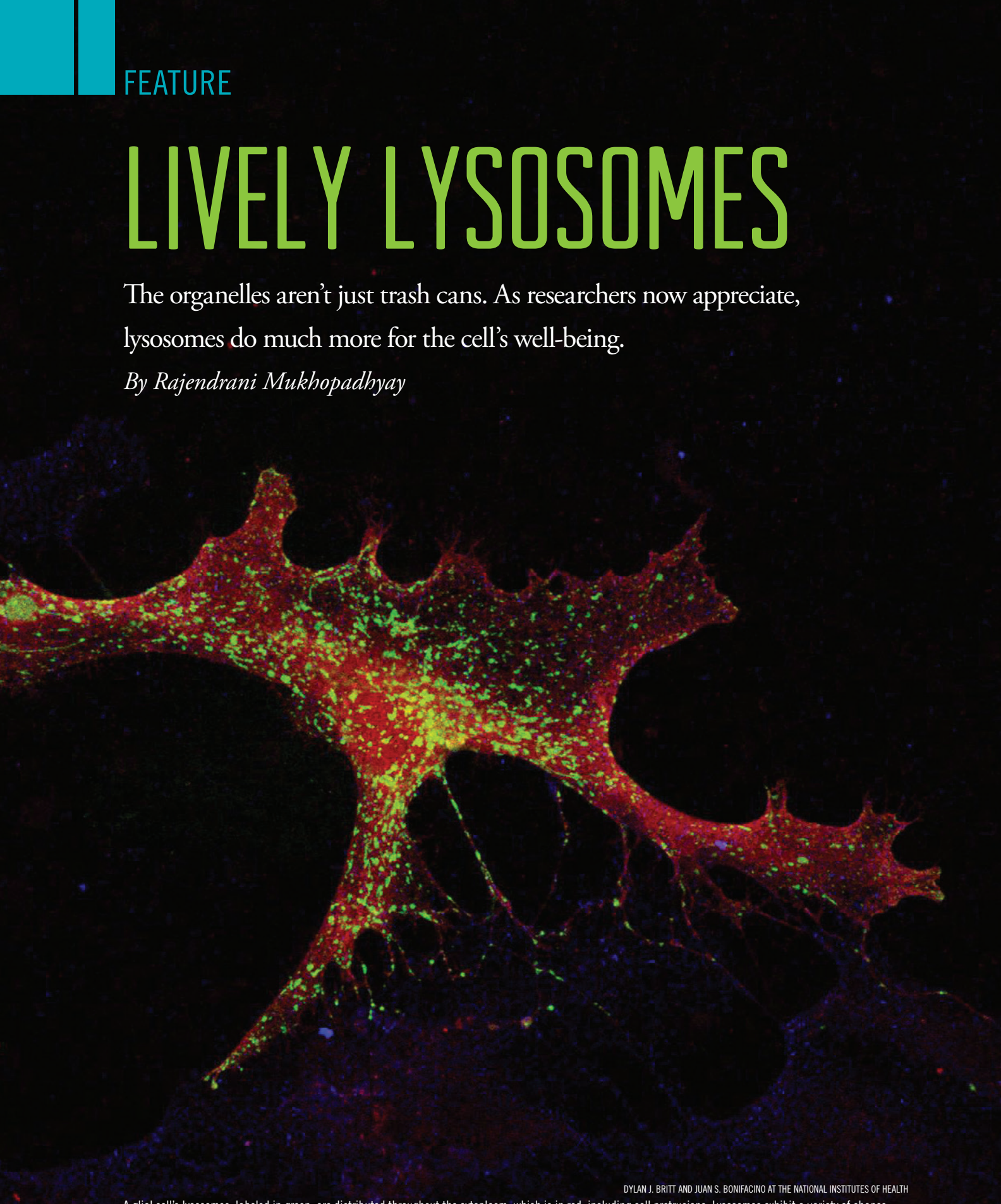
FEATURE

LIVELY LYSOSOMES

The organelles aren't just trash cans. As researchers now appreciate, lysosomes do much more for the cell's well-being.

By Rajendrani Mukhopadhyay

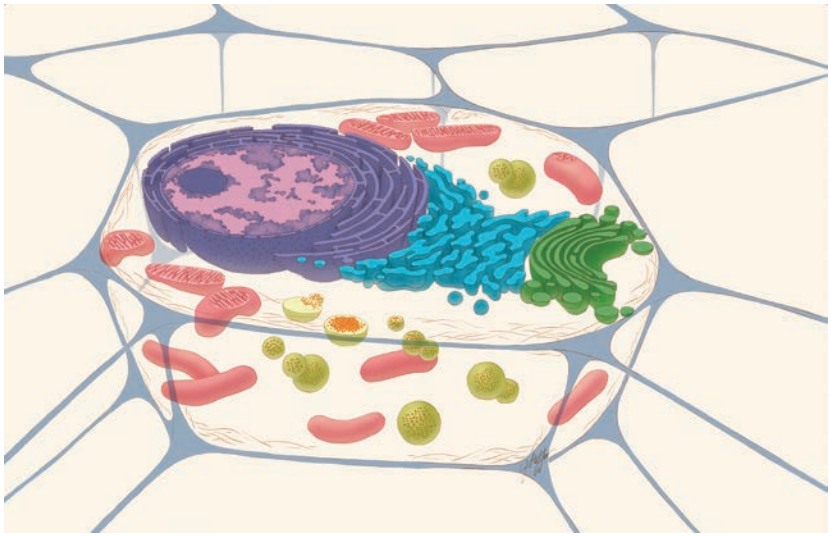


DYLAN J. BRITT AND JUAN S. BONIFACINO AT THE NATIONAL INSTITUTES OF HEALTH

A glial cell's lysosomes, labeled in green, are distributed throughout the cytoplasm, which is in red, including cell protrusions. Lysosomes exhibit a variety of shapes, ranging from spherical to tubular.

Lysosomes are having a Cinderella moment. Gone is the perception that lysosomes simply sit in a corner of a cell, mutely cleaning up whatever is sent their way. Lysosomes now are seen as critical signaling checkpoints that move around the cell and take part in important decisions about cellular biosynthesis and degradation. They once were thought to be involved in only rare genetic disorders. But now researchers are beginning to appreciate that diseases as common as Alzheimer's and certain cancers have roots in lysosomes too.

Along with the reassessment of the capabilities of lysosomes comes the awareness that scientists have more questions than answers about exactly what the organelles are capable of doing. Lysosomes, says Roberto Botelho at Ryerson University in Canada, "are much more fun than people thought."



THE NATIONAL INSTITUTES OF HEALTH

A typical drawing of an animal cell, sliced open to reveal cross-sections of organelles. The lysosomes are the green spheres. The red dots within the green spheres signify cellular components that need to be broken down.

Trash can

In 1955, Christian de Duve at the Catholic University of Louvain in Belgium and colleagues described a membrane-bound organelle that housed at least five enzymes. These enzymes degraded a variety of substrates in a pH around 5. In proposing that the organelle was involved in cellular digestion, de Duve and colleagues called the organelle a "lysosome," the Greek word for "digestive body."

In subsequent years, researchers found that there are at least two ways for molecules to wind up in one of the hundreds of lysosomes in a cell. One way involves endocytosis, in which molecules outside of the cell are brought inside the cell in packages. Some of the packages are fated to become late endosomes, which are slightly acidic organelles that mature into lysosomes.

Another way is autophagy. This is a major housekeeping mechanism within the cell, clearing away components that are about to expire. The cleared components arrive at lysosomes in vesicles known as autophagosomes.

Once molecules are in a lysosome, nucleases, proteases, lipases and other hydrolytic molecules attack them. Exporters on the membrane carry out the bits and pieces of the degraded molecules. The pieces go into the cytoplasm either to provide energy or to be reused by the biosynthetic pathways.

In 1963, Henri-Gery Hers, who had joined de Duve's group, discovered that people missing a lysosomal glucosidase succumbed to a severe glycogen storage disorder. That finding introduced the idea that a host of diseases could be linked to the inability of the lysosome to produce specific enzymes and thus degrade particular molecules. Lysosomal research at that point became focused largely on the clinical aspects of disorders associated with the lysosomes and finding therapies for the disorders.

Disorders related to the inability of the lysosome to break down and remove various types of molecules became known as lysosomal storage disorders. These included Gaucher, Fabry and Niemann–Pick diseases, among others. There are now more

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Lysosome, not lysozyme


DE DUVE

In an article published in Nature Cell Biology on the 50th anniversary of the lysosome's discovery, Christian de Duve was peeved with scientists who confused "lysosome" with "lysozyme," a bacterial enzyme discovered by Alexander Fleming of penicillin fame. "I trusted biochemists to be able to distinguish between the Greek roots soma and zyme," he wrote in the 2005 perspective. "This trust was sadly misplaced. Even today, I am still sometimes given credit that is due to Fleming."

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than 50 known lysosomal storage disorders, most of them rare genetic diseases.

One of the notable breakthroughs in this area was enzyme-replacement therapy, during which certain missing or defective lysosomal enzymes are replaced with functional enzymes, as Roscoe Brady's team at the National Institutes of Health did with Gaucher disease.

By the 1980s, it seemed scientists knew what they needed to know about the basic workings of the lysosome. "Who wanted to work on lysosomes? It was more interesting to work on the nucleus, where all the genetic information is contained, or mitochondria that make energy for the cell to function or the (endoplasmic reticulum), where proteins are synthesized," says Juan Bonifacino at the NIH. "Lysosomes were just involved in degradation. They were a trash can."

Then came an unexpected finding.

'They didn't like the idea'

David M. Sabatini at the Whitehead Institute is the first to admit that he should have listened to his father's advice. When Sabatini was in graduate school at Johns Hopkins University in the early to mid-1990s, he identified a kinase that is targeted by an immunosuppressant drug called rapamycin. That serine-threonine kinase is the mammalian target of rapamycin, or mTOR. Scientists soon found mTOR to be a critical player in cellular growth and implicated in a number of cancers.

mTOR comes in two complexes. One, mTORC1, is exquisitely tuned to amino acid levels in the cell. Researchers showed that the presence of amino acids triggered the activation of mTORC1. But how and where the kinase checked in on the amino acid levels was a mystery.

Sabatini is a second-generation scientist. His father, David D. Sabatini, is a cell biologist at New York University. "When I first identified mTOR as a graduate student, I remember I was talking to (my dad) about it. He said, 'David, one of the things you have to do is you have to localize this within the cell,'" recalls the younger Sabatini. "I was a typical obnoxious child, and I was like, 'You know, I don't think that's interesting. That's old school.' The funny thing is that it turned out that the localization was the key thing."

In 2008, nearly a decade after he began working with mTOR, the younger Sabatini, who also is with the Howard Hughes Medical Institute, led a team that made a surprising discovery. When the team deprived cells of amino acids, mTORC1 was diffuse throughout the cytoplasm. When the team added amino acids, the kinase quickly congregated on the surface of lysosomes.

"I remember the first few times I presented this finding, people would stand up and say that the lysosome was a trash can. Some people would be more charitable and say the lysosome was a recycling bin," recalls Sabatini. "They didn't like the idea. The finding was met with a bit of resistance because it was one of the first that implicated there was something different about lysosomes."

The resistance turned to curiosity when Sabatini's group published the finding in the journal Science later in 2008. A critical kinase that oversaw cell growth was making the lowly lysosome its headquarters when activated.

Sabatini "is single-handedly responsible for putting the mTORC1 signaling complex on the lysosomal membrane," says Michael Overholtzer at Memorial Sloan Kettering Cancer Center. "That really brings the lysosome to the forefront."

Clearly not a dead end

The next indication that the lysosome wasn't a mere refuse receptacle came in 2009 from Andrea Ballabio's

laboratory at Telethon Institute of Genetics and Medicine in Italy. His group published a paper in Science that showed that lysosomal genes are regulated by a single protein called transcription factor EB, or TFEB.

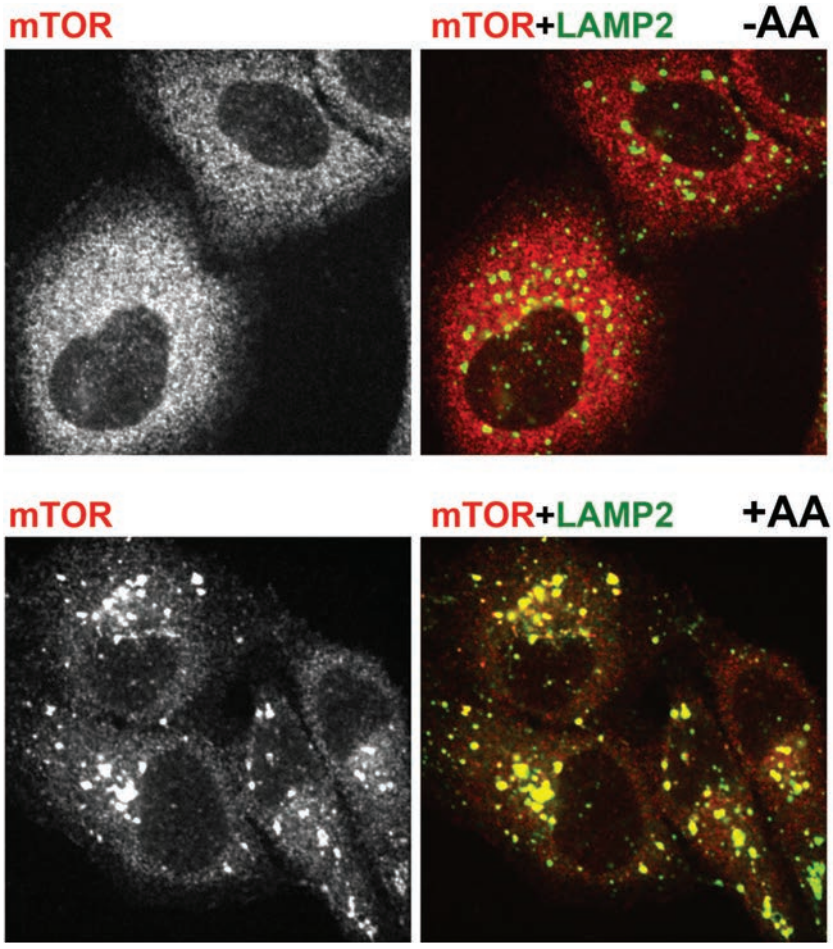
Researchers knew that a single cell contains hundreds of lysosomes, enough to make up about 5 percent of the cell's volume. But they thought the number stayed the same over the course of a cell's lifetime.

Ballabio and colleagues suspected otherwise. "We postulated that any cell needed to have a mechanism to modulate lysosomal function," he says. "This was actually a relatively new way of thinking, because the traditional view of the lysosome was of a static organelle not subject to regulation and adaptation. But we postulated that there was a network of genes encoding for lysosomal proteins that would be jointly regulated" by a common entity.

Ballabio and colleagues analyzed the expression of genes encoding lysosomal proteins under multiple conditions and situations. And they did so without picking up a pipette.

"We didn't even do the experiments ourselves because the experiments were out there in the databases," says Ballabio. "We looked at microarray databases, where there are experiments done under many different conditions, and looked at all known genes encoding lysosomal proteins."

Ballabio's team discovered that the expression levels of the lysosomal genes went up and down in a coordinated fashion. When they looked at the promoter regions of the lysosomal genes, they found that there is a common sequence, the CLEAR site, in many lysosomal gene promoters. This site was a known target site for the transcription factor TFEB. Shortly thereafter, Ballabio's group found that TFEB regulates autophagy, which implicated TFEB in controlling both cargo delivery to the lysosome and degradation.



ROBERTO ZONCU AT THE UNIVERSITY OF CALIFORNIA, BERKELEY

Immunofluorescent pictures show mTOR in red and a lysosomal marker in green. The top two pictures are from amino acid-starved cells. mTOR is dispersed and does not localize with lysosomes. The bottom two pictures are from cells that were starved and then given amino acids. There mTOR clusters on lysosomes.

Deciding factor

Then the worlds of TFEB and mTORC1 collided. In 2012, the groups of Sabatini and Ballabio demonstrated that TFEB and mTORC1 show up on the same spot of the lysosomal membrane. When nutrients are abundant in the cell, mTORC1 phosphorylates TFEB and keeps it inactive on the lysosome. When nutrients, such as amino acids, drop in abundance, mTORC1 becomes inactive and no longer phosphorylates TFEB. The unphosphorylated and active transcription factor takes off for the nucleus to turn on lysosomal genes and turn up the cell's degradative capabilities to either reshuffle allocation of materials or provide energy.

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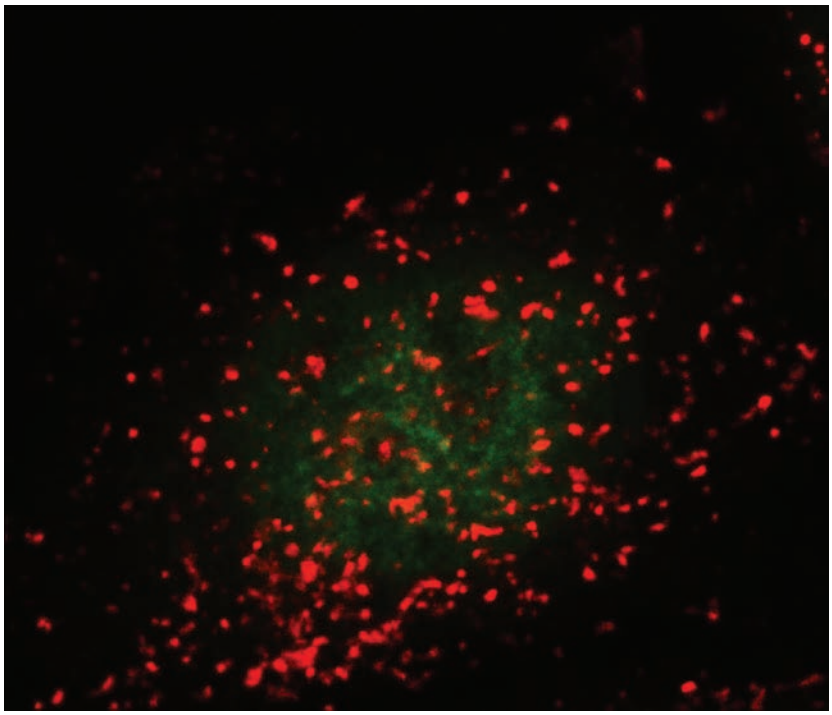

ANDREA BALLABIO AT THE TELETHON INSTITUTE OF GENETICS AND MEDICINE

Lysosomes are seen as the red dots. The green dots show active TFEB in the nucleus.

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With the finding that TFEB and mTORC1 partner, says Overholtzer, it is obvious that "the lysosome is not simply a dead end." It directly communicates with the nucleus, the cell's main control center, and partakes in decisions about growth and degradation.

'Much more complicated'

The lysosome's signaling roles appear to be even more sophisticated than first thought. Haoxing Xu at the University of Michigan, Ann Arbor, leads a research team studying a class of calcium channels found spanning the lysosomal membrane. Mutations in the channels, called mucolipin TRP proteins, cause a rare neurodegenerative disease in children.

Xu says there is some evidence that when the amino acid levels are low and mTORC1 is not active, the calcium channels kick into action, releasing calcium, an important signaling ion, from the lysosome into the cytoplasm.

This lysosomal calcium signaling regulates TFEB. Ballabio's group discovered that during starvation, lysosomal calcium release activates a phosphatase that dephosphorylates TFEB. The dephosphorylated TFEB moves into the nucleus to kick off more lysosome biogenesis and autophagy.

Taken together, mTORC1, TFEB and the calcium channels "constitute a signaling network to regulate when the degradation should occur and when degradation should be terminated," says Xu. "It's much more complicated than previously thought."

On the move

It's becoming abundantly clear that lysosomes are not one-trick ponies. For example, they are capable of repairing the plasma membrane.

In 1997, Norma Andrews' group, now at the University of Maryland, showed that lysosomes can function as calcium-regulated secretory vesicles. They don't just take things in; they are capable of releasing molecules. The finding was met with a lot of resistance at the time, since "conventional lysosomes were not expected to do that," says Andrews.

In 2001, the group moved their findings further along by demonstrating that the lysosome responds to calcium entering through tears in the plasma membrane by fusing with the boundary to heal it. The calcium-controlled process is known as lysosomal exocytosis.

But for exocytosis to happen, lysosomes need to move. As researchers now appreciate, lysosomes don't just sit in a spot. Depending on conditions in and surrounding a cell, lysosomes move back and forth between the center and the periphery of the cell. They do so by coupling to microtubule motors, kinesin and dynein through an elaborate set of adaptor molecules, says Bonifacino, adding that the attachment to motors "allows

the lysosomes to patrol the whole cytoplasm, looking for places where they can exert their activity."

But the movements and duties of the lysosome can be hijacked, explains Andrews. That's exactly what the protozoan Trypanosoma cruzi, which causes Chagas disease, is capable of doing. The pathogen recruits lysosomes to the plasma membrane, makes them fuse with the plasma membrane and tricks them into reforming with the parasite in them. When the lysosomes travel back to the cell interior, the parasite burrows out of the organelles and takes over the cell.

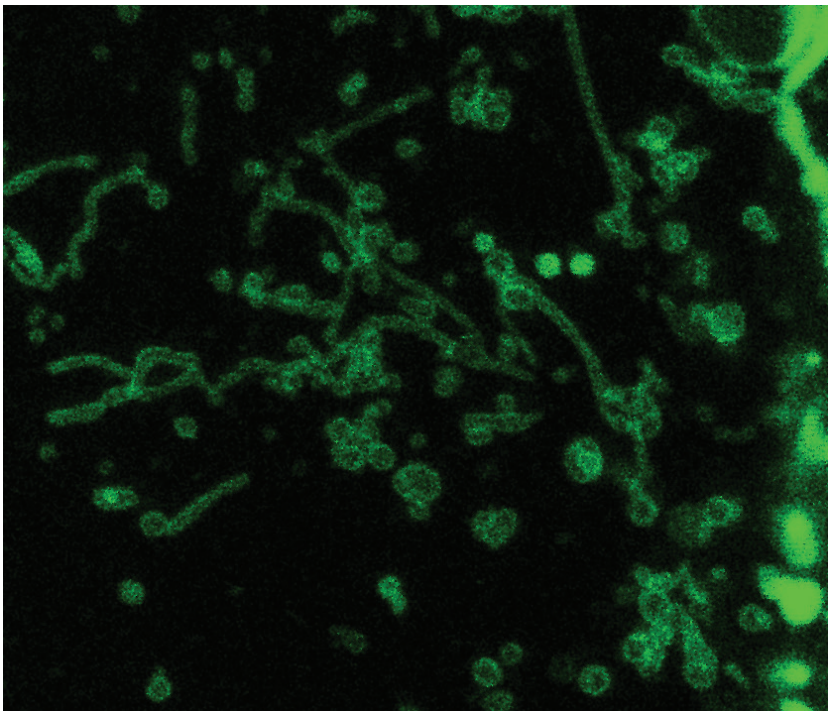
Indeed, defects in lysosomal movement are implicated in disease. If lysosomes are forced to be immobile in a normal cell, "a lot of things go wrong in the cell," notes Bonifacino. He gives the example of autophagy. If lysosomes are forced to hold still, autophagosomes build up without having lysosomes nearby to fuse with. This spells trouble for the cell.

Cell migration and adhesion also rely on moving lysosomes. "Late endosomes or lysosomes move to sites of cell adhesion or migration, and they bring adhesion molecules and signaling molecules like mTOR or MAP kinases that remodel those adhesive structures," says Bonifacino. "That allows the cell to move. If you inhibit lysosome motility specifically then the cells become less mobile."

New questions

The renewed interest in lysosomes brings with it new questions. For example, researchers know that lysosomes in certain cell types, such as the immune cell's macrophages, can be long and snakelike. In other cells, lysosomes tend to be round sacs, ranging from 100 to 1,000 nanometers in diameter.

One tantalizing question: Is there a difference between tubular and round lysosomes? In the case of the macrophages, the cells that engulf and destroy all kinds of unwanted matter, the snake shape is thought to help the lysosomes better pass on peptides from unwanted matter to the plasma membrane so that the immune system knows which entities to search for. But, as Ryerson University's Botelho stresses, "Very, very little is known about tubular lysosomes."



HAOXING XU AT THE UNIVERSITY OF MICHIGAN

Not much is known about the long, snakelike tubulated lysosomes.

Very little also is known about the physical organization of the lysosome. Researchers estimate there are more than 50 types of enzymes inside the lysosome. Do these enzymes flit about like attendees at a cocktail party? Or are they assigned to specific places like workers in a factory? No one knows.

Even for something as critical as mTORC1, the details are hazy. So far researchers know that there are small GTPases that physically anchor mTORC1 to the lysosome. The GTPases have their own set of regulators that in turn are controlled by a proton pump, the vacuolar ATPase, which maintains the acidic pH of the lysosome interior. But how exactly is mTORC1 detecting amino acid levels,

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the job that it's known for doing?

Sabatini says his group has identified a protein that appears to transmit information about amino acid levels from the lysosome interior to mTORC1. But, he adds, they are working on proving that what they have found is a bona fide amino acid sensor.

Extending the reach of lysosomes

It's not just nit-picky molecular questions that are coming up about lysosomes. There are some fundamental questions too. For example, are all lysosomes the same?

"It's very likely that the composition of the lysosome changes from organ to organ depending on the specific metabolic needs," says Roberto Zoncu at the University of California, Berkeley, who was the postdoctoral fellow in Sabatini's group when it spearheaded the mTORC1 localization. "For example, in the liver, you have a lot of glycogen production and storage. It's possible that lysosomes might be specialized in handling sugars." But, he adds, this aspect of lysosomes is not well-explored.

Researchers are wondering if, even within a single cell, there are differences within the hundreds of lysosomes. Different groups of lysosomes can be tasked with different jobs in the cell. For example, Andrews says, "my prediction would be there is a population specialized in associating with the plasma membrane and is involved in plasma membrane repair."

Another big question is about the influence of the lysosome on an entire organism. "Just how far does this system go? If the lysosome is a signaling hub, what is the full range of actions that it can have on the body?" says Zoncu. If the lysosome plays critical roles in signaling cell growth and degradation, how do these roles play out on whole-body parameters, such as growth and metabolism?

Researchers also are now very interested in studying the lysosome's roles in diseases such as neurodegeneration and cancer. "Some cancers upregulate their lysosomal complement massively," says Zoncu. "There are several reports now showing that some cancer types, especially Ras-based cancers, are literally addicted to lysosomal functions. Whether this is a stress response pathway or if it's a way for them to scavenge nutrients, I think this is a great direction of investigation."

For neurodegenerative diseases, Bonifacino uses Alzheimer's to illustrate how researchers are starting to think lysosomes may be involved. A signature of Alzheimer's disease is an accumulation of plaques in the brain. The plaques are aggregates of a peptide called beta-amyloid, which is secreted from neurons and glial cells into the areas around the cells.

Although this extracellular beta-amyloid was long thought to be toxic to neurons, says Bonifacino, recent work suggests that beta-amyloid inside the cells may be to blame for causing neuronal damage. Here changes in lysosome function could lead to damaging accumulation of beta-amyloid inside cells.

The element of surprise is the continuous thread in lysosome research. Even the discovery of lysosomes happened as a tangent. De Duve's group actually was chasing the action of insulin on the liver when it stumbled across the acidic digestive body in cell-fraction studies. Surprise after surprise came with associations with signaling molecules and other unexpected features of lysosomes.

So, these days, researchers no longer relegate lysosomes to the corner. They put lysosomes on center stage and continue to be beguiled.

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Meet Timothy Karr

By Rajendrani Mukhopadhyay

Sperm fascinate Timothy Karr. A postdoctoral stint with Bruce Alberts in the early 1980s changed Karr's interests from the biochemistry and biophysics of polymers to the developmental and genetic contributions of sperm to the reproduction and evolution of a species. These days, Karr, a visiting scientist at the Kyoto Institute of Technology in Japan and an adjunct professor at Arizona State University, is analyzing the molecular changes that happen to mammalian sperm as they travel through the male reproductive system and become capable of fertilizing an egg.

Karr recently became an associate editor for the journal Molecular & Cellular Proteomics, which is published by the American Society for Biochemistry and Molecular Biology. Rajendrani Mukhopadhyay, the ASBMB's chief science correspondent, spoke with Karr to learn about his research interests and career trajectory. The interview has been edited for length and clarity.

What is your research about?

We're looking at using proteomics to follow the changes that occur in sperm composition during their transit through the epididymis as they acquire fertilization competency. (Author's note: The epididymis is the duct through which sperm moves before exiting the body. It's present in male mammals, birds and reptiles.)

How did you become interested in sperm maturation?

As an insect development biologist, I learned that sperm are a central element of all animal and plant organismal fitness. As I started learning more about reproductive biology, it became clear that the maturation process (of sperm) is still a very mysterious one and complicated. The journey that sperm make (through the male reproductive system) is essentially unknown in terms of molecular details. The work has practical implications (for fertility) along with the plain-old fact that I like to make biological discoveries.

Why do proteomics? What can it do that other methodologies can't?

There are some systems you can learn about only by doing proteomics because transcriptomics is a minor player. Sperm are made by the testes, which is a very complex organ that transcribes a very large number of genes, of which only a fraction end up in the sperm. Doing the transcriptome of the testes confuses you as to what's actually in the sperm. Sperm are made of predominantly proteins and lipids and other things, but, in terms of transcription, they are mostly silent. People are starting to realize they can leapfrog over the transcriptomic analysis and directly analyze the protein components in sperm.

We have begun trying to connect the dots between what is changing in sperm and how they acquire the ability to fertilize at the proteomic level. The

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PHOTOS COURTESY OF TIM KARR

Karr studies how sperm changes on a molecular level as it makes its way through the reproductive system.

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hope is that it will lead us to a focus on important components of this system that could be used for further studies of reproduction.

How did you become interested in science?

It was a natural consequence of the way I grew up. I grew up in the middle of central Arizona, about 60 miles from Phoenix, near the Agua Fria River, away from civilization. I had exposure to a lot of desert nature. A young child's fascination with the creepy-crawlies, the noises at night and the animals — I was immersed in it. I didn't have a choice. I naturally gravitated toward curiosity-driven understanding of the world.

The Arizona desert is quite hot. We didn't have electricity and air conditioning. In the summer, I remember there was a flat rock. I would take water out from the well, pour it on the rock and watch how fast it evaporated. I still remember how fascinated I was, toying around with the conditions under which (evaporation) would happen. I remember observing nature and trying to put rational thinking behind it.

What did your parents do?

They mined gold. It was a way to accumulate enough gold to go into town and trade it for food and stuff. It wasn't for money making or profit making. It was subsistence living. It was no-electricity, no-running-water kind of existence. We grew some of our own food. We had goats for milk. We had donkeys to haul water.

When the sun went down, we were inside. The school that we went to was a one-room school with eight grades. Once a month, the book mobile would come by, a large, old-style Winnebago filled with books. I would get a huge stack of books. I loved to read, and my sister loved to read also. Between the time the sun went down and the time we went to bed, I read. That also had a huge influence on me. I gravitated toward books about science and scientists.

Where did you go to college?

I had a scholarship to Stanford. But when I got there, I couldn't go because I couldn't afford it. I ended up going to a junior college nearby, because I had to work to support myself for a couple of years before transferring to (the University of California), Santa Barbara. I did my undergraduate, and then I obtained my Ph.D. in the chemistry department at UC Santa Barbara.

Who was your adviser?

His name is Daniel Purich. He's at the University of Florida now, and he's still doing lots of wonderful things. He's the reason I'm here.

What did he do?

He was a fantastic mentor and never let me believe, for one second, that I'd made a wrong decision for going into science. He's so inclusive in his desire to bring people in and encourage them.

What happened after your Ph.D.?

I did a postdoc with Bruce Alberts at (the University of California, San Francisco) and also Thomas Kornberg at UCSF. I did two postdocs over the course of about five years before I took my first academic position (at the University of Illinois).

How did you start working on sperm?

I went to Bruce's lab to work on T4 DNA replication. I had done my thesis work on microtubules but strictly from a biophysical and biochemical

While a visiting scientist at the Kyoto Institute of Technology in Japan, Karr takes in the scenery near Kyoto's Ryozen Gokoku Shrine.

standpoint. I wanted to continue working on systems that polymerized. Bruce had done unbelievable work in the area of (DNA replication), so I was fortunate enough to get into his lab and start working on that for my first year. Then Bruce decided to work on Drosophila, so I was one of his point people to get that jump-started in his lab.

I knew nothing about developmental biology or genetics. It was like doing another Ph.D. It was great and wondrous, remaking myself as a developmental biologist. During that process, I (learned) that Drosophila make very long sperm. Sperm gigantism had been noted for 100 years … These sperm are as long as the male.

I discovered that this whole sperm entered the egg intact and formed a structure in the egg. It was a rather stunning discovery. Using cell biological techniques including 3-D microscopy, I published, in 1991, the first three-dimensional reconstruction of sperm in a fertilized egg.

But the paternal product in the egg was (considered) an anomaly. I had a bit of an uphill struggle, and, until I went to England, I never got funding for this work. It had a negative impact on my career, because nobody understood (paternal effects in fertilization) and nobody wanted to hear about it. Because I couldn't get funding, I couldn't make enough progress to satisfy anybody. With the new and emerging idea of epigenetics of paternal products, I've been able move forward.

I also became interested in Wolbachia, because I was constantly trying to think of ways to show that the father provides more to the fertilized egg than just DNA. (Author's note: Wolbachia is a genus of bacteria that infects insects and some nematodes. It is one of the world's most com-

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mon parasitic reproductive microbes, because it gets passed along from one generation to the next through insect and nematode reproductive systems.)

Why did you go to England?

They gave me money to study sperm. There was a person who had taken notice of me when I published a couple of Nature papers on Wolbachia. He was a theoretical biologist who had written part of his thesis about Wolbachia, and he was fascinated that somebody actually had done experimental work on it. A couple years later, he contacted me and said, "We have an opening here. Are you interested?"

I was at the University of Chicago at the time. One of the evolutionary biologists from Chicago had recently moved to Edinburgh. He and a couple others decided to support the (University of Bath's) application to get me a Royal Society Wolfson Research Merit Award.

The Royal Society agreed. I had a five-year window with a healthy chunk of money and a salary, because the Royal Society also said they would match my salary at Chicago. It was wonderful. I continued my Wolbachia and sperm work unabated for a few years.

What brought you back to the States?

I wish I was still there. But it didn't work out for the family for a number of reasons. It was the worst possible time (to move back) from a funding standpoint, because it was 2008. Our country was financially bleeding to death. It was very difficult to get a senior-level job. They wouldn't let me bring my money from the U.K. I was stuck.

But I had made a commitment to my family, which is far more important than being a professor at the University of Bath. I went back to Arizona and was fortunate enough to get a research position at (Arizona State University) and continue to be productive.

What do you think you bring to the table as a MCP associate editor?

The field of proteomics has been highly technologically driven. MCP is distinguished by the fact that it also promotes cellular function. Protein biology is so much more complex than (that of) nucleic acids at the chemical level that it's been a huge challenge to get traction on the technology. I really like the idea of using the technology to discover new things about systems that are involved in evolution, development and reproduction. We are garnering new insights into aspects of human diseases through the evolutionary lens. I think that angle is very important for the journal, and it's something I will try to promote. People should be comfortable with applying these powerful technologies to fundamental questions about evolution and development.

What advice would you give younger scientists?

I can only use myself as an example. I never wanted to do anything else. I never would discourage anybody from wanting a life of discovery. The only mark I can leave is if I discovered something. The rest follows along. I've been bruised and battered by the academic system. I've had commensurate financial complications. But I never, for a second, ever thought about not doing it. It's the only reason I'm still here.

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An artist named Crick

By Bree Yanagisawa

The union of science and art is firmly underway. Artists and scientists are bonding over shared interests in discovery and experimentation, collaborating on shows and installations that ask fundamental questions about life processes and new technologies, and exploiting art's potential to help make science more digestible.

For the artist Kindra Crick, this coming together is nothing new.

Crick's paternal grandfather is Francis Crick, co-discoverer of the structure of DNA, and her stepgrandmother, Odile Crick, is an artist who drew the first published images of DNA that accompanied Francis Crick's original paper with James Watson.

As part of a 2015 fundraiser for a new biomedical research center at the Francis Crick Institute in England, the late Nobelist's granddaughter was invited to contribute a sculpture for auction. Provided with a blank, double helical structure and the theme "What's in your DNA?" Crick chose to give each helix its own form. One side she painted a vibrant blue to which she added seedlike structures that twisted along the length of the helix and were meant to represent art and the infectious nature of human ideas. The other side featured handwritten diagrams copied by Crick from pictures of her grandfather's chalkboards. She titled the piece "What Mad Pursuit."

To Crick, the merging of both sides in the sculpture was not only complimentary, as DNA bases are, but integral to who her family is and who she has become.

A child of science and art

Crick was raised outside of Seattle in Bellevue, Wash., in what she calls "a very techie household."

Both her parents and her maternal grandmother were programmers who encouraged experimentation, and the objects of science were never far from her play space. As a young child she was given chemistry kits and space in the garage for experiments.

Time spent with her paternal grandparents was formative. "My grandad would always encourage my curiosity and instilled in me a great love of books, puzzles and learning," she says. "He taught me to question assumptions."

Crick remembers there being a plethora of artist's resources on hand when she'd visit Francis and Odile. "My grandmother would give me full access to watercolors, pastels, drawing, and would even hire models," she says. "I had a much enriched opportunity to explore both disciplines."

When it came time to choose a career, Crick opted for the science side of her interests, enrolling in the undergraduate program in molecular biology at Princeton. She enjoyed her coursework, but the actual research wasn't all she'd hoped it would be.

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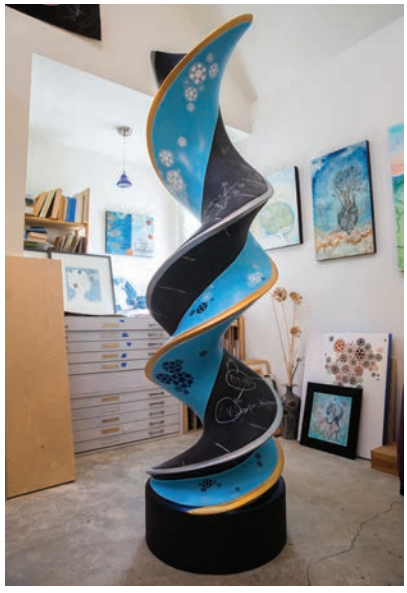
KINDRA CRICK

Odile and Francis Crick attend a youth theater performance of Hello Dolly featuring their granddaughter Kindra in the title role.



ALEX CRICK

Kindra Crick's piece, What Mad Pursuit, is an homage to her inherited love of science and art.

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"I always enjoyed lab work to some extent, but there was always something missing for me," says Crick. "I like making things and building things."

To meet her creative needs, Crick created posters and marquees for several theater groups on campus. After graduation, she spent time in a lab that studied the breast cancer-associated genes BRCA1 and BRCA2. While there, she found herself as intrigued by the imagery she saw under the microscope as she was by the work's scientific questions.

When it came time to decide about graduate training, Crick felt tasked with arriving at her own research direction. But she stumbled. "When you're in science you should pick a question, and I wasn't sure if I had my question," she says.

Instead of forcing herself into a lifestyle that wasn't fitting, she enrolled at the School of the Art Institute of Chicago.

The empathy molecule

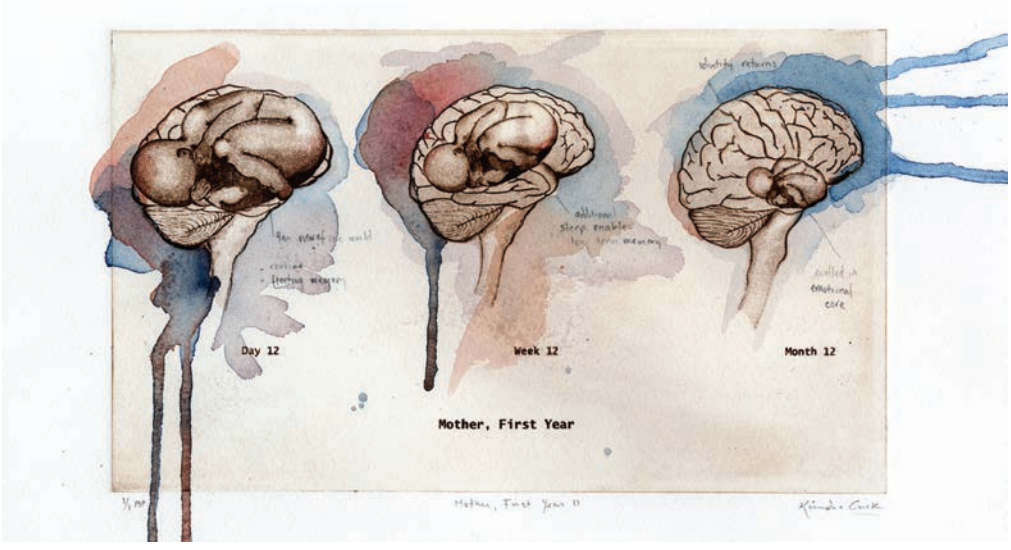
Though she enjoyed both disciplines from an early age, Crick never thought to make science-informed art. "My art practice and my research had always been separate," she says. But in 2007 she gave birth to a daughter and "became fascinated with the biological mechanisms that could be involved in the overwhelming sensation of love that one feels for a newborn."

The curiously intense emotions helped to mesh fully her love of science and her love of art and led to the creation of pieces with scientific undertones. A new series of paintings delivered abstract concepts through schematic images resembling biology textbook diagrams. "I started using the concept of diagramming, but instead of it being factual and based on measurements it was very emotive," Crick says.

The first piece in this science-art fusion is called "Mother, First Year II." It features three brains, each representing a different time after birth: day 12, week 12 and month 12. An image of a fetus is shown in the first brain, overwhelming all aspects. As time goes on, the fetus nestles inside the emotional core of the brain.

Crick got a range of reactions to the piece based on whether the viewer took the image literally or figuratively. Many who immediately understood the work tended to be parents themselves, while others asked her if the diagrams were backwards.

"One of the things about art is that you're speaking to a very specific audience sometimes," says Crick. "The art isn't supposed to be taken literally."



KINDRA CRICK

Crick's first piece to intentionally fuse science and art was inspired by her love for her newborn daughter.

Art as outreach

Crick's methods for creating her art bear some relationship to the scientific process. As she identifies new questions

that interest her, she takes time to dig through research literature before getting started in the studio.

Although she now works explicitly with scientific concepts, Crick insists she isn't making art that's meant to teach audiences about science. During a recent partnership with NW Noggin, a group based in Portland, Ore., and founded by an artist and a neuroscientist who pair art with science outreach, Crick collaborated on a piece intended to inspire wonder.

Working with postdoc John Harkness of Washington State University, Vancouver, Crick created a sculpture that represents an aspect of Harkness's research on perineuronal nets, which are believed to support the preservation of memory in neurons.

Titled "Your joys, Sorrows, Memory and Ambition" — a phrase taken from a larger quote by her grandfather — Crick's piece is a towering spectacle. More than eight feet tall, it features neuron cables interspersed with glowing LED lights encased by wire mesh nets. The wire nets cradle the neurons, visually depicting the supportive relationship perineuronal nets provide neurons within the human brain. Crick purposely exaggerated the net structures to draw attention to their important role.

In late April, 2016, as part of a weeklong outreach trip by NW Noggin, the piece was installed at The Phillips Collection in Washington, D.C., for an event that showcased the brain and our perceptions of beauty. While there, the group also performed science outreach at local schools to bring its joint science and art curriculum from the Pacific Northwest to the East Coast.

Connecting comfortably

As Crick moves forward with her art, the influence of science remains prominent. Her most recent series, "Cerebral Wilderness," features old diagrams of brain anatomy overlaid with topographical maps of the Mt. Hood wilderness and diagrams of melting glaciers. The aged feel of the pieces evokes a sense of the continuity of nature and of scientific mystery.

Given her experience of motherhood, her formative time with her grandparents, and a life of separating, connecting and finally combining science and art, Crick is mindful of continuity and of her inheritance.

She's learned, she says, that "not only do we pass on our genetics. We pass on our ideas."

KINDRA CRICK

Postdoc researcher Josh Harkness and Crick with their collaborative piece inspired by perineuronal nets.

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The promise of BEST

One school makes the most of an NIH-funded career-development program

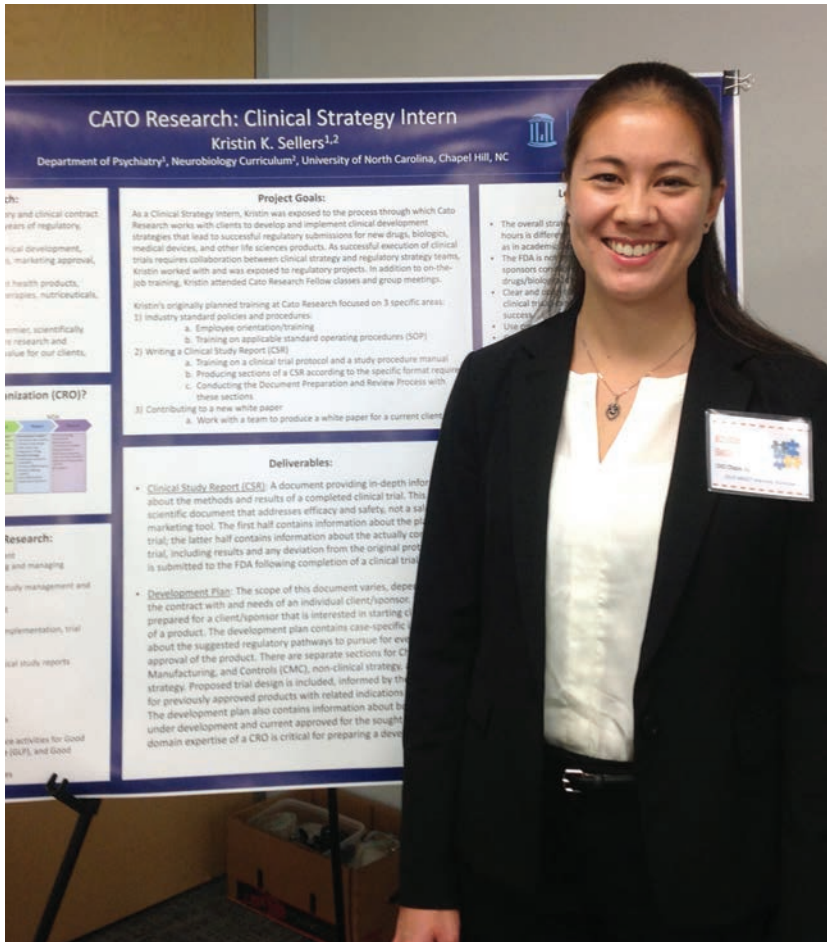
By Patrick Brandt

There is broad consensus among policy makers, career experts, university administrators and others in the life sciences that the historical, apprentice-based model of graduate and postdoctoral training is no longer sustainable. In recent years, myriad recommendations have been advanced by the National Institutes of Health, scientific societies, university faculty members, thought leaders and trainees to overhaul the model and adapt training to the realities of today's research environment (1–13).

In 2012, the National Institutes of Health released the Biomedical Workforce Working Group Report, which suggested, among other things, that the number of Ph.D.s awarded to students interested in biomedical research careers was outstripping job openings in the field. The report's first recommendation was the creation of a competitive grant program that would enable institutions to train graduate students for a wide variety of careers in science — not just tenure-track research positions.

Within a year of the report's release, the NIH had committed more than $25 million to the funding of experimental career- and professional-development programs through a new initiative called Broadening Experiences in Scientific Training, or BEST. Ten BEST awards were announced in 2013 and another seven in 2014 (14, 15). My institution, the University of North Carolina at Chapel Hill, was one of the 2014 awardees.

Our experience with BEST has been enlightening and encouraging. UNC's version of the program consists of three interlocking components:



PATRICK BRANDT

A UNC ImPACT student was funded for a clinical internship with a contract research and development organization.

internships, career-focused peer groups and improved alumni network mapping.

Internships

In 2015, UNC started the Immersion Program to Advance Career Training, or ImPACT, a 160-hour paid internship program that supports 30 senior graduate student and postdoc interns each year.

The purpose of a UNC BEST internship is to provide an immersive experience in a career path not normally represented in an academic setting. As interns learn about the pros and cons of their desired career paths, build their resumes, and hopefully get new letters of recommendation, they also receive paychecks at their current stipend or salary levels and maintain

their health insurance benefits. Funding comes from university sources, an endowment from the Burroughs Wellcome Fund and matching funds provided by some of the internship hosts. Interns have worked in the following areas:

• research and development at a local biotech company, pairing whole genome sequencing and computational computer programming;

• policy at the science policy division of a local NIH institute;

• outreach at a local science museum engaging the public about the microbiome;

• teaching at a local college, developing and delivering an undergraduate course; and

• business development with a new UNC startup company.

We will be tracking career satisfaction, compensation and other metrics over the next several years to gauge the success of the ImPACT program and already can report that satisfaction is impressively high among interns, host organizations, internship supervisors and research mentors.

Our survey results show that 93 percent of internship supervisors were satisfied or very satisfied with hosting an intern, 73 percent said they would be likely or very likely to offer the intern a position in the organization, and 100 percent said they were likely or very likely to host an intern again.

The interns who responded to our post-internship survey agreed or strongly agreed that the internship had made them more competitive for the job market.

We anticipated that the research mentors (that is, the principle investigators) of the trainees would be the least enthusiastic about the internships. One could argue that they have the most to lose, at least in the short term, since the productivity of their laboratories are affected while the interns are away. However, 86 percent of principal investigators surveyed after the return of the interns reported that the interns' strengths across seven categories were about the same or higher compared with before the internship, 89 percent agreed that the internship would have a positive effect on the trainee's competitiveness, and all but one of the PIs reported that the interns had met or exceeded their expectations.

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The gains of ImPACT trainees

GENTRY

Leanna Gentry, a pharmacology doctoral student, worked part time at Cato Research in Durham, N.C., a contract research organization. Working with senior regulatory scientists at Cato on a regulatory affairs project, she learned firsthand about regulatory legislation, Food and Drug Administration compliance, how to submit new investigational drug applications, and regulatory reporting. Two months after completing her internship, Gentry graduated and was hired at Cato as a scientist without the need for a postdoctoral training period. Her position allows her to contribute to both clinical and regulatory strategy. Gentry says, "The internship gave me experience in drug development that I could not have gained otherwise in graduate school. Thanks in large part to the ImPACT award, I was able to secure a position in the competitive field of clinical research without additional postgraduate training."

HAGAR

Jon Hagar, a microbiology Ph.D. candidate, worked part time at a mid-sized biotech company called Parion Sciences, also in Durham. His main goal was to evaluate the scientific and commercial merit of candidate pipeline technologies. He was vigorously recruited for a full-time position at Parion but instead pursued an industry postdoc. With great recommendations and his industry experience from Parion, he was chosen for the highly competitive postdoc program at Genentech in San Fransisco. He will start his postdoc in July. Hagar says, "My time at Parion solidified my interests in early-stage drug development and business strategy. Insights I gained into these will be useful whether I pursue an industry career or academic career, the latter benefiting from my being better able to mentor trainees interested in industry and tailor projects to have translational potential."

MAINZ

Emilie Mainz, a chemistry doctoral student, participated in a full-time internship at BD Technologies in Research Triangle Park, N.C., working on a single-cell, next-generation sequencing technology that will be released this year. Her supervisors at BD were so impressed with Mainz that they encouraged her to apply to BD's competitive, rotational position known as the Technology Leadership Development Program. The program, which Mainz will begin in July, prepares high-potential Ph.D.s for leadership roles across all aspects of research and development innovation within BD. Mainz says, "ImPACT supplied the rare opportunity to develop new technical skills while building a valuable network within the medical device industry. These experiences solidified my career path and undoubtedly made me a more competitive candidate."

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Career cohorts

The career cohort model began as a grassroots effort led by trainees and since has been fostered and expanded by our office. Led by graduate students and postdocs who are all interested in the same career path, UNC's career cohorts are organized around science policy, teaching-intensive careers, science and business, academic careers, and science communication. Each group has a faculty leader and receives a modest program budget from the university and from the BEST grant.

Cohorts generally meet once a month to network, share information, work on individual development plans or attend events with invited speakers. Each career cohort maintains a listserv for distributing announcements, job opportunities and career-related information, and each year we work with two or three cohorts to develop and fund a workshop series related to their careers of interest. For example, this academic year we held workshop series on science policy, pedagogy skills and science communication. The career cohort model empowers trainees to take control of their own career learning, provides leadership opportunities for trainees, and enables our office to respond quickly to new career interests and multiply our programming in a sustainable way.

Alumni network mapping

Trainees expect to have access to graduate program training outcomes, and UNC is committed to reporting complete and transparent alumni placement data (16). The university recently concluded a census of the 1,100 alumni who have graduated with a life science Ph.D. since 2000. Through a variety of online and personal contacts, we confirmed current titles, employers, and city and state information for 91 percent of our alumni. Aggregate reports of this information are publicly available to prospective students, current trainees and others.

Institutions that openly report these sorts of outcomes are at a competitive advantage when it comes to recruiting the best trainees — many of whom enter training with defined career aspirations. Presenting these data to our faculty also helps to create a training environment where career success is measured by many different outcomes and not just tenure-track attainment. Current trainees benefit from this expanded alumni network map when we invite alumni back to UNC for career networking lunches, seminars and workshops. We also connect individual trainees with alumni for informational interviews and, in some cases, actual job placements.

If institutions are to continue attracting a diverse pool of new trainees and preparing them to affect positively the changing scientific workforce, the graduate and postdoctoral training model will need to change. Universities, both those with and those without NIH BEST awards, are encouraging this process of change by devoting resources to career and professional development and implementing experimental training initiatives. We intend to keep the pressure on and the dialogue going as we pull and prod the entrenched training model out of its historical rut toward a new track of success for all stakeholders.

Where to go for more BEST information

The approaches taken by participating BEST institutions; how the results of various BEST programs will be shared with the research community; and a blog, news feed and discussion forum on best practices can be found at the consortium website: www.NIHBEST.org.

More information about UNC's career cohorts model is available at tibbs.unc.edu/career-cohort/.

UNC maps its alumni network and makes aggregate reports of alumni information publicly available at tibbs.unc.edu/unc-impact-program/unc-life-science-phd-placement-data/.

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Continental shift

A young Indian scientist's journey to the United States

By Soma Chowdhury

I was not the most focused kid in school. After finishing my primary studies, I more or less stumbled into an undergraduate zoology program with a vague sense that I liked biology and found botany boring. In the same unthinking way, I rode the science-student tide to a zoology master's degree at the University of Calcutta in India.

It was around this time that I met my future husband, Shurjo, who was my classmate at the university. He had been more strategic with his academic life and helped me bring a similar, if belated, focus to my academic career.

PHOTOS COURTESY OF SOMA CHOWDHURY

The author with her parents and husband on her wedding day.

A few months into our relationship, Shurjo started preparing for the American Graduate Record Exam so that he could go to the United States and get a Ph.D. in primate genomics. We didn't really know what him pursuing that Ph.D. meant for our relationship until the moment he was offered a graduate assistantship from Louisiana State University. It immediately became clear that, if we wanted to be together, I would need to be willing to move to the U.S. and to take the GRE myself. Without stopping to think about the life-changing nature of this decision, I decided to start studying.

I told my parents that I wanted to go to America for graduate school. As small-town folks from the Indian state of West Bengal who had spent almost all their lives within a 20-mile radius of where they were born, they didn't know how to react. America! My mom didn't even know where it was and had to be told I'd be going to the other side of the globe. I thought that the real hurdle would be convincing my father that this was a good thing. He hadn't even wanted me to apply to colleges in Calcutta after I finished high school, nervous as he was for me to leave the safety and security of our small town and incur the financial burdens of big-city living. But, to my surprise, he eagerly agreed.

Shurjo soon left India for Baton Rouge, La. I had no idea where that was. All I knew about America was what I'd heard about New York City, Las Vegas and Niagara Falls. I channeled the sadness I felt when he left into studying even harder for the GRE. I worked so hard, in fact, that I didn't recognize myself. Never in my

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life had I been so motivated.

My GRE score was decent, and I managed to land a graduate assistantship at LSU. It was a great relief. But soon the next dose of reality hit. I was going to need money — money for an air ticket, clothes, a visa and paraphernalia related to the trip.

Given my finances at the time, the total amount of money was enormous. I felt desperate but still determined to join Shurjo. He had saved some money from his graduate stipend, which would cover a few things. A couple of weeks after I was accepted at LSU, I applied for a travel scholarship offered by the University of Calcutta, never thinking that I would get it. I did get it, and it covered my air ticket. So that I could shop for the basics of starting a new life, my father took a loan out against his retirement account.

As overwhelming as coming up with the money felt, it was easy compared to the next and most difficult hurdle: getting a U.S. student visa. At the time I didn't realize that this would be such a challenge.

At the U.S. embassy in Kolkata, I was told by a consular official that my parents' finances were inadequate for me to have any true ties to my own country. The fact that I already had funding from a U.S. university did not matter. In an instant, my passport was pushed back at me through the narrow slit in the thick glass window. I was crying like a baby when I called Shurjo from a local phone booth next to the embassy. I'd had no clue that a student visa could be denied in the blink of an eye by a consular official who was officially mandated by her government to treat me as a possible immigrant.

I felt helpless. I had only a month before the fall semester started at LSU, but I couldn't get a new interview at the embassy for another two weeks. Desperate, I took the first possible interview slot. My father went to work gathering everything he could to prove that he was financially stable and would not be dependent on my earnings in the U.S. He also made a will in which he left all his property to me in the hopes that this would convince the embassy officials that I had roots in India. My future father-in-law notarized a document saying that he would help me if I needed any financial help while in the U.S. I was incredibly grateful for all the help I was getting from those around me. It all felt so surreal.

The author's husband on a brief visit home. She left India and joined him at Louisiana State University a few months later.

After 14 agonizing days flooded with anxiety, I appeared at the U.S. embassy for the second time. A different officer asked one or two questions and approved the visa. He didn't even look at all the documents I had so painstakingly gathered.

At first, I was in shock. I couldn't come to terms with the arbitrary nature of the whole process. I told my father, who had been waiting apprehensively outside the embassy, what had transpired. There were no more hurdles.

The next two weeks were a blur of preparations, and I didn't get a chance to contemplate the gravity of what was happening. There were a million other things to worry about. I almost never had spoken to anyone in English before, never had flown in an airplane, hadn't been to an airport, never had cooked anything edible, and never had lived without my parents for more than a month.

On the day of my flight, I checked my packing list one last time, taking special care to note the pressure cooker and the spices, and hurriedly jotted down a few recipes from my mother. I was the first person from my extended family to step outside of India. Many of my friends, neighbors and relatives came to celebrate that moment and to bid me adieu. I looked through the back window of the rented SUV that would take me to the airport and saw everyone waving.

As we drove off, my friends and relatives gradually grew smaller, and I realized I was leaving everything I knew behind. I felt simultaneously blank, numb, thrilled and nervous. As I boarded the flight to Chicago, I was struck by a great sadness and began to

sob uncontrollably.

After 36 hours in a dystopian world of airports and airplane interiors, I landed in Baton Rouge. While I was on the flight, I had thought a lot about what I would be doing when I first saw Shurjo again. He was waiting for me with two of his friends, in almost as much shock as I was. Where I come from, displays of affection in public are frowned upon, so I could not even give him a hug. The moment we saw each other, both of us nervously smiled, equally unsure if we were indeed in the same baggage claim area, actually together, or if the whole thing was a cruel and stress-induced hallucination.

I remember it took quite some time for our happy new reality to sink in. Another chapter of my life was soon underway, and I found myself surviving grad school, dealing with endless visa issues, understanding Southern accents, learning how to cook and feeling for the first time in my life what it meant to be homesick.

Chowdury's parents on their first visit to the United States. They'd never before flown on an airplane or seen snow.

It's been 10 long years since I arrived in the U.S. Shurjo and I are still facing the two-body problem while looking for jobs (thankfully, this time, on the same continent). I survived grad school with a master's degree, discovered a flair for cooking and moved from Baton Rouge to the Washington, D.C. area with Shurjo. After many years of fooling myself that I wanted to do research, I took a leap of faith and became a science writer. Our U.S. visa issues finally got resolved.

I can't say that I've sorted out everything in my life. But, for now, I think I've stopped meandering and found the right direction, both personally and professionally.

Soma Chowdhury (chowdurysoma15@nih.gmail.com) is the communications editor at the National Institute of General Medical Sciences.

Know your audience

A blueprint for successful science outreach

By Jeanne Garbarino

Science outreach can mean many things, and the effectiveness of any particular outreach endeavor can vary just as much as the array of activities that fall under the science outreach umbrella.

As director of the Science Outreach Program at The Rockefeller University in New York City, a full-time program aimed at establishing equitable access to science research opportunities for urban K – 12 communities, I have learned that being effective at science outreach has little to do with fancy equipment, elaborate presentations or expensive reagents. Instead, effectiveness really comes down to one simple question: How well do you connect with your target audience?

By presenting science in contexts that are familiar to our audiences, we have been able to grow our program, establish partnerships, and engage and support local students and teachers. Here's how we do it.

PHOTOS COURTESY OF THE ROCKEFELLER UNIVERSITY

Kids at Rockefeller's annual Science Saturday festival watch a liquid nitrogen demonstration.

We try to understand who our audience is and where they come from

At Rockefeller, we serve K – 12 students and teachers from communities within New York City. If, in this urban context, I am going to center outreach activities on, say, ecosystems, I will avoid introducing the topic using unfamiliar examples, such as salt marshes or microbiomes. Instead, I might ask the students to highlight all of the things that exist at a subway station, and use their daily experiences riding the train as an entry point for teaching about relationships and networks. When the students map out how different conditions, such as leaks from heavy rains or track fires from too much garbage, can affect the entire subway system, it opens up conversations about ecosystem connectedness. Once basic, familiar frameworks are established through the subway example, I can then move on and talk about the variety of the planet's ecosystems.

We map out goals and relevant talking points

Through much trial and error, we have learned that less is often more when it comes to communicating science. Because science encompasses such an amazing breadth of information about our world, those of us doing outreach should be equipped with a roadmap of relevant goals and talking points for every outreach project. Without this kind of defining framework, we can ramble and our message can lack purpose.

Science Saturday, our annual science festival for 5- to 13-year-olds, features more than 35 unique, hands-on learning stations. With just a few minutes to engage kids at each station, we work ahead of time to define a few core elements of the communication strategy for each station.

First, we identify the ultimate goal of the station. Is it meant to educate, raise awareness, dispel misconceptions or perhaps promote specific ideas? Once we're clear on the goal, we arrive at the three most important talking

points we need to cover to get to that goal.

For instance, our "Sweet hide and seek" learning station, facilitated by Rockefeller's bionutrition department, aims to educate young kids about the link between obesity and sugar and promote healthy eating habits. This learning station is designed as a game, and kids have to guess how many grams of sugar are in common drinks like juice and soda. The conversations about this activity name three main talking points: many common drinks have sugar in them; when you drink them, sugar gets into your body; when there is too much sugar in your body, it can affect your health.

Students learn about ethics and the genetics of disease in Rockefeller's LAB Experience program.

We try to tell a good story that is relatable

Once we've identified our goals and talking points, we think about how to weave them into a narrative that includes relatable elements. These narratives can take the form of a few sentences or a series of interrelated and fun activities that convey real-world application. We might even do something as simple as ask the audience a question, such as, "Do you ever wonder how digestion works?"

This strategy has been really helpful for our Learning at the Bench After School Program, which aims to teach New York high school students about metagenomics and microbial community formation. These topics by themselves could be daunting to any teenager. To make them more accessible, we tell this particular story through food. Our program has teamed with New York's iconic store, Murray's Cheese. Murray's has its own cheese caves, and our students are able to visit and observe the microbiome of the caves and learn how microbial communities affect the aging process and flavors of cheese.

A Rockefeller LAB student swabs the floor of a cheese cave for microbes.

We stay flexible

While it is important to plan your outreach strategy, it is also important to be able to go where your audience takes you. There are times when I have spent ages planning an outreach event or curriculum, keeping in mind every possible detail and direction that could interest my audience, just to have to throw it all out the window. I've learned that, no matter how prepared I think I am, when my material is not connecting, I need to switch it up.

A few weeks ago, about 20 students from a specialized high school came on a school field trip to our learning lab through our LAB Experience program. These students had a history of truancy, were behind in their academic credits, and were, on average, much older than our typical high school classes. I started teaching our normal curriculum, but the students were not engaged at all and were saying things like "I don't trust scientists" and "I'm too dumb for science." I realized that, in order to make an impact, I had to toss our planned agenda and do something totally different. So I took them to the cafeteria for coffee, and then we set out on a walk around campus.

To keep things relaxed while building their trust, I invited them to bring up any ideas or questions they had about science. Letting them lead the conversation as we strolled, I periodically pointed out some of our interesting lab spaces or cool equipment, which opened the door for deeper conversations about scientific issues that were relevant to them, such as vaccinations, the development and treatment of cancer, and how to become a scientist.

We emphasize connection

We have had thousands of students and teachers come through our program in the past few years, and successful execution of our events always comes down to how relevant we've made them for our audiences. We've learned that being able to relate to, understand, prepare for and respond with flexibility to our audiences is often the difference between an outreach project that engages and one that fizzles. For more about doing successful outreach, please check out the outreach miniseries on our blog, The Incubator (http://incubator.rockefeller.edu/).

Jeanne Garbarino (jgarbarino@rockefeller.edu) directs the science outreach program at The Rockefeller University in New York City.

Research spotlight

A Q&A with Kathy Goodson

By Andrew Macintyre

Kathy Goodson is a research fellow and the director of communications at the Potomac Institute for Policy Studies. The Potomac Institute is an independent public policy institute located in Arlington, Virginia, and is focused on the role of science and technology in society. Goodson also works on a variety of Secretary of Defense and naval science and technology projects related to communications and education. I asked her about the skills she learned during her scientific training that prepared her for a career in science policy research.

What are the key experiences and decisions that have enabled you to reach your current position?

Attending Virginia State University was vital to determining some of the decisions that led to my current career. As an undergraduate at Virginia State University, I received invaluable experience and exposure to amazing scientific, medical and pharmaceutical research. I developed relationships with mentors that have been key to some of the insights I have been afforded. I didn't know or think it at the time, but Virginia State University was the first key stop on a lifelong journey.

What skills did you learn during your scientific training that prepared you for your current role?

Focus, great note taking, perseverance and patience. My analytical, organizational and scientific writing skill sets as well as my skills in coordinating people and resources came from my graduate education.

What is the biggest challenge that you have faced in pursuing your career? What have you done to overcome it?

Coordinating with graduate research advisers from separate academic institutions and different scientific disciplines. Never underestimate the power of developing people skills. Working with scientists from varying disciplines has given me keen perspective on conducting research and led me to take a more collaborative approach. Ultimately, I believe that a collaborative approach is fundamental to the practice and promotion of education in science, engineering and technology.

What advice would you give to young people who want to pursue a career similar to yours?

Literally talk with someone who is doing what you want to do. I firmly believe exposure is a powerful commodity that often is lost at all ages.

What can young scientists do to learn more about careers in your field? Attend events and network. There is a great resource called Linktank where think tanks in the Maryland, Virginia and Washington, D.C., area list events that are open for attendance. The best way to learn about something can be to immerse yourself in the environment. Join a group for an event and see what it is all about firsthand.

Kathy Goodson

What are your hobbies?

Jogging, reading and floristry.

What was the last book you read?

One of the last books I read was "Seveneves" by Neal Stephenson. It is a science fiction novel depicting post-survival awareness and challenges as humans move on from an uninhabitable earth. I love science fiction because it's not always fiction. Some of the best everyday inventions are the spawn of great science and technol-

ogy endeavors that were at one time thought of as fiction.

Do you have any heroes, heroines, mentors or role models? If so, how they have they influenced you?

Science communication involves an individual who can interpret scientific information and present it in a way that is accessible to individuals with varying levels of scientific expertise. I have been fortunate to have many such individuals in my life and even more fortunate to be able to do the same for others. A mentor can be anyone who does something that you're interested in doing yourself. If you find someone who is willing to share their time, enjoy and soak up information like a sponge. And don't forget to return the favor with someone else.

What is it that keeps you motivated?

I absolutely love science. There is something new to learn every day. My (work has) allowed me to see amazing research being undertaken, and I am excited for the opportunity to assist in the translation of those research efforts through science policy.

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