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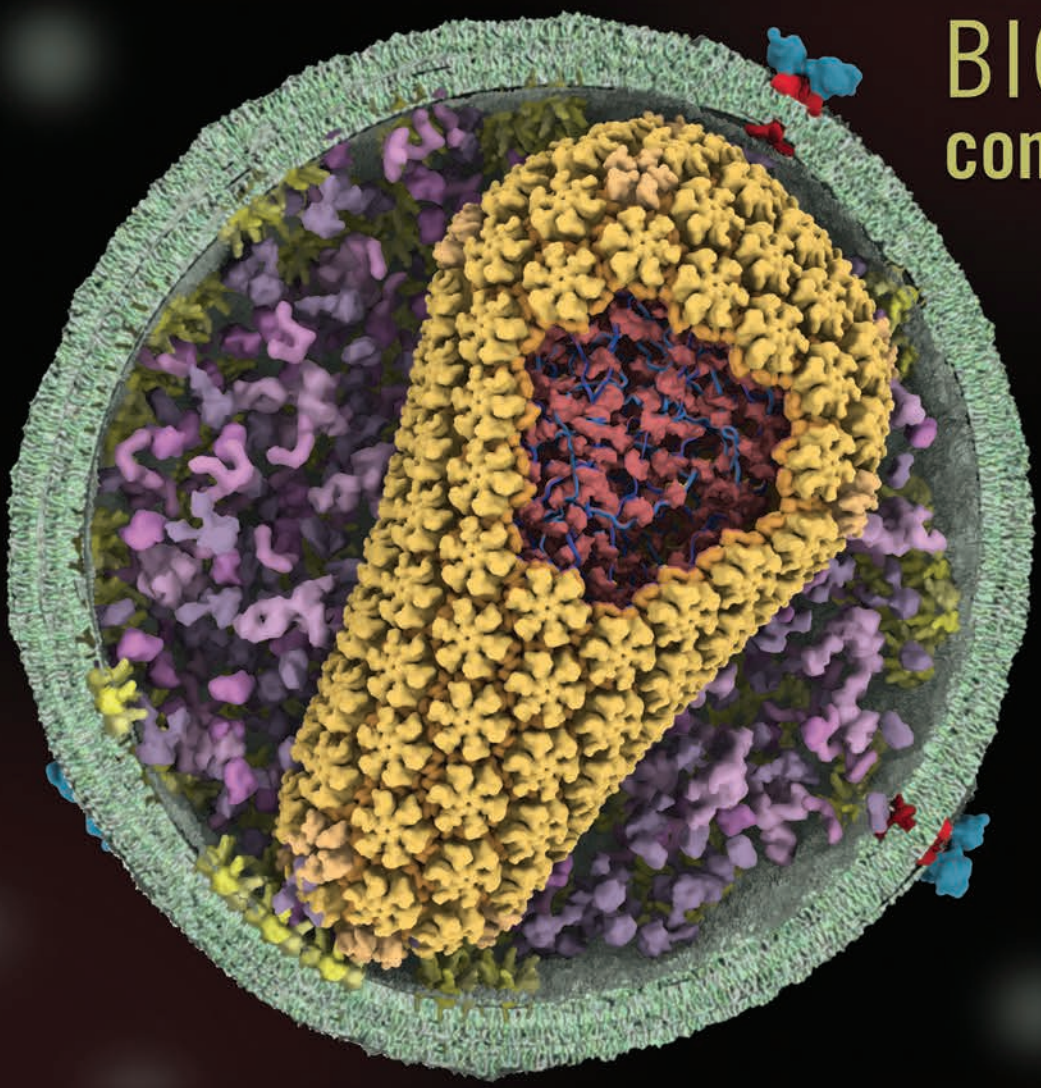
ASBMBTODAY

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



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'More than pretty'

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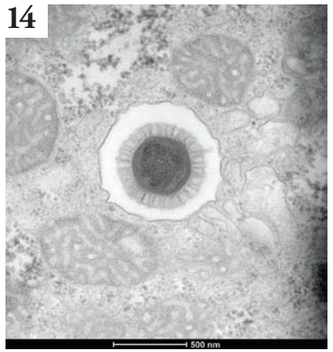

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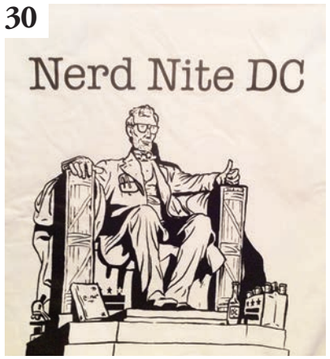

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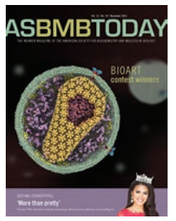
Four ASBMB members won the FASEB BioArt competition. Our cover features the winning image by Janet Iwasa of the University of Utah.

Nina Davuluri image courtesy of Bruce Boyajian/The Miss America Organization



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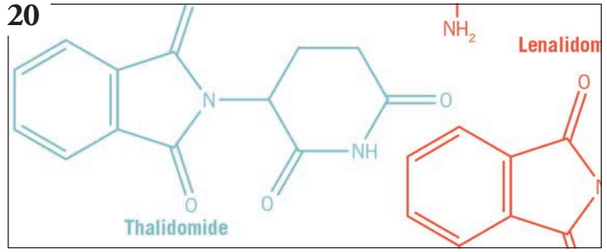

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Wow!

By Steven McKnight

My essay entitled "The curse of committees and clubs," hereafter termed the C^3 essay (1), really hit a nerve. The purpose of the essay was to raise the question of whether our system of allocation of federal grant resources in support of biomedical research is optimal.

Two things happened because of my use of the inflammatory noun "riffraff." First, I mistakenly offended young scientists. For this, I am deeply sorry. Second, inclusion of the volatile word in the C^3 essay prompted widespread attention. For this, I am simply delighted. This was my first brush with social media, and I can clearly see its power. If serious debate can be channeled in this way, our research enterprise will undoubtedly benefit.

Let's start with the young scientist issue. If there is any doubt of my commitment to fostering the careers of young scientists, here are some facts.

• Five years ago, the journal Cell asked me to write an essay on any topic of my choice. I chose to write an essay titled "Unconventional wisdom" that was solely devoted to my advice to young scientists (2). I hope that some of my critics might read this essay; as best as possible, it tells young scientists the formula I molded to the benefit of my own career.

• About two decades ago, I cofounded a biotechnology company with Robert Tjian and David Goeddel. The company, Tularik Inc., was successful in many ways, including the creation of hundreds of jobs for young scientists. Tularik's success allowed me to make a variety of philanthropic donations. Among these, the largest was given to University of Texas Southwestern Medical Center in honor of my parents, Sara and Frank McKnight. Over the past 15 years, this endowment has invested millions of dollars in one thing and one thing only — young scientists.

• Knowing just how difficult it is for graduate students and postdoctoral fellows to find first-rate jobs in either academia or industry, I have always directed a small laboratory, typically consisting of no more than two to four trainees. By managing a small laboratory, I have been able to devote significant attention to my trainees, and I am exceptionally proud of their track record in finding good jobs subsequent to their training in my laboratory.

• While at Tularik, it was my job to direct the biological research efforts of the company. The single most important challenge of that job was to hire and mentor young scientists. I can hardly overemphasize the pride I take in the successes of Tularik's biologists, many of whom are biotechnology industry leaders.

• I moved back to academia in 1995 and for the past two decades have served as chairman of the department of biochemistry at UTSWMC. Again, my single most important challenge as chairman has been the task of hiring and mentoring young scientists. The successes of the young scientists I have hired and mentored at UTSWMC represent the legacy I will leave behind this coming year when I step down. Nothing has been more important to me at both Tularik and UTSWMC than helping mentor young scientists to independence and success.

Now to the central point of the C^3 essay. I do not believe that the study sections that judge National Institutes of Health grant applications are nearly as good as they should be. I was roundly criticized in social media for failing to quantify or justify this assessment. My next two essays, for the December and January editions of ASBMB Today, will deal with this flaw head-on. Trust me — I will take off the gloves and fight bare-fisted in those two essays.

Between now and then, let me try to explain where I am coming from. For the purpose of simplicity, I will use a sports analogy.

In the state of Texas, tens of thousands of young kids begin competing in organized football during elementary school. The enterprise is highly inclusive and exceedingly diverse. By the time these kids get to high school, they know a lot about the sport and have begun to develop skills. In high school, however, a weeding-out process begins. Not all kids make the junior varsity and varsity teams, and not all kids — even if they make the team — are apportioned equal playing time. As things progress to college, the weeding-out process becomes all the more acute. Playing on Friday nights as a high-school athlete in Texas is lots of fun with broad participation. Playing on Saturdays as a college athlete may be equally fun, but only the most competitive kids are on the field. The final weeding-out step comes when players are drafted by the National Football League — 32 teams sport 53-man rosters, meaning that only 1,696 young men are eligible to suit up for Sunday football. These are the best of the best athletes and are rewarded accordingly.

I think of science in this same way. Lots of kids begin to learn about science in elementary school and high school. A fraction of these budding scientists choose to major in research disciplines in college, a smaller fraction choose to become professional scientists by earning Ph.D. degrees, an even smaller fraction choose to pursue postdoctoral studies, and an NFL-like weeding-out process takes place for those few scientists who win independent jobs in academia, research institutions or for-profit biomedical research companies.

No politics dictate which football player makes it to the NFL. It is the best of the best who make the cut for one simple reason. If an organization does not know how to choose and develop the very best football players, the team will lose most of their games, the fans will not fill their stadium, television will not care to broadcast their games and the organization will fail. Historically, the same could be said for professional science. Universities, medical centers and top-flight biotechnology companies do their utmost to recruit and mentor the cream of the crop of our scientific workforce.

Having hired scores of scientists in both academic and industrial settings, I am familiar with the process. A search committee is selected, a job advertisement is posted, hundreds of applications are evaluated and a handful of the top candidates are invited for on-site interviews. Whereas many criteria are weighed in preparation for making the final decision on which candidate to tap, by far and away the most important consideration is the potential of the candidate to make substantive, original discoveries. Like in the NFL, it should be the desire of academic and industrial scientific organizations to field the strongest possible teams.

Now, at least in academia, an entirely new metric has insidiously contaminated our enterprise. Instead of perceived capacity to make unique discoveries being at the very top of the list, this critical premise has begun to be replaced by "fundability." If a job candidate is working in a trendy field liberally funded by the NIH, such as the ENCODE project, he or she may well be chosen over a superior candidate. How sad it is to have witnessed this change over the tenure of my decades as a biomedical researcher.

When science funding used to be driven in a bottom-up direction, one had tremendous confidence that a superior grant application would be funded. Regrettably, this is no longer the case. We instead find ourselves perversely led by our noses via top-down research directives coming from the NIH in the form of requests for proposals and all kinds of other programs that instruct us what to work on instead of asking us what is best.

Given the huge impact of fundability on our scientific workforce, the people sitting on NIH study sections now exert exceptional influence on our profession. I am hypersensitive to this situation, and I am simply unwilling to ignore the quagmire in which we now find ourselves. I may be wrong. Our system for distributing billions of taxpayer dollars to the biomedical enterprise may need no tweaking whatsoever. This is a debate; debate is healthy. Over the next two years, I will be offering my take. I welcome yours!

Open Channels

Steven McKnight's "President's Message" in the September issue – titled "The curse of committees and clubs" – prompted several reader comments on our website and two formal responses. We have printed some on page 35.

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.

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2. McKnight, S.L. *Cell* **5**, 817 – 819 (2009).

Upcoming ASBMB events and deadlines

NOVEMBER

Nov. 6: Deadline for volunteered abstracts for the 2015 ASBMB annual meeting in Boston

Nov. 7: The ASBMB and Florida Biomedical Career Symposium, Jupiter, Fla.

Nov. 11: Deadline for travel-award applications for the 2015 ASBMB annual meeting in Boston

Nov. 11 – 15: ASBMB exhibits at the Annual Biomedical Research Conference for Minority Students, San Antonio, Texas

DECEMBER

Dec. 1: Deadline for 2016 ASBMB Special Symposia topics

Dec. 5: Deadline for Undergraduate Affiliate Network Chapter renewals

Dec. 7 – 9: ASBMB exhibits at the American Society for Cell Biology annual meeting in Philadelphia, Booth 1004

ASBMB
American Society for Biochemistry and Molecular Biology

On posturing and policy

By Benjamin Corb

In a New York Times op-ed last month, U.S. Rep. Andy Harris, R-Md., highlighted some problems facing the biomedical research community — problems that we wrestle with regularly while advocating on behalf of the American Society for Biochemistry and Molecular Biology and in support of the National Institutes of Health (1).

Harris, a physician and former NIH-funded investigator, notes that the average age of a first-time R01 grantee is 42 and that the median age of all NIH grantees is 52. He points to research showing that early-career scientists conduct some of the most innovative research (2). So far, it would seem, we have no beef. He sounds like a champion for our cause. But, reading on, we see that is not the case. Harris takes a laudable position but then promotes flawed policies found in draft legislation now in circulation.

First, Harris relies not on an increase in NIH appropriations, a possibility considering that he is in the majority party and on the committee that funds the NIH, but suggests eliminating a budget mechanism known as "the tap." The tap siphons money from the NIH and other agencies to fund small public health programs. Second, Harris proposes a mandate to lower the average age of R01 recipients based on the flawed logic that age determines how innovative a scientist is.

First, let's look at the tap. Congress established the tap in 1970, and, each year since, the tap has funded activities that assess the effectiveness of federal health programs and identify ways to improve them. The tap also supports activities that cut across the U.S. Department of Health and Human Services — activities that build the infrastructure for research evaluation, including data collection and analysis.

You want to know how to fund the best science and get more young investigators into the fold? Adequately invest in science!

The NIH contributes about $700 million to the tap — a sizeable sum, to be sure. I wonder, however, why Harris doesn't simply propose a $700 million appropriations increase for NIH. Based on his voting record, perhaps his real plan is to defund programs with which he is at political odds while using the tap as cover.

Nonetheless, with that $700 million back in the NIH's pocket, Harris' plan next mandates that the agency lower the average age of an R01 recipient or face penalizing budget cuts. This would be a foolish way to fund science.

Yes, some young investigators do tremendous work. Craig Mello, who won the Nobel Prize in medicine or physiology in 2006 for the discovery of RNA interference, did his prize-winning work early in his career. But, if he were a young investigator in today's funding environment, he likely wouldn't win NIH funding — not because the NIH hates young scientists but because the NIH is underfunded and rejects tons of great projects. Furthermore, age is not the determining factor for greatness. Senior investigators also do amazing research.

It's appalling that Harris would propose that Congress knows how to best fund science. The peer-review process, while not perfect, should determine which projects to fund. To parcel out funding based on age is a mistake at best and malfeasance at worst.

You want to know how to fund the best science and get more young investigators into the fold? Adequately invest in science!

Paylines are dreadfully low but not because mostly senior investigators win grants. They're low because Congress hasn't passed an NIH appropriation in nearly a decade; because the NIH budget has been flat for more than a decade and its purchasing power today, thanks to inflation, is weaker than it was before the doubling period; and because members of Congress are more interested in perpetuating political dogma than perpetuating programs about which they claim to care so much.

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2. http://www.nber.org/papers/w11359

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

Alberts, Klinman win National Medal of Science


ALBERTS


KLINMAN

Two American Society for Biochemistry and Molecular Biology members — Bruce Alberts of the University of California, San Francisco, and Judith P. Klinman of the University of California, Berkeley — won the National Medal of Science. President Obama made the announcement in early October. Alberts and Klinman will receive the medals during a ceremony at the White House later this year. The annual National Medal of Science was created by statute in 1959 and is administered for the White House by the National Science Foundation. A committee of presidential appointees nominates candidates for the medal, which recognizes those who have made outstanding contributions to science and engineering.

Charpentier, Doudna receive Janssen award


CHARPENTIER


DOUDNA

Pharmaceutical giant Johnson & Johnson this summer named two ASBMB members the winners of its annual Dr. Paul Janssen Award for Biomedical Research. The company honored Emmanuelle Charpentier of Hannover Medical School and Jennifer Doudna of the University of California, Berkeley, for their work with CRISPR/Cas system for gene editing. "The transformational research by Drs. Doudna and Charpentier has uncovered molecular details of an amazing bacterial immunity mechanism. Their findings enable dramatic improvements in the speed, efficiency and flexibility of genome editing," Craig Mello, chairman of the award's independent selection committee, said. "It is widely applicable in biomedical research and its practical applications extend to engineering the genes of plants and animals." Charpentier and Doudna received the award in September and will share the $100,000 prize. For more on Dounda, see our August cover story at bit.ly/1ACWpJG. *Charpentier image courtesy of Humboldt-Stiftung / Sven Müller.*

Schnell to lead Society for Mathematical Biology


SCHNELL

Santiago Schnell of the University of Michigan Medical School will be the next president of the Society for Mathematical Biology. He will take the helm in July. Schnell, whose research focuses on chemical kinetics to combat protein-aggregation diseases, is director of the in-silico protein analysis module at the university's Protein Folding Disease Initiative, co-director of the university's Systems and Integrative Biology Training Grant and a fellow of the Royal Society of Chemistry.

Shilatifard named department chairman


SHILATIFARD

Ali Shilatifard, formerly of the Stowers Institute for Medical Research, has been tapped to lead the biochemistry and molecular genetics department at the Northwestern University Feinberg School of Medicine. Shilatifard, a past winner of the ASBMB-Amgen Award, "is an internationally recognized leader in chromatin biology, gene expression and epigenetics, and on how the misregulation of these pathways contributes to human cancer," said Eric G. Neilson, a medical school vice-president and dean. "We are privileged and excited to have him spearhead our new (department)." Shilatifard discovered early in his career the function of the protein ELL, found in translocation with the MLL gene in childhood leukemia, and since then has made numerous other significant contributions to the field.

ICIS honorary lifetime award for Samuel


SAMUEL

The International Cytokine and Interferon Society named Charles E. Samuel of the University of California, Santa Barbara, a recipient of the 2014 Honorary Life Membership Award. The award recognizes researchers who have made substantive contributions to the cytokine/interferon field. Samuel, an associate editor for the ASBMB's Journal of Biological Chemistry, received the honor for his basic research on the antiviral mechanisms of interferon action. His lab has focused on the regulation and function of PKR and ADAR1, two interferon-inducible enzymes that are also double-stranded RNA binding proteins. PKR, an RNA-dependent protein kinase, controls the translational pattern in cells through phosphorylation of initiation factor eIF2α. ADAR1, an RNA-specific adenosine deaminase, deaminates adenosine to produce inosine in RNAs with double-stranded character, thereby leading to genetic recoding and altered RNA structures. Samuel received the award in Melbourne, Australia, in October at the ICIS annual meeting.

In memoriam

Frank and Mary Loewus

Frank A. Loewus, 94, and his wife, Mary W. Loewus, 91, passed away on Jan. 21 and March 12, respectively, in Pullman, Wash. The couple had a lifelong and fruitful scientific collaboration that allowed them to publish groundbreaking work on the biosynthesis of ascorbic acid (vitamin C) in plants and the discovery of myo-inositol as a metabolic precursor in plants.

Frank was born on Oct. 22, 1919, in Duluth, Minn. He earned his B.S. in forestry at the University of Minnesota in 1942. Then he served in the U.S. Army Air Corps as a first lieutenant and as an intelligence officer in the Philippines and Japan during World War II. After his honorable discharge in 1946, he continued his education at Minnesota, where he earned an M.S. in 1950 and a Ph.D. in 1952 while working for David Briggs on the chemistry of amylose retrogradation.

Mary was born Feb. 15, 1923, in Duluth. She earned a B.S. in 1945 and an M.S. in 1950 from the University of Minnesota. It was there that she met Frank. The couple wed in 1947. Mary earned her Ph.D. in biochemistry in 1953.

After completing his doctoral studies, Frank worked from 1952 to 1955 at the University of Chicago in the Birgit Vennesland and Frank Westheimer lab, where the research focused on the discovery of NAD/NADH and their functions.

The couple then headed off to California together. Frank joined the U.S. Department of Agriculture Western Regional Research Laboratory in Albany, Calif., and worked there until 1964, while Mary worked at the University of California at Berkeley. Following that, both joined the State University of New York in Buffalo, where Frank was a professor and Mary was a research associate in the department of biology from 1965 to 1975.

In 1975, Frank was elected president of the Phytochemical Society of North America, and the couple moved to Washington State University, where they stayed through 1990, when they both retired.

The Loewuses' contributions are recognized and remembered with travel awards given annually to student members of the PSNA. Frank in 1993 received the Charles Reid Barnes Life Membership award from the American Society of Plant Physiologists and in 2007 the PSNA Phytochemistry Pioneer Award.

Solomon Shankman

Solomon Shankman, a chemist, the founder of Shankman Laboratories in Los Angeles and an avid hiker, passed away Aug. 1, just shy of his 99th birthday.

Shankman was born in Toronto on Aug. 27, 1915. He earned a Ph.D. in chemistry in 1939 from the University of Toronto. That same year, he moved to Los Angeles to work for William T. Thompson Vitamin Company.

In 1946, he opened Shankman Laboratories to offer services analyzing food and vitamin products. Among his most significant scientific contributions are the invention of a method to analyze amino acids in 1952 and the development of the techniques for lyophilization of foods. As an employer, Shankman was considered ahead of his time, providing his employees with medical insurance, maternity leave and the ability to influence company decision-making in the 1950s. A friend who spent time reading to Shankman, who was legally blind in his later years, told the Los Angeles Times that Shankman "was always on the side of the downtrodden, the worker, the oppressed."

Some put the number of miles Shankman hiked, since he took up the pastime the late 1970s, at 35,000, but friends report that Shankman himself estimated it was more like 42,000. Regardless of the exact number, Shankman hiked the vast majority of them in Griffith Park during his daily walks at the crack of dawn for 35 years until he was 95. "The King of the Park," as he was known, met hundreds of people, made lots of friends and organized an annual party for dog walkers. He also was active in the community, working for the Grandfather Gardening program at Logan Street School, volunteering at the Braille Institute and contributing to the fundraising efforts of United Cerebral Palsy.

Shankman spent 43 years married to Elizabeth Stern, a renowned cancer researcher from the University of California, Los Angeles, who established for the first time a link between herpes virus and cervical cancer and showed that the prolonged use of oral contraceptive pills was associated with cervical dysplasia. Shankman took up walking when Stern passed away.

Another friend told the Los Angeles Times: "He thirsted for new ideas. He dared to have his perceptions challenged. At an age when most people think they have it all figured out, Sol was still asking questions. He was still growing." To read more about Shankman's walking adventures, visit lat.ms/1rVsbPc.

Written by Mariana Figuera

Walther Stoeckenius, 1921 – 2013

Editor's note: Walther Stoeckenius, emeritus professor at the University of California, San Francisco, died in August. He was 92. In recognition of his contributions and to draw attention to two of his seminal publications in the Journal of Biological Chemistry, the journal in 2011 published a "Classic" article about his life and work. Here, we've republished that article (edited for length, clarity and style).

By Nicole Kresge, Robert D. Simoni and Robert L. Hill

In 1971, Walther Stoeckenius discovered that Halobacterium halobium contains a purple pigment that is chemically similar to rhodopsin and works as a light-driven proton pump. This discovery set Stoeckenius on a research path centered on bacteriorhodopsin, which included the creation of a bovine-soybean-halobacteria chimera that produced ATP when exposed to light and the discovery of a class of proteins that are phosphorylated in a light-dependent manner.

Stoeckenius was born in 1921 in Giessen, Germany. He earned his M.D. from the University of Hamburg in 1950, after which he spent 18 months doing clinical work as an intern. In 1952, he began postdoctoral work at the Institute for Tropical Medicine in Hamburg, using electron microscopy to study the development of poxviruses. Two years later, he joined the University of Hamburg as an assistant professor and became a docent for the pathology department in 1958. At Hamburg, Stoeckenius continued to use electron microscopy to explore the fine structure of cells and the lipid membrane.

In 1959, Stoeckenius left Germany to become a research associate in Keith Porter's laboratory at The Rockefeller University. After a few months, he became an assistant professor at Rockefeller, remaining there for eight years and eventually becoming an associate professor. He continued to work on membrane structure, studying H. halobium, until he accepted a professorship at the University of California, San Francisco, in 1967.

IMAGE COURTESY OF THE ROCKEFELLER UNIVERSITY

In San Francisco, Stoeckenius focused on biochemical techniques rather than electron microscopy. In collaboration with Dieter Oesterhelt, he discovered that H. halobium contains a purple pigment (bacteriorhodopsin) that is chemically similar to rhodopsin (1) and plays an important role in light energy storage in halobacteria, working as a light-driven proton pump (2).

This discovery led to a collaboration with Efraim Racker in which Stoeckenius and Racker created a thoroughly unnatural vesicle. As reported in their 1974 Journal of Biological Chemistry article (a), they used sonication to recombine membrane lipids from soybeans, bacteriorhodopsin from halobacteria, and ATPase from beef mitochondria. The resulting artificial vesicles produced ATP when exposed to light. The chimeric vesicles also formed a simple model system for a biological proton pump capable of generating ATP from ADP and Pi.

Stoeckenius continued to study bacteriorhodopsin and its light-driven proton uptake in bacteria. As reported in a 1980 JBC paper, he discovered that phosphorylation is regulated by light absorbed by bacteriorhodopsin (b). Using [^{32}P]orthophosphate pulse labeling, Stoeckenius and John Spudich identified a class of phosphoproteins in H. halobium. Exposing labeled whole cells to light resulted in rapid dephosphorylation of two of the proteins, which were rapidly rephosphorylated upon darkening of the cells. The light sensitivity of the proteins was responsive to the presence of retinal, indicating that the dephosphorylation depended on rhodopsinlike (retinal-containing) photoreceptors.

Stoeckenius was elected to the National Academy of Sciences in 1978.

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Stoeckenius' "Classic" articles in the JBC

(a) Reconstitution of purple membrane vesicles catalyzing light-driven proton uptake and adenosine triphosphate formation.
Racker, E. & Stoeckenius, W. J. Biol. Chem. **249**, 662 – 663 (1974).

(b) Light-regulated retinal-dependent reversible phosphorylation of Halobacterium proteins.
Spudich, J.L. & Stoeckenius, W. J. Biol. Chem. **255**, 5501 – 5503 (1980).

Robert T. Schimke, 1932 – 2014

By Robert D. Simoni and Ralph A. Bradshaw

Robert Tod Schimke, an emeritus professor of biology at Stanford University, died Sept. 6 at age 81. An outstanding scientist, he had spent almost his entire career at Stanford, where he was renowned as irreverent, creative and unpretentious and as a leader, scholar and teacher with high values and standards. Students at all levels gained from their association with him, flourished and grew. He left behind an enviable legacy.

Schimke was born in Spokane, Wash., in 1932. He earned both A.B. (1954) and M.D. (1958) degrees from Stanford and completed a two-year residency training at the Massachusetts General Hospital in Boston. He then served in the Public Health Service at the National Institutes of Health in Bethesda, Md., from 1960 to 1966 before he returned to Stanford in the pharmacology department in the School of Medicine. He served as chairman of the department from 1970 to 1973. He then moved to the biological sciences department, which he chaired from1978 to 1982. He was named the American Cancer Society research professor of biology in 1983.

One of Schimke's artworks.

Schimke made several pioneering discoveries. In the 1960s, while working in the Biochemical Pharmacology Laboratory at what was then the National Institutes of Arthritis and Metabolic Diseases, he demonstrated that the rate of protein degradation can be regulated, an important mechanism controlling protein levels in cells. While researchers had assumed that steady-state level of proteins in cells resulted from the balance between synthesis and degradation rates, they had devoted far more attention to studying the regulation of synthesis. Schimke showed that, for both arginase (1) and tryptophan pyrrolase (2), degradation

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rates were regulated and that degradation rates and synthesis rates together controlled steady-state levels. This work established protein turnover as a major field of biochemistry.

He was also a leading early contributor in demonstrating hormonal control of gene expression. In his tryptophan pyrrolase work (2), Schimke showed that the increase in its activity resulting from the administration of hydrocortisone or tryptophan is a product of both enzyme synthesis and enzyme stabilization.

"Studying the time course of changing enzyme levels as well as the enzyme's incorporation and loss of isotopic amino acids in response to the two agents, (Schimke's team) showed that hydrocortisone increased the rate of tryptophan pyrrolase synthesis whereas tryptophan decreased the rate of its degradation," a 2007 tribute in the Journal of Biological Chemistry said (6). "This led to their conclusion that 'rates of enzyme synthesis are mediated by hormonal action, whereas substrates or cofactors act by altering the rate of enzyme degradation.'" This work was selected as a JBC Classic article (6).

Schimke's group explored extensively the role of hormone action in gene regulation by studying estrogen effects on ovalbumin synthesis in hen oviduct. Advances in novel technology, including those allowing isolation of specific mRNAs by immunoprecipitation of polysomes carrying ovalbumin nascent chains (3), marked this work. Importantly, this work emerged during the dawn of recombinant DNA technology and modern molecular biology, and Schimke and colleagues were the first to express a eukaryotic gene, dihydrofolate reductase in E. coli (4).

In the late 1970s, Schimke and his lab studied the mechanism of resistance to the killing effects of the cancer drug methotrexate in tissue culture cells. As this work progressed

and DNA technology advanced, it became clear that the major mechanism for drug resistance was an increase in gene copy number, amplification of the gene that was the drug target — in this case, dihydrofolate reductase. Schimke and his colleagues used cDNA sequences complementary to dihydrofolate reductase mRNA to quantitate dihydrofolate reductase mRNA and gene copies in both the sensitive and resistant lines. They found that the dihydrofolate reductase gene multiplied selectively about 200 times in the resistant line. Similarly, they showed that when the resistant cell line grew in the absence of methotrexate, it eventually lost its resistance due to a decrease in the dihydrofolate reductase gene copy number. Thus, they concluded that selective multiplication of the dihydrofolate reductase gene accounted for the overproduction of dihydrofolate reductase (5).

"In the paper, Schimke suggested that the extra genetic material might have resulted from a number of processes including tandem duplications, unequal exchanges between sister chromatids, disproportionate replication of specific genes and retention of specific chromosomal fragments," the JBC tribute said (6). This work was selected as a JBC Classic article (6).

The importance of this pioneering work went well beyond resistance to chemotherapeutic agents and established, surprisingly, that genomes can be quite unstable. Furthermore, the clinical implications were important, as one of the other major mechanisms of drug resistance in cancer patients was amplification of the gene for P-glycoprotein, the multidrug transporter that effectively reduced drug levels in cells by pumping the drug out of the cells.

Other spinoffs of this work included the induction of gene amplification in tissue culture cells as one method by biotechnology companies to produce large amounts of proteins for therapeutic use. This approach has been used to produce proteins such as erythropoietin and tissue plasminogen activator. Pursuing the mechanisms underlying selective gene amplification led to Schimke's discovery that the selective pressures on cells from interruption of cell-cycle events were critical for induction of genomic instability leading to gene amplification.

In 1995, Schimke, long an avid and competitive cyclist, was hit by a car while riding in the hills behind the Stanford campus. The accident left him a quadriplegic and confined to a wheelchair. Partly due to the accident, he became an emeritus professor and turned to his other life passion: painting.

In spite of limited dexterity in his arms and hands, he produced more than 400 works of art that testify to the same energy, originality, creativity and indefatigable spirit that characterized his research. His paintings have been exhibited at Silicon Valley Open Studios, Stanford's Center for Integrated Systems and the Google corporate headquarters. Others are on display at Genentech, Amgen, the National Institutes of Health, the headquarters of the American Society for Biochemistry and Molecular Biology, the Stanford University biology department, and the Jennie Smoly Caruthers Biotechnology Building at the University of Colorado Boulder.

Throughout his career, Schimke was a forceful and effective leader. In addition to serving as chairman of two departments at Stanford, he served as a member of the editorial board (1975 – 1981) and as an associate editor (1983 – 2002) for the JBC. His leadership was instrumental in establishing the high standards of the journal. He was elected president of the ASBMB in 1988. He served on countless advisory boards. He won election to the National Academy of Sciences in 1976 and to the Institute of Medicine in 1983.

On a more personal level, he was certainly one of a kind — a maverick more interested in new ideas and opening up new areas of thought than in conforming to any so-called accepted standards. As an illustration, he was fond of giving seminars with no slides and only the minimal use of a chalkboard. More than one person noted that he managed to get more across in an hour this way than someone showing 50 fancy slides. He developed and relished having a reputation as a critical, practical, no-nonsense scientist.

Schimke mentored more than 100 undergraduates, graduate students and postdoctoral fellows in his laboratory, and many went on to have distinguished careers and leadership positions in the biomedical sciences. The enduring love, respect, admiration and appreciation of his students and colleagues were periodically demonstrated by reunions that drew dozens of former lab members from around the world. Schimke relished their success and always was delighted to learn of their recent research. He was a force of nature, impossible to replace.

Find out more

- See Schimke's art collection at www.stanford.edu/group/schimke.
- Read an ASBMB Today feature on him at http://bit.ly/1BXVbr1.

In memory

Donations may be made to
Robert T. Schimke Graduate Fellowship Fund,
Department of Biology
Gilbert Hall
Stanford, CA 94305-5020

Accolades

In recognition of his many contributions to science, Schimke received the following accolades:

- the Boris Pregel Award from the New York Academy of Sciences (1974)
- the William C. Rose Award from the ASBMB (1983)
- the Alfred P. Sloan Jr. Prize from the General Motors Cancer Research Foundation (1985)
- the Lila and Murray Gruber Memorial Cancer Research Award from the American Academy of Dermatology (1988)

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FASEB BioArt contest winners

The Federation of American Societies for Experimental Biology announced in October the winners of its third annual BioArt contest. Four members of the American Society for Biochemistry and Molecular Biology submitted three of the winning entries.

"Biological scientists create a variety of images and videos as part everyday research activities — from the collection of image-based data to the visualization of results," said Joseph R. Haywood, a professor at Michigan State University and the president of FASEB. "These spectacular winning entries illustrate only a small segment of the exciting research being conducted throughout the country."

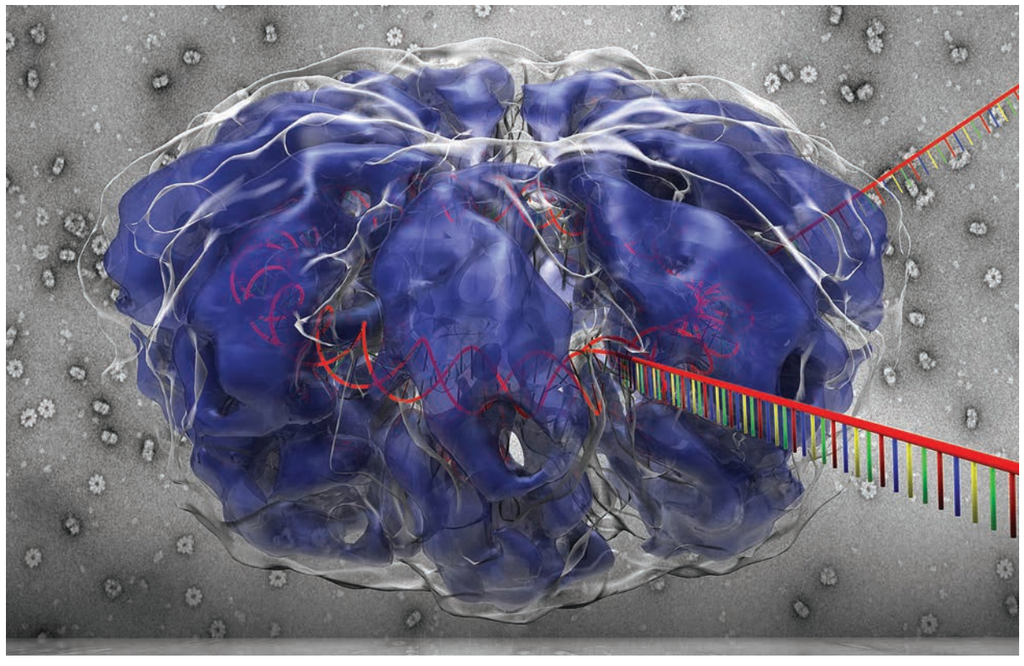
The winning images, all of which were derived from research supported by the National Institutes of Health, will be displayed for the next year at the NIH Visitor Center and Nobel Laureate Exhibit Hall.

For more information about the competition and to see all 10 of the winning entries, plus two featured videos, visit www.faseb.org.

Gökhan Tolun[1,2], Alexander M. Makhov[1,3] (ASBMB), Steven J. Ludtke[4] and Jack D. Griffith[1] (ASBMB)

[1]University of North Carolina at Chapel Hill
[2]National Institutes of Health
[3]University of Pittsburgh School of Medicine
[4]Baylor College of Medicine

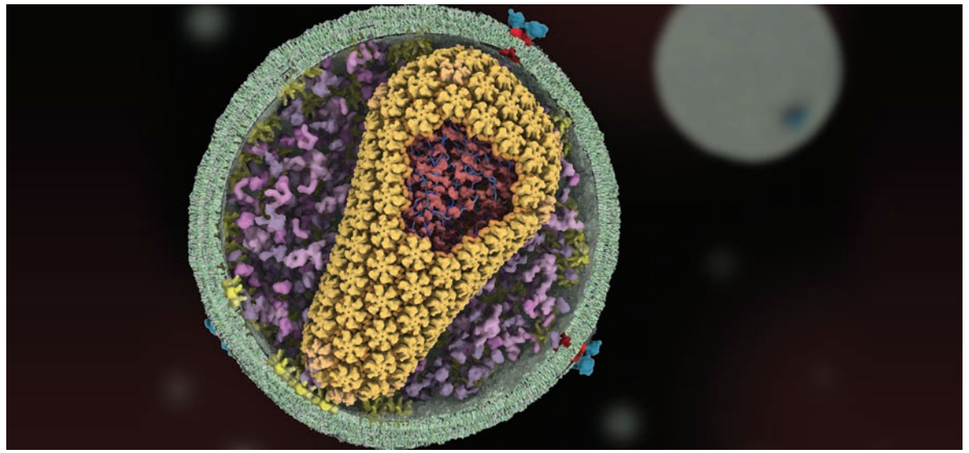
Research focus: Viral replication



The infected cell protein 8, or ICP8, of herpes simplex virus 1, or HSV-1, has a vital role in viral replication. It is involved in DNA replication, recombination and repair. To determine the structure of ICP8 when it is bound to single-stranded DNA, researchers used a method called single-particle reconstruction, which uses specialized software to generate a three-dimensional structure from the two-dimensional electron microscopy images. The reconstructed structure of ICP8 (blue) shows that it is composed of two nine-subunit rings that are stacked on top of each other and illustrates a hypothesized mechanism joining two single DNA strands (red lines) to form a double helix. One of the original electron microcopy images used for single-particle reconstruction can be seen in the background. The National Cancer Institute, National Institute of General Medical Sciences and National Institute of Environmental Health Sciences provided support for this research.

Janet Iwasa (ASBMB)
University of Utah

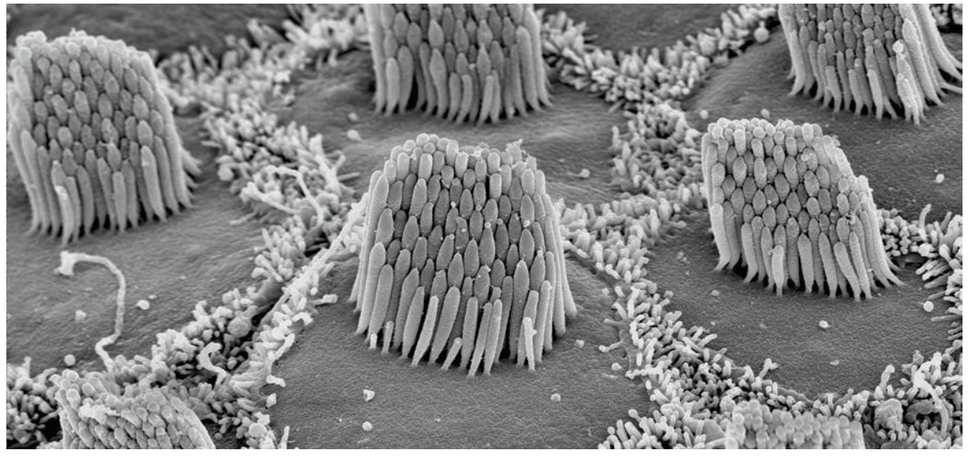
Research focus: HIV



This 3-D model of a human immunodeficiency virus particle shows the membrane (green) surrounding the viral capsid (yellow-orange pinwheels) with the viral RNA genome (blue lines) inside. It was created as part of the Science of HIV project, which is funded by the National Institute of General Medical Sciences. The goal of the project is to create a scientifically accurate and visually compelling 3-D animation of the HIV life cycle, highlighting structural findings. Three-dimensional animation software is used to convert crystallographic and electron microcopy data into illustrations and animations.

Peter Barr-Gillespie (ASBMB) and Kateri Spinelli
Oregon Health & Science University

Research focus: The mechanism of mechanotransduction by the inner ear



To hear, sensory hair cells in the inner ear detect sound waves as vibrations and transmit this information to the brain. This scanning electron microscopy image shows the surface of sensory hair cells from a chick. Each hair cell has a tuft (or hair bundle) of thin and long projections, which are known as stereocilia. Vibrations cause the hair bundles to oscillate, activating ion channels and turning sound into a chemical signal. Supporting cells also are apparent in this image; they form a furry outline around the sensory hair cells. Expanding our knowledge of how hair bundles work should lead to better methods for detecting and treating hearing loss and disrupted balance. The research is supported by the National Institute on Deafness and Other Communication Disorders.

Large DNA virus produces rare sugars

By Kelly Hallstrom

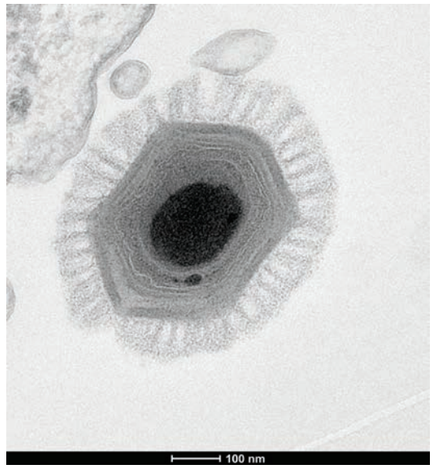
Viruses generally are defined as protein-packaged genomes rather than as independent organisms because they are unable to propagate on their own. However, recent studies have shown that some large DNA viruses encode genes for metabolic pathways that make the viruses less dependent on host cell machinery for their propagation. In other words, they carry more genes that support their own survival compared with other viruses. As such, some think these large DNA viruses are evolutionary bridges between nonliving viruses and living organisms.

In a recent **Journal of Biological Chemistry** paper, researchers reported finding that a nucleocytoplasmic large DNA virus from the Mimiviridae family encodes genes that allow it to produce a rare type of sugar. Nucleocytoplasmic large DNA viruses have large genomes, and some are known to carry genes that encode glycosylation systems, including genes for enzymes and substrates required for the production of complex carbohydrates.

In the JBC study, the authors aimed to identify and characterize the first two enzymes encoded within a Megavirus chilensis gene cluster thought to be involved with a glycosylation pathway. Sequences from two genes in this cluster had been shown to be homologous to bacterial enzymes involved in the production of 2-acetamido-2,6-dideoxy-L-hexoses, which are types of sugars called 6-deoxy-hexosamines. What is striking about these 2-acetamido-2,6-dideoxy-L-hexoses specifically is that they are produced in the L-enantiomer as opposed to the more common D-enantiomer. Although the L-enantiomers of 6-deoxy-hexosamines have been observed on the surfaces of some bacteria, they are otherwise rarely found in nature.

Through a series of sequence, structural and activity analyses, the authors found that the first gene product in the cluster, Mg534, is a 4,6-dehydratase-5-epimerase. The second gene product, Mg535, is a bifunctional 3-epimerase, 4-reductase. Acting sequentially, Mg534 and Mg535 generate the L-enantiomer of the sugar UDP-L-N-acetylrhamnosamine, which is rare in nature like other 6-deoxy-L-hexosamines but confirmed by the authors to be present in M. chilensis viral particles.

No homologues were found in giant viruses from other groups for Mg534 or Mg535 or for Mg536, the next gene product in the cluster that the authors identified as a potential GlcNAc 2-epimerase. However, other large DNA viruses are known to carry genes for rare sugar production, indicating there is a specific and important role for these sugars in the lifecycle of these viruses.



TEM images of Megavirus chilensis in infected Acanthamoeba castellanii cells.

The authors speculate that these sugars could be involved in mediating interactions between viral particles and host cells or perhaps in protecting the virus from cellular components during replication within host cells.

The authors indicate that carrying genes for certain sugars and metabolic pathways makes these viruses less dependent on host cells for these components. In turn, this may allow the viruses to infect a greater range of host cells.

Kelly Hallstrom (kelly.n.hallstrom@gmail.com) is a Ph.D. candidate at the University of Massachusetts Medical School.

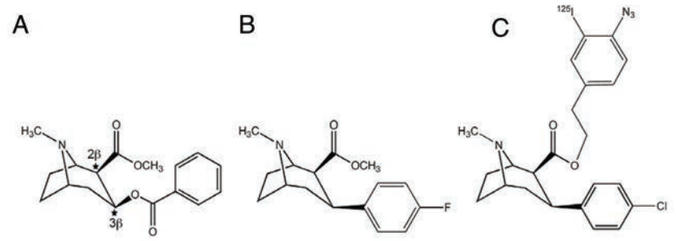
Unraveling the ligand–protein interaction between cocaine and the dopamine transporter

By Jen McGlaughon

What do schizophrenia, attention deficit hyperactivity disorder, Parkinson's disease, bipolar disorder, autism spectrum disorder and cocaine all have in common? It turns out they are all linked to the role of the dopamine transporter, or DAT, which is an integral membrane protein responsible for the reuptake of dopamine from the synapse. Drugs that bind to DAT to prevent the reuptake of dopamine are used to treat the diseases mentioned above, among others.

However, cocaine, which is also a DAT blocker, leads to profoundly negative effects, such as addiction and psychomotor stimulation. Understanding how different DAT blockers produce distinct behavioral and chemical responses could be the key to developing better drugs to treat dopaminergic disorders and also addiction to DAT blockers like cocaine.

Despite the wide use of DAT blockers, there is still relatively little known about how the drugs interact with DAT. The authors of a paper in the **Journal of Biological Chemistry** sought to determine precisely how cocaine interacts with DAT, thereby leading to a better understanding of how different responses are generated.



Chemical structures of cocaine, CFT, and RTI 82.

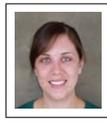
Rejwi Acharya Dahal of the University of North Dakota School of Medicine and Health Sciences and collaborators used computational and biochemical approaches to identify the site of cocaine binding to DAT. The authors performed irreversible labeling with a cocaine analog, RTI 82, which has a 4′-azido-3′-iodophenylethyl, or AIP, moiety that forms a covalent bond with the protein upon ultraviolet irradiation. Using computational modeling and small-molecule docking, they were able to narrow down the possible site of AIP adduction to the Phe319 residue of the transmembrane domain TM6.

IMAGE COURTESY OF THE DRUG ENFORCEMENT ADMINISTRATION

To verify their model, the authors used several biochemical approaches: methionine substitution of the residues flanking Phe319 and cyanogen bromide mapping of the mutants, followed by substituted cysteine accessibility method protection, or SCAM, analysis.

They concluded that the binding of the tropane pharmacophore of the analog occurs within the DAT S1 site, which is highly conserved in mammalian transporters. The binding leads to the AIP adduction to the Phe319 residue, which is situated at the interface between the S1 and S2 sites. This likely plays a key role in transitioning of the transporter between conformational states, and the authors predict that cocainelike molecules block transport by inhibiting these transitions.

By better understanding how cocaine binds to DAT, future research can begin to focus on developing improved strategies for treating cocaine addiction.



Jen McGlaughon (jla254@cornell.edu) is a graduate student in the molecular biology and genetics department at Cornell University.

A new epigenetic target for treating all cancers

By Maggie Kuo

What doesn't kill you makes you stronger. This slogan for personal resilience is unfortunately the motto by which cancer cells exist. Reduced oxygen, which usually prompts cells to die, makes tumor cells harder to destroy and more resistant to cancer treatments. However, investigators at the Nanyang Technological University in Singapore recently reported in the journal **Molecular & Cellular Proteomics** a promising drug target that could stop the tumor before it builds its strength.

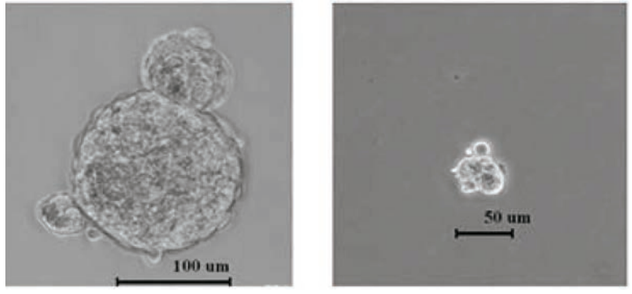
In the early stage of cancer, the tumor grows faster than blood vessels can, reaching a point at which it becomes deprived of oxygen, or hypoxic. To sustain itself, the tumor takes on new physical characteristics and acquires improved survival and self-renewal capabilities. Attacking the tumor at this advanced stage becomes challenging because of its diverse traits and enhanced hardiness. However, tumors of all cancer types have to go through the initial hypoxic stage, so drugs targeting the proteins responsible for the hypoxia-induced evolution could be used for a wide range of cancers.

Gene expression requires not only the direct translation of the DNA into proteins but also physical alterations to the structure of the chromatin to allow for the transcription. Several studies have ascribed the changes in gene expression of cancer cells to chromatin-structure modifications. Many have investigated the role of transcription factors called hypoxia-inducible factors in controlling these epigenetic changes. However, hypoxia can induce changes outside of hypoxia-inducible factors, motivating the researchers led by Siu Kwan Sze to investigate the role of HP1BP3, or heterochromatin protein 1, binding protein 3, a novel chromatin-organizing protein they had previously discovered to be important in chromatin condensation and gene-transcription regulation.

The investigators subjected A431 squamous cancer cells, a cell line commonly used to study tumor progression, to three oxygen-level conditions that reflected the phases of a tumor's development. Normoxic, normal oxygen level, represented the phase during which the single cancer cells proliferate into a tumor. Hypoxic corresponded to the point at which the tumor has outgrown the surrounding blood vessel network. Hypoxic followed by normoxic simulated the late stage, when the tumor evolves to sustain itself. The researchers used quantitative proteomic techniques to identify which chromatin-bound proteins changed with the oxygen conditions. They found high amounts of HP1BP3 in the condensed chromatin from cells exposed to hypoxia compared with those in normoxic conditions. They also observed that hypoxic cells had more condensed chromatin than normoxic cells. Their data supported that HP1BP3 was sensitive to oxygen level and that the chromatin compacting that occurred with hypoxia could be mediated by the protein.

The investigators next removed HP1BP3 from the cells to identify the downstream genes that the protein affected. They reported that fewer HP1BP3-deficient cells survived when exposed to hypoxia, radiation and chemotherapy drugs compared with HP1BP3-present cells. HP1BP3-deficient cells also formed smaller tumors, indicating that these cells had reduced renewal capacity. The data supported that HP1BP3 regulated genes that conferred self-proliferation and increased survival.

The authors conclude that hypoxia influences HP1BP3's interaction with the chromatin to promote condensation. This change shifts the genes expressed to favor traits that promote cell vitality. Depleting HP1BP3, then, could diminish the tumor's progression and increase the tumor's sensitivity to cancer treatments, killing the tumor at the hypoxic stage before it becomes stronger.



HP1BP3-deficient cells (right) formed smaller tumor spheres than HP1BP3-present cells (left) in hypoxia.

Maggie Kuo (mkuo@asbmb.org) is an intern at ASBMB Today and a Ph.D. candidate in biomedical engineering at Johns Hopkins University.

Taking aspirin plus fish oil? Consider this

By Aditi Dubey

A study in the **Journal of Lipid Research** recently focused on using natural compounds to combat inflammation. Researchers at the University of Western Australia showed that fish oil supplementation in healthy adults increased factors that help mitigate inflammation. What's more, their results also indicated that aspirin may not have any additional benefits when it is taken with fish oil.

Our immune system is a highly complex network of biological processes that initiates rapid, protective responses upon injury or infection. Inflammation is a part of this immune response, triggered by factors such as histamines and prostaglandins that are released into the extracellular milieu while macrophages neutralize pathogens and injured tissues are restored. We recognize inflammation as pain, redness and swelling. However, inflammation must be controlled and cleared in a timely fashion for normal health. In fact, prolonged and excessive inflammation can lead to several problems, such as arthritis, periodontal disease and atherosclerosis.

After damage is contained, small molecules called mediators help resolve inflammation. Of these mediators, specialized pro-resolving mediators, or SPMs, are dual-acting anti-inflammatory and pro-resolution molecules that are synthesized locally at the site of infection itself, so that the resolution can be fast and doesn't accidentally affect healthy tissues.

SPMs stimulate removal of dead cells and microbes from the inflamed site. Clinicians manage inflammation with natural and synthetic compounds that act on SPMs and regulate their concentration.

The study in the JLR by lead author Anne Barden and colleagues focused on SPM derived from eicosapentaenoic acid and docosahexaenoic acid, two essential n-3 polyunsaturated fatty acids known as EPA and DHA for short. Metabolism of EPA and DHA by lipoxygenases and acetylated COX-2 produces SPM. In a double-blind, controlled trial, the researchers gave human subjects fish oil capsules for n-3 fatty acid supplementation in conjunction with either aspirin or a placebo.

Aspirin is a nonsteriodal anti-inflammatory drug that acetylates COX-2. In 2010 alone, an estimated 43 million adults in the United States used aspirin regularly. Despite their popularity, NSAIDs have been associated with gastrointestinal bleeding and renal problems. Therefore, having a natural alternative to NSAIDs for managing inflammation could be beneficial.

Using mass spectrometry to measure levels of SPM in plasma, the authors demonstrated that fish oil increases SPM in as few as five days in healthy humans. However, aspirin did not show synergistic benefits when taken with the supplements. This presents an interesting outcome: A natural compound increases SPM enough that aspirin is not needed. But this is the case for healthy individuals. To establish the benefits of n-3 fatty acid supplements over aspirin, researchers must examine the dose, duration and side effects of these agents in both healthy individuals and those with chronic inflammation.

The anti-inflammatory benefits of long-chain polyunsaturated fatty acids derived from marine oils long have been accepted. Now, with this study, researchers can begin to understand the mechanism by which they counteract inflammation and perhaps piece together an improved approach for dealing with inflammation.

This presents an interesting outcome: A natural compound increases SPM enough that aspirin is not needed.

Aditi Dubey (dubeyad@scarletmail.rutgers.edu) is a graduate student studying the mechanism of selenocysteine incorporation at Rutgers University Robert Wood Johnson Medical School.

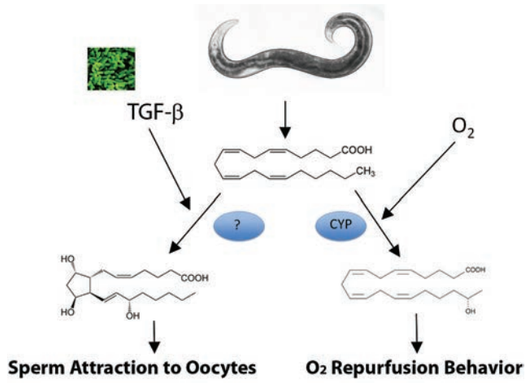
C. elegans studies uncover roles for eicosanoids in development and stress

By Jennifer L. Watts

Eicosanoids are powerful, short-range signaling molecules derived by oxygenation of 20-carbon polyunsaturated fatty acids, or PUFAs. These effectors, including prostaglandins, leukotrienes and thromboxanes, are produced in mammals by cyclooxygenase and lipoxygenase enzymes and act as regulators of pain, inflammation, immunity, blood pressure and reproduction. Two recent studies indicate that eicosanoids generated by cyclooxygenase-independent pathways mediate reproductive and behavioral functions in the roundworm Caenorhabditis elegans.

Prostaglandins and other eicosanoids are produced in many invertebrates, although their precise functions in physiology are not well understood (1). There is no evidence for cyclooxygenase or lipoxygenase enzyme activities in C. elegans (2), even though these nematodes synthesize a wide range of 20-carbon PUFAs, including arachidonic acid and eicosapentaenoic acid (3, 4). Synthesis of PUFAs is important, because C. elegans mutants that lack the ability to insert double bonds in fatty acids display a range of developmental and neurological defects (4 – 7). The new studies describe crucial functions for specific eicosanoids derived from PUFAs.

Sperm must locate an oocyte for successful reproduction. In C. elegans, sperm attraction to oocytes requires PUFAs, which are precursors for F-class prostaglandins synthesized independently of cyclooxygenase activity (8 – 10). Recently, Michael Miller's group at the University of Alabama showed that pheromone-sensing neurons in the C. elegans nose secrete a TGF-β ligand that stimulates the cyclooxygenase-independent synthesis of PGF1α and PGF2α in the germ line during favorable growth conditions (11). When food is limited and nematode crowding occurs, secreted ascaroside pheromones reduce TGF-β production (12). TGF-β levels in neurons signal through conserved pathways to regulate R-Smad activity in developing oocytes, which inhibits the conversion of PUFAs into F-class prostaglandins (11). When fewer prostaglandins are produced by oocytes, sperm are less efficient at locating the fertilization site, leading to reduced fertilization rate. Thus, environmental conditions sensed by females ultimately affect sperm function.



The C. elegans genome also encodes several PUFA-metabolizing cytochrome P450 enzymes, or CYPs, which convert eicosapentaenoic acid and arachidonic acid to epoxide and hydroxyl derivatives (2, 13). A recent study from H. Robert Horvitz's lab at the Massachusetts Institute of Technology used an unbiased genetic screen to discover a role for polyunsaturated fatty acids and CYP-13A12 in an eicosanoid-mediated response to a movement behavior that occurs after oxygen deprivation followed by reoxygenation (14). In mammals, oxygen deprivation followed by reoxygenation causes reperfusion injury due to inflammation and oxidative damage. In C. elegans, this damage can be modeled by examining movement increases that occur after the transfer of worms from no oxygen to 20 percent oxygen. The EGL-9 protein uses molecular oxygen to hydroxylate the hypoxia-inducing factor, or HIF, inhibiting HIF transcriptional activity. Pre-exposure to low oxygen concentrations or inhibition of EGL-9 activity protects mammals from reperfusion injury and blocks the C. elegans movement response. The Horvitz study showed that in the presence of oxygen CYP-13A12 produces eicosanoids that drive the reperfusion response (14).

Thus, C. elegans provides a means to dissect phenotypes and pathways employing cyclooxygenase-independent synthesis of eicosanoids. Importantly, cyclooxygenase-independent synthesis of F-class prostaglandins also has been observed in mammals (11). Furthermore, CYP-generated eicosanoids likely are involved in more diverse physiological responses than previously appreciated.

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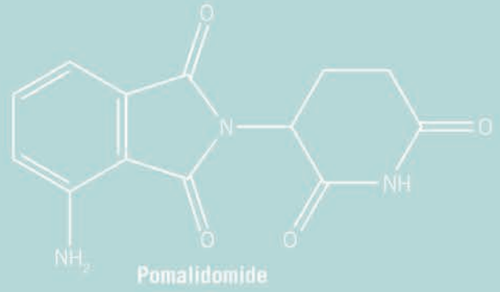

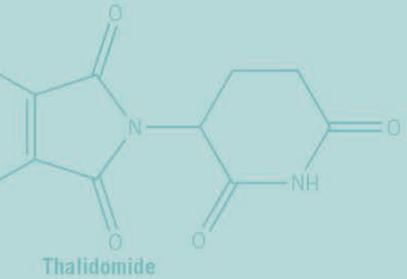

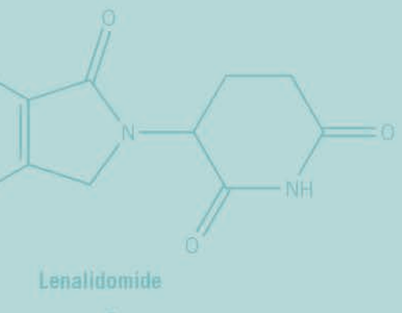

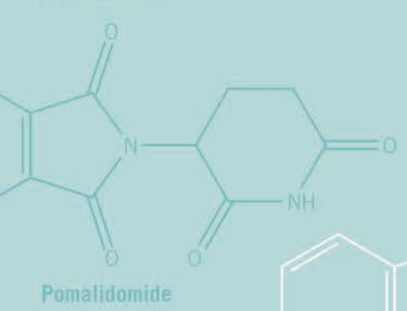

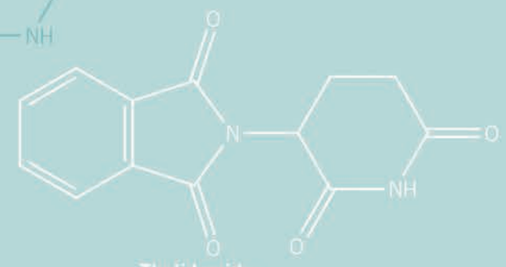

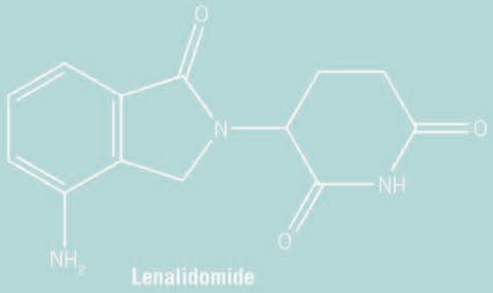

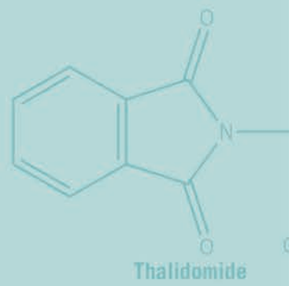

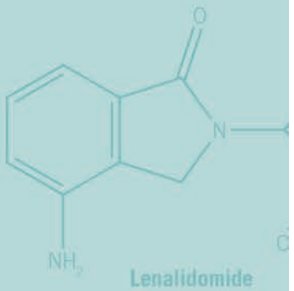

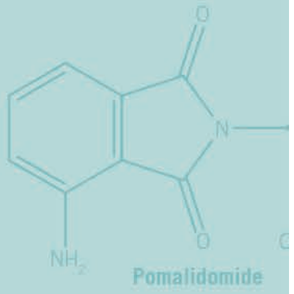

The drug of good and evil

Thalidomide's unusual mechanism of action is starting to give researchers hints as to why it can save or wreck lives

By Rajendrani Mukhopadhyay

Thalidomide is a molecule with a split personality. Notorious as the drug that caused thousands of babies to be born with grotesque deformities in the 1950s, it now has become the frontline defense for some cancer and immune-compromised patients. Until recently, researchers did not understand how this single molecule could have such extreme effects. But emerging research is showing that thalidomide acts at the molecular level in an unusual way, which could explain its Dr. Jekyll-and-Mr. Hyde effects.

Over the past four years, several groups have shown that thalidomide and drugs like it bind to a component in a ubiqutin ligase complex. Upon binding, thalidomide and its structural analogs change the proteins that the ubiquitin ligase targets for degradation.

The fact that thalidomide modifies interactions between proteins has been a revelation. Protein-protein interactions "have always been considered difficult to target with small molecules," says Nicolas Thomä at the Friedrich Miescher Institute for Biomedical Research in Switzerland. When an established drug like thalidomide was shown to affect protein-protein interactions, Thomä adds, "that immediately caught our attention."

As William Kaelin, a Howard Hughes Medical Institute investigator at the Dana-Farber Cancer Institute, notes, thalidomide has made researchers rethink how they can approach development of therapeutics. He says, "Thalidomide opens up a new paradigm for how you could drug proteins."

Troubled history

Thalidomide first commercially appeared in 1957 when a German company called Chemie Grünenthal, later known as Grünenthal, began marketing the drug in Europe to treat morning sickness in pregnant women as well as insomnia. According to a 2013 New York Times story, the drug was so in demand in some European countries that it became nearly as popular as aspirin. Soon, 40 countries around the world, though the United States was not among them, had made thalidomide available.

But the ominous signs quickly appeared. The first known victim of thalidomide was a girl born on Christmas Day of 1956 to a Grünenthal employee. The baby had no ears. By 1960, more than 10,000 women who had taken the drug while pregnant had given birth to babies with ghastly physical deformities, including spinal cord defects and flipperlike arms and legs. About 40 percent of the babies, known as "thalidomide babies," are thought to have died within the first year of birth.

Few of these babies were born in the U.S. In 1960, a new employee joined the U.S. Food and Drug Administration. As an ease-into-the-job type of project, new hire Frances Oldham Kelsey was asked to review the application for thalidomide for approval for use in the U.S. As Kelsey looked through the information supplied by Grünenthal and its U.S. distributor, William S. Merrell, she grew concerned about the lack of safety information for the drug. Kelsey doggedly pursued more safety data, which led to the outing of evidence in Germany in the fall of 1961 that linked birth defects to the drug. The next year, the drug was withdrawn from the global market.

The scale of the disaster wrought by thalidomide was so large that the World Health Organization launched its International Drug Monitoring program in 1968. Grünenthal apologized to thalidomide victims in 2012.

Discovering other uses

Although thalidomide had become the poster child for a drug gone

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wrong, doctors continued to prescribe it – but for different reasons. In 1964, an Israeli doctor at the Hadassah University Hospital, Jacob Sheskin, prescribed thalidomide for a leprosy patient's insomnia. The patient had a painful reaction to leprosy called erythema nodosum leprosum, which brings on fever, weight loss and arthritis. Much to Sheskin's surprise, the patient's condition dramatically improved. Sheskin then tried the drug on several other patients and got the same result.

The WHO carried out a trial in the 1970s and determined that thalidomide was then the best treatment option for erythema nodosum leprosum. In 1998, Celgene won FDA approval to market the drug to treat skin lesions caused by leprosy. The drug was administered with stringent controls to make sure female patients did not become pregnant during the course of the treatment. However, once other drugs, such as prednisolone, were shown to be more effective for treating leprosy, the WHO no longer supported the use of thalidomide. Brazil is one country that continues to use thalidomide to treat leprosy. About 1,000 Brazilian babies have been born with thalidomide defects in the past two decades because of inadequate supervision during the drug's administration.

In 2000, at a meeting of the American Society of Clinical Oncology, Bart Barlogie at the University of Arkansas for Medical Sciences reported that thalidomide slowed the progression of multiple myeloma in people who had failed to respond to conventional therapy. After sufficient case studies accumulated, the FDA extended its approval of thalidomide to treat multiple myeloma in 2006.

Currently, Celgene markets thalidomide along with two structural analogs it has developed, lenalidomide and pomalidomide. All three are approved by the FDA to treat multiple myeloma and have become frontline drugs for treating the relapsed and more resistant cases of the disease. Multiple myeloma is a cancer caused by malignant plasma cells. Under normal circumstances, B cells mature into plasma cells, which are immunoglobin factories. But when plasma cells become cancerous, they spin out of control and produce bone tumors. A patient has multiple myeloma when he or she has more than one tumor. Though structurally similar, lenalidomide and pomalidomide are more efficacious than thalidomide in treating multiple myeloma. The three drugs are known collectively as immune modulating drugs, or IMiDs.

Mysteries of the molecular mechanism

The mechanism by which thalidomide and the other two IMiDs acted was not understood until Hiroshi Handa at the Tokyo Medical University and colleagues published a paper in the journal Science in 2010. In that paper, they identified a protein called cereblon that was bound by thalidomide. Cereblon, which is ubiquitously expressed, belongs to an ubiquitin ligase complex. Thomä says there were many publications on a plausible mechanism for thalidomide's mode of action, but Handa's team was the first to pull out cereblon. "They, without a doubt, established thalidomide as a molecule that binds ubiquitin ligase," he says.

The finding made researchers sit up for two reasons. Conventional thinking had dictated that drugs couldn't target ubiquitin ligases, because the enzymes were much too essential for protein degradation and turnover. Also, scientists had assumed the ubiquitin ligase complex had too many protein-protein interactions within it for a drug to target one of the interactions specifically.

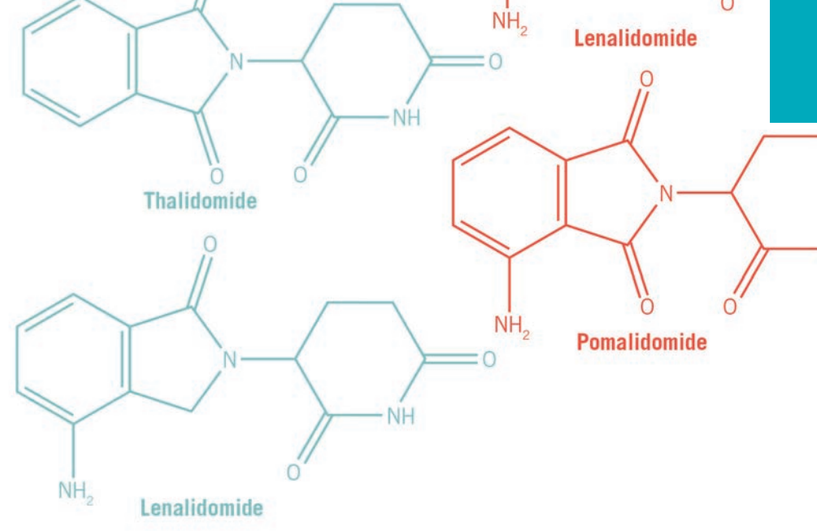
But here was thalidomide, developed some 50 years ago on solely phenotypic screens, capable of binding to a part of a ubiquitin ligase complex. The binding hinted that "some effects that you see of thalidomide, good and bad, have something to do with the ubiquitin ligase" modifying its function, says Thomä.

Other studies followed using the other two analogs of thalidomide. Two teams, one led by Kaelin and the other by Benjamin Ebert at Harvard Medical School, independently showed earlier this year that the ubiquitin ligase is able to target two zinc-finger transcription factors, IKZF1 and IKZF3, for degradation when lenalidomide is bound to cereblon. A group from Celgene also published the same result. The finding began to give clues as to why IMiDs work against multiple myeloma.

IKZF1 and IKZF3 have opposite effects on the survival of T and B cells of the immune system. In the case of T cells, IMiDs help the cells survive by downregulating IKZF1 and IKZF3. When those two transcription factors are expressed, they repress the expression of the interleukin-2 gene in T cells and keep the cells dormant. However, when IKZF1 and IKZF3 are degraded, which is what happens when an IMiD binds to the ubiquitin ligase, interleukin-2 gene expression triggers the stimulation of T cells.

In contrast, IMiDs cause malignant B cells to die. The presence of IKZF1 and IKZF3 normally promotes the development of the B cells into mature, antibody-producing plasma B cells. The degradation of IKZF1 and IKZF3, which, again, is what happens when an IMiD binds to the ubiquitin ligase, triggers apoptosis of B cells. In myeloid myeloma, B cells turn malignant, so that's why IMiDs are effective in treating the disease.

"It's always been a paradox," says



Rajesh Chopra of Celgene of the IMiDs' ability to kill malignant B cells but trigger T-cell stimulation. But the emerging picture of the mechanisms of action of IMiDs on IKZF1 and IKZF3 "explains that duality of function." The differences in effect, says Chopra, allow researchers to start thinking about how to exploit the variations in protein networks inside cells with a single drug.

Finding more puzzle pieces

This summer, Thomä and colleagues reported the crystal structure of thalidomide bound to cereblon. That work revealed another aspect of thalidomide's mechanism of action: When the drug binds to cereblon, the protein can't bind to one of its usual targets, the homeobox transcription factor MEIS2. Downregulation of MEIS2 in chicken embryos at the proximal limb-bud region has been shown to be important for limb development.

Putting together the puzzle pieces that they have so far, researchers think that IMiDs modify cereblon's choice in binding partners, making it turn to new substrates like IKZF1 and IKZF3 at the cost of losing MEIS2 and possibly other native substrates. "Here's an example where the drug bound to the protein alters – in a qualitative way – the function of the protein," says Kaelin.

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"It is perhaps the most exciting aspect of the whole field now. It's a completely novel mechanism of action for a drug, where the presence of a drug modulates the substrate specificity of the ubiquitin ligase."

– BENJAMIN EBERT, HARVARD UNIVERSITY

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But researchers stress that they still don't know which substrate causes thalidomide's ugly side effects. "The story is not simple," cautions Handa. "Maybe other substrates might be involved."

Handa's group, in collaboration with researchers from Celgene, also has produced a crystal structure of lenalidomide bound to cereblon and one of its binding partners in the ubiquitin ligase complex. The structure shows how three tryptophan residues in the C-terminal domain of cereblon are critical for binding to one part of the IMiD's structure.

The structures collected by various research groups also showed that another part of the drug partially sticks out from the complex into solution, hinting that this exposed portion of the drug could be responsible for the altered preference of substrates targeted for ubiquitination.

"Since part of the molecule is exposed in the putative substrate-binding region, the small molecules themselves may form part of the interface with the substrate adaptor and the substrate," says Ebert, who has consulting and research collaboration ties with Celgene. The molecules "may directly modulate what proteins bind to the cereblon and therefore what proteins get ubiquitinated and degraded."

Thalidomide, lenalidomide and pomalidomide all bind to the same site on cereblon at its C-terminal region. But because they have a number of differences in the part of the structure that sticks out into the solvent, researchers say that differences at the atomic scale, at one or two carbon sites on the rings of the drugs, may explain the differences in efficacy of the three drugs for treating multiple myeloma. The finding that a few atomic changes make a significant impact on the efficacy of the different IMiDs "highlights that the iMIDs are not the same," says Chopra.

Indeed, Celgene scientists insist that lenalidomide and pomalidomide not be lumped together as "thalidomide analogs." "They look structurally the same, but the substrate of consequence may be different," says Chopra.

Hope for more

The recent findings are exciting, say the researchers, because they suggest that drugs developed down the road may be able to modify the activity of a protein complex rather than simply target it for disruption. "It is perhaps the most exciting aspect of the whole field now," says Ebert. "It's a completely novel mechanism of action for a drug, where the presence of a drug modulates the substrate specificity of the ubiquitin ligase."

But fundamental questions remain.

For example, although thalidomide causes limb deformations in humans, zebrafish and chickens, it doesn't cause fetal defects in mice or rats, Handa points out. This prompts the question: What is different about the rodent and murine forms of cereblon that do bind thalidomide but somehow bypass its devastating effects?

Researchers also point to the 1995 work of Robert D'Amato's group at Boston's Children Hospital, which demonstrated that the drug inhibited the growth of blood vessels and had antitumor activity. No one has yet figured out what causes the drug's antiangiogenic effects or, for that matter, its sedative effects, which is the effect that put thalidomide on the world stage in the first place in the 1950s.

"There's a bit of a discovery phase in place right now so that we better understand the range of functions that cereblon can assume when occupied by different IMiDs," says Celgene's Tom Daniel. And Ebert adds, "There is an enormous hope that this could be the beginning of a new class of drugs that induces degradation of a variety of disease-relevant proteins."

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DEFYING STEREOTYPES:

‘More than pretty’

Former Miss America Nina Davuluri confronts stereotypes about beauty, ethnicity and intelligence

By Geoffrey Hunt and Rajendrani Mukhopadhyay

Beauty. Glamour. Style. These are the characteristics normally associated with beauty queens. And make no mistake: Miss America 2014 Nina Davuluri has each of them in abundance. But she also is smart as a whip, with a degree in brain behavior and cognitive science and a passion for STEM education. These qualities have helped make Davuluri one of the most visible examples of how misleading stereotypes can be.

“Science was pushed in my household since I was very young,” says Davuluri, a Michigan native of Indian descent. “It was something I really excelled in.” As the daughter of two physicians, she concedes, “it was just my mindset that I was going to be a doctor because that’s what my parents told me.”

Helping to motivate her were the teachers who took the time to foster her interest in science and math. Davuluri has particular affection for her fifth-grade teacher: “I was struggling with grasping a concept in a math class,” she recalls. “She took the time after school to sit down with me and help me through that process. It was the first time I remember having a breakthrough moment when something just clicks in your brain and the lightbulb goes off and you go, ‘Oh, I get it!’”

Outside of the classroom, Davuluri’s determined nature drew her to a number of competitions, starting with a dog/owner lookalike contest that she won when she was in third grade. When she was 16, Davuluri started competing in beauty pageants. She was named Miss Michigan Outstanding Teen in 2006 and came in second in the 2007 Miss Teen America competition, collecting enough winnings to support her undergraduate education at the University of Michigan, from which she graduated in 2011.

Motivated by the allure of scholarship money that could help support her pursuit of an advanced degree in medicine, Davuluri returned to pageantry competition in 2012. After being named Miss New York 2013, she was selected as a contestant for the Miss America pageant. On September 15, Davuluri beat out 51 other competitors to become Miss America 2014.

However, after being crowned, Davuluri was subjected to a slew of disparaging comments about her ethnicity. Never one to back down, she faced her critics head-on, establishing her personal Miss America platform as “Celebrating diversity through cultural competency.” “The biggest thing I realized is that many of these remarks aren’t necessarily meant to be malicious but are simply a factor of ignorance,” she explains.

The goal of her platform is to focus attention on “understanding everyone’s beliefs and backgrounds and finding that common ground so we can all communicate in an open, honest and respectful manner,” says Davuluri. “This is something I’ve essentially been promoting my entire life.”

IMAGE COURTESY OF BRUCE BOYAJIAN/THE MISS AMERICA ORGANIZATION

Nina Davuluri

IMAGE COURTESY OF THE US DEPARTMENT OF EDUCATION

Nina Davuluri joins U.S. Attorney General Eric Holder, left, and U.S. Secretary of Education Arne Duncan at an event about STEM education.

Davuluri also has used her spotlight to advocate tirelessly for science, engineering, technology and math education. She has traveled more than 200,000 miles in the past year, giving dozens of speeches promoting STEM at middle and high schools, lobbying members of Congress and appearing at high-profile events with the likes of President Obama and U.S. Secretary of Education Arne Duncan. “I’m out there meeting with people, advocating for causes that are very important,” she points out. “The general public sees that one night of the competition” on TV, she laments. “They don’t see what we do the other 364 days of the year.”

Davuluri insists she is not any different from her fellow contestants. “A wide array of talent is on the Miss America stage,” she says. “We really do go on to become doctors and lawyers and physicians and engineers.” To support the effort of these women in their scholarly pursuits, the Miss America organization established the Miss America Foundation STEM Scholarship in 2013, which Davuluri is helping to underwrite with a portion of the $92,000 she won from the pageant.

Davuluri’s connection to education came full circle when she gave a speech last year at her alma mater, St. Joseph High School in Michigan, where she got to thank her former teachers and “tell them how much of an impact (they had),” she says. “I can honestly say I wouldn’t be as good of a Miss America if it weren’t for my education.” Now a role model herself, Davuluri has helped ensure that the next time a little girl hears the line in the pageant’s theme song about how Miss America is “more than pretty,” she’ll be able to believe it.

Geoffrey Hunt (ghunt@asbmb.org) is the ASBMB’s public outreach coordinator. Follow him on Twitter at www.twitter.com/thegeoffhunt. Rajendrani Mukhopadhyay (rmukhopadhyay@asbmb.org) is the senior science writer and blogger for ASBMB. Follow her on Twitter at www.twitter.com/rajmukhop.

There She Is, Miss America

There she is, Miss America
There she is, your ideal
The dream of a million girls who are more than pretty
Can come true in Atlantic City
For she may turn out to be the Queen of femininity

There she is, Miss America
There she is, your ideal
With so many beauties she took the town by storm
With her all-American face and form

And there she is
Walking on air, she is
Fairest of the fair, she is
There she is – Miss America

LYRICS BY BERNIE WAYNE

Young grasshopper becomes the teacher

By Paul Sirajuddin

As he summer approached, new faces started appearing in the hallway, lab and office spaces. And as if by cue, shared equipment was found to have been accidentally mishandled or sometimes put offline. Having gone through this before, I knew that summer intern season was upon us.

As a second-year postdoc at The Johns Hopkins School of Medicine now, I have had the opportunity over the years to mentor many people, ranging from high-school students up to visiting faculty. Though we had a handful of interns in our group this year, I was tasked with directly supervising one in particular: a bright and cheery rising second-year medical student from California.

Now that fall has arrived, I look back and ask myself: Why have summer interns every year?

Since our lab mainly involves basic science in studying the effects of potential chemotherapeutic drugs in cancer-cell lines, any intern coming to work here has to get caught up to speed on cell and molecular biology techniques relatively quickly to accomplish anything for the summer. There's little room for error — despite the huge learning curve for both the mentor and the mentee.

Looking through my intern's résumé, I noticed she had a bit of relevant lab experience. A huge sigh of relief! Still, there was a great deal of background information and new techniques to teach her for our constantly evolving projects.

As I started training her on the techniques we use, I debated just how much detail and effort to give and how ambitious a project to assign her, knowing she would be leaving in only two and half months.

At times, mentoring a summer intern can feel like doing the work of two people. Indeed, there were dozens of questions, some of which I did not know the answers to.

After we got to know each other, I recalled my time shortly after college when I was a summer intern at the National Cancer Institute with the goal of learning as many techniques as possible. I was fortunate to work with people who were passionate about their work and who went to great lengths to make sure I learned and understood what I was working on. I realized that a collaborative environment is beneficial not only to the lab goals but also to my own. For this year's summer intern, I knew the hours would be long, but I decided to challenge both of us to be ambitious and continue this approach.

At times, mentoring a summer intern can feel like doing the work of two people. Indeed, there were dozens of questions, some of which I did not know the answers to. Having to spend extra time showing my student multiday techniques in addition to having my own responsibilities meant I ended up staying late into the evenings. Then there was a particular Western blot assay that just did not seem to cooperate, and we both had to troubleshoot, painstakingly going through every step of the assay to see where something might have gone wrong.

As time went on, my intern became more competent and almost fully independent and produced beautiful results. Seeing her present her results with confidence at the end of the summer seminar series, I was proud of all she had accomplished in such a short time and knew that she had had a worthwhile experience.

I found, in mentoring, that I learned much more about myself and what I truly understood. For me, knowing that I made a positive impact in someone else's career gave me the motivation to perform at my best, maintain a higher work ethic standard and never stop learning. Although it was more work on my part than anticipated, the extra time put in achieved both of our goals.

Next summer might be many months away, but I am already looking forward to having more interns.

Paul Sirajuddin (psiraju1@jhmi.edu) is a second-year radiation oncology postdoctoral fellow at The Johns Hopkins School of Medicine. A native of Michigan, he ventured to the East Coast for a postbaccalaurate fellowship at the National Cancer Institute in 2008 and then earned his Ph.D. from the Georgetown University Lombardi Comprehensive Cancer Center in 2013.

Meet Charlie Garnett Benson

By Andrea Anastasio

Tell us about your current career position.

I am an assistant professor at Georgia State University, an urban, public research university in Atlanta. In addition to running my research lab, I teach introductory biology and tumor immunology. I have also taught molecular biology, principles in biology for biology majors, and a seminar on careers in biology.

What are the key experiences and decisions you made that have helped you reach your current position?

Wow. How did I get here? That is the million-dollar question, right? Because all the statistics say there are very few people that look like me in my current position. The key decision that helped me reach this position was choosing my college major based on what I naturally excelled at. I changed my major four times before I finally decided to pick something I was actually good at, even though I had no idea what career I was going to use it for! I knew at the time that I was great at science. Even though I absolutely did not want to be a medical doctor, I decided to switch my major to biology anyway. The key experience that helped me reach my current position was being a (Minority Access to Research Careers) program fellow at Hampton University after I changed my major to biology. In addition to receiving all of the career guidance, research experience and training tools as a part of the program, I also found my first mentor, Edward G. Smith, who is still a mentor to me to this day.

How did you first become interested in science?

I don't remember a time when I was not interested in science. It was always my favorite subject, and all of my science teachers throughout elementary and high school were always my favorite ones. I thought it was something about them at the time, but later I realized it was the subject.

Were there times when you failed at something you felt was critical to your path? If so, how did you regroup and get back on track?

Yes! All of the time. How can you not fail when you are the first to discover or try something new? It happens all of the time. My most vivid memory of failing comes when I think back to not doing so well the first time I took my Ph.D. qualifying exam in graduate school. Since I was the first African-American female to go through that particular program, I felt like a complete failure. But I realized that this was the only career for me and that I was more than capable of giving them what they wanted and to not take it personally. So I regrouped and gave them more than, I am sure, anyone else had the first or second time taking that exam! I realized afterward that I was a better scientist as a result of that experience. So, from that point on, whenever I felt like I failed at something critical to my career path, I knew that it was serving its purpose to make me a stronger scientist. I don't look at obstacles along my path as obstacles anymore, because I realize they are the path.

What advice would you give to young scientists from underrepresented backgrounds who want to pursue careers in science similar to yours?

Don't stop until you get here. There are a lot of statistics demonstrating that while women get 50 percent of the Ph.D.s in science and technology, only a tiny fraction are from underrepresented backgrounds. There is a drop-off after graduate school and postdoctoral studies that must be reversed. I think people spend a lot of time telling young scientists about all the challenges they will face along the way, and not enough of us are telling them how absolutely fantastic a career this is once you get here. Unfortunately, we don't get the benefit of having our career glamorized all over the popular media like athletes and

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Casual learning over beers at Nerd Nite

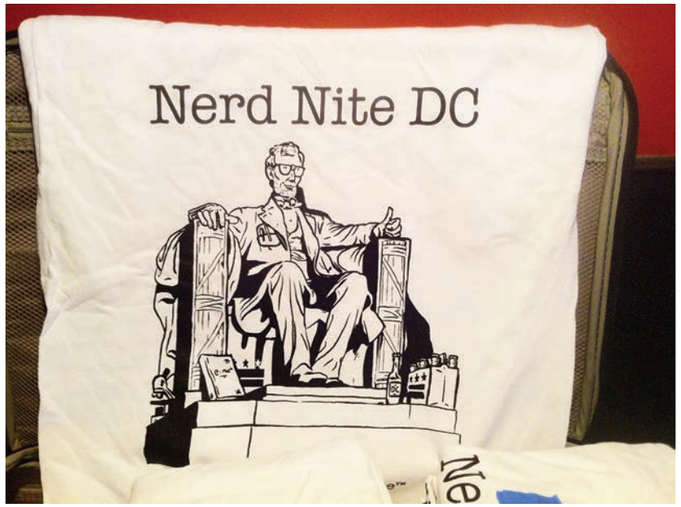
By Maggie Kuo

Zombies always point their tangent vectors toward their targets. Because they do so, I can calculate how much faster I need to run to avoid being eaten. I learned this zombie apocalypse survival tip and other surprising facts at Nerd Nite in Washington, D.C.

Nerd Nites can be found in more than 80 cities around the world. At these events, enthusiasts give 20-minute presentations on whatever topics inspire them. The D.C. Nerd Nite hosted Halloween-themed talks in October: the charmingly macabre world of illustrator and writer Edward Gorey, the 10 most bizarre mammals and how calculus can be used to fight zombies. Nerd Nites are held in bars, theaters and art spaces: It's learning over drinks.

The Nerd Nite event I attended could have been a local music show. The spotlights focused on the presenters on the stage, and the audience stood in the dim, blue-pink lighting. The bar in the back was never still, and indie music played overhead in between the presentations. TV screens were mounted throughout the venue so the audience in the back stood in different directions to see the slides instead of aligning toward the main stage. The crowd was supportive and receptive, following the two rules of Nerd Nite: "Please stay quiet(ish) during the presentations" and "Nerds get funnier with more drinks."

The presenters shared a passion for sharing their passions. Sara Nemati, a high-school biology and physical science teacher in Montgomery



County, Md., who talked about bizarre mammals, says, "I've always wanted to present, because I feel like I have the enthusiasm for science that I can share." Colin Adams, a mathematics professor at Williams College in Massachusetts, spoke about using calculus to fight zombies. Always thinking about "interesting ways to get people to listen to really beautiful mathematics long enough to understand how beautiful it is" and a fan of zombie shows and movies, he saw the "Pride and Prejudice and Zombies" adaptation of Jane Austen's "Pride and Prejudice" and was inspired to combine zombies and calculus.

The attendees were a mix of those who had gone to previous Nerd Nites and loved them and friends they brought to experience it for the first time. The people I talked to were involved in science in some way. I met several who worked in science policy, and the presenters and organizers were researchers, educators and outreach professionals. But everyone enjoyed enriching themselves and came out because a presentation piqued their interest and they wanted to hear more.

Nerd Nite offers a refreshing alternative to current social outings. "I work on educating science and tech, and there are not a lot of places where you can play with it and have fun with the material," says Cat Aboudara, the organizer of Nerd Nite in D.C. "I really like how this is a place where you can be excited about science and tech and history and it's still playful. It elicits conversation and laughter, and people being inspired and wanting to find out more."

Nerd Nite started in 2004 with an evolutionary biology Ph.D. student at Boston University, Chris Balakrishnan, and the Midway, the bar he frequented. Balakrishan studied the parasitic indigobird and conducted field research each fall in Cameroon. After being in the field for several months, he would return to the bar and regale the bartenders and patrons with his exploits. At one point, Matt Wasowski, the main organizer of Nerd Nite, recounts, the bartenders said, "Chris, we're sick of hearing you tell the same stories over and over again about the birds. Can you just get it over with in one fell swoop?" Balakrishnan recruited his colleagues to present their research at the bar, and Nerd Nite formed.

"Nerd Nite's overall goal is to make people slightly smarter for one night," Wasowski writes in an email, "and slightly drunker as well." Getting involved is simple: Attend a Nerd Nite and volunteer to present by submitting your contact information.

Maggie Kuo (mkuo@asbmb.org) is an intern at ASBMB Today and a Ph.D. candidate in biomedical engineering at Johns Hopkins University.

MINORITY AFFAIRS CONTINUED

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celebrities do. My advice is to realize that this is the best-kept secret career and for them to focus on that until they get here. That, and to realize that they won't have to go through it alone, even if they are the only person from an underrepresented background at their institution. There are established scientists everywhere who can help you navigate through difficulties when they come. That is a great benefit of pursing this career in the digital age, when some good advice or a good mentor is just a click or tweet away. In 2013, I began a company called Beyond the Codon with this exact mission in mind.

What are your hobbies?

Shopping, traveling and watching my son play the sport of each season.

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

I am inspired every time I hear a story about someone being the first to do something new. Someone had to be the first to do every new, bold or innovative thing. They all serve as role models, as they constantly remind me that if someone has to be the first, why not me? Heroes and heroines, for me, are all the individuals and their families who have battled cancer. Their stories are heroic and inspire me every day to keep going and make an impact in the treatments available for victims of this disease.

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Providing hope in a hostile environment

By Andrew D. Hollenbach

I used to be passionate about research. I still am, in its purest, most idealistic form: I love getting results that make me scratch my head in confusion or data that make us rethink a long-held hypothesis in ways that I could never have imagined. However, basic research has morphed from the search for such results into the acquisition of data to satisfy that ever-rising, ever-changing bar of achievement.

After having a major grant not discussed because of a "modest publication record in specialty journals" and a manuscript rejected after major revisions due to an unfair review by someone I believe to be a contentious competitor, I feel like the main character in the children's book "Alexander and the Terrible, Horrible, No Good Very Bad Day" by Judith Viorst. As the bar to obtaining funding and getting published has been raised to almost unachievable levels, this means I must consider halting my research program. In these difficult times in academic science, which are hitting my research program particularly hard, I ask myself, "Why do I do this? Why do I subject myself to working hard and doing my very best with little to no recognition?"

Whenever I feel like this, I think back to my years as a postdoctoral researcher at St. Jude Children's Research Hospital in Memphis. When I started working there in 1995, the clinics were housed in the first two floors of the research building. Because of this layout, every morning when I walked into work and every evening when I left to go home, I would see the children being treated for cancer. These children would be bald from harsh chemotherapy treatments or have tattoos where they were receiving radiation treatments.

Despite their conditions, they would be playing in the atrium, dragging their IV stands behind them. The only care they had was having fun in the moment. I knew that many of these children probably would not survive. These families came to St. Jude, a place where everyone was treated regardless of ability to pay, because like the saint for whom the hospital was named, the patron saint who provides hope to those who have none, the men and women who worked there provided hope to these families when it seemed no hope was possible. These families searched for anything that would give them even a few extra months with their children. Even today, this desire for the smallest glimmer of hope strikes a deep emotional chord in me.

In our chosen profession of academic research, it seems that everything we do is about that dreaded impact factor or just how much our work will impact the larger field of science or clinical knowledge. However, the families and children at St. Jude couldn't care less about this impact factor. To them, the impact of our work is very real and very tangible — providing hope that a novel treatment will save their lives or provide them a little more time on this earth.

These impressions, which are so strong they still resonate with me to this day, remind me of why I continue to deal with the constant frustrations of academic science. Yes, I love research. I love investigating the biological underpinnings of why a tumor forms and then devising potential methods to inhibit this process. However, in the midst of trying to perform work with the highest impact, the truth behind why this work is truly important has been lost. Although academic science may have erased my idealistic notions of basic research in its purest form, my memories of the children and families at St. Jude remind me that we work as scientists to save lives and to provide people with hope.

In these difficult times, it seems like all we ever hear is complaints about grants, funding, decreased budgets, job attrition and our increased workloads to compensate for this attrition. However, patients remind us that we must never lose sight of why we entered the healthcare profession: to understand biology so we can develop novel therapies and provide people with hope. If we can keep sight of this fact, it might not make the realities we face any easier to deal with, but it will give us direction and inspiration to keep pushing forward.

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Reader responses

Re: "The curse of committees and clubs," September issue

'Don't yearn for the good old days'

By Mary F. Roberts

Not all of us "old" folks feel that study sections today have less-qualified scientists, as Steve McKnight alleges in his recent column (1). What a preposterous statement! The National Institutes of Health has managed to attract dedicated and superb reviewers who take the job seriously.

There is both breadth and depth in study sections these days. From my experiences, it is often a joy to listen to my much younger colleagues whose critiques are insightful and well-justified. They do a better job of identifying unusual and creative science than what I remember from 20-odd years ago. Breaks in these meetings also can lead to productive and lively science conversations. You can learn a lot by talking with the current crop of reviewers (but you actually have to interact with them).

Yes, there is a lot of specialization today, but collaborations in fairly different areas are easier to establish now. The Internet provides forums for discussions of all sorts of scientific topics. From my aged perspective, science is still a wonderful, although woefully underfunded, enterprise.

A few words are in order about the olden times for which McKnight yearns. Clubism was certainly alive and well back then. It was a fairly restricted club too — with woefully few exceptions: Women and minorities were rarely members. What a joy that the white-male clubism, or you-don't-look-like-me-and-you-didn't-train-with-my-buddies-so-you-can't-be-top-tier attitude, is gone.

Don't yearn for the good old days. Live in the present, and be amazed at the spectacular scientists who, with an abundance of breadth and talent, have taken on the burden of NIH reviewing!

Mary F. Roberts (mary.roberts@bc.edu) is a professor of chemistry at Boston College and co-chair of the ASBMB 2015 annual meeting program planning committee.

REFERENCE

1. http://bit.ly/1roIJ3i

#riffraff

By Darren Boehning

In a recent column, American Society for Biochemistry and Molecular Biology President Steve McKnight discussed what he felt was decreased quality of peer review of grants at National Institutes of Health study sections (1). He provided two main hypotheses for why quality has suffered:

1) The average scientist of today is not of the same quality of those 40 or 50 years ago and, thus, is incapable of adequately reviewing the most creative proposals.

2) If you are not member of the "scientific club" that defines your discipline, it is impossible to get a fundable score.

These hypotheses were presented in a purely anecdotal manner, with no specific evidence to substantiate the claims.

Indeed, former ASBMB President Jeremy Berg stated that no real data exist regarding the quality of peer review over time (2). Anecdotally, Berg noted that he sees no correlation between scientific stature or career stage and the quality of peer review, and I wholeheartedly agree. There have been other critiques of these two hypotheses by McKnight (3, 4, 5), so I will not repeat them here.

What I would like to comment on is the derogatory manner in which the column was written. In the course of presenting his case, McKnight made statements such as these:

"First, the average scientist today is not of the quality of our predecessors";

"Biomedical research is a huge enterprise now; it attracts riffraff who never would have survived as scientists in the 1960s and 1970s";

"unfortunately, study sections are undoubtedly contaminated by riffraff";

and

"what might be expected from a grant review committee composed largely of second-tier scientists with limited knowledge of the breadth of biology and medicine."

There are other questionable passages throughout the piece, but the labeling of the latest generation of scientists as "riffraff" struck a raw nerve with a lot of people, including me. One wonders what motivated the president of the ASBMB to express himself in this manner. I think the members of the ASBMB and many others in the scientific community would like clarification regarding these comments and an apology.

Eventually, the column took off on social media, resulting in the expression of a lot of anger and resentment. It even spawned several new Twitter hashtags, including #riffraff, #riffraffgate and #iamriffraff. The source of this anger and resentment is clear. The latest generation of scientists has it harder than any before. Paylines are historically low, the postdoc bottleneck is the worst it ever has been, and just publishing a paper requires innumerable supplemental figures and many years of work. If McKnight would listen to the younger generation instead of belittling it, he would realize the incredible talent and potential of those scientists. Most importantly, as president of the ASBMB, he should be functioning as our advocate rather than our critic.

Around the time McKnight's column was making its rounds on social media, the NIH released a list of BRAIN Initiative grantees (6). I couldn't help but think that if these people represent the riffraff that is polluting science today, I am proud to be a part of it. #iamriffraff

REFERENCES

1. http://bit.ly/1roIJ3i
2. http://bit.ly/1vJ4KrC
3. http://bit.ly/1s5GjGe
4. http://bit.ly/1Em1OHV
5. http://bit.ly/1uStlOb
6. http://1.usa.gov/1ponvwI

Darren Boehning (Darren.F.Boehning@uth.tmc.edu) is an associate professor at University of Texas Health Science Center at Houston and a co-director of the biochemistry and molecular biology graduate program there. He has been an ASBMB member since 1998.

Reader comments

As an interdisciplinary scientist, I share many of (Steven) McKnight's concerns about the funding of science (in the U.S.) as well as the acknowledgement of the specialization that might have crept into many old and new fields. I hold that the current situation is the direct result of the many successes of McKnight's generation of scientists. The importance of fundamental biomedical research, molecular biology, genetics and the new subfields they have spawned is now recognized by most informed citizens, politicians, businessman and investors who fund it in the public and private sectors. In many ways the new landscape of science, including increased specialization, should not be held to the same standard as that of the previous generation. It is fundamentally different than before — larger, more complex — but certainly still as important. I also hold that turning back the clock will not fix its current ills either. It is reasonable to look critically at the landscape of funding, conferences, publishing, peer review, societies and disciplines. What is working? What needs fixing? Or, even, what needs to be reformed or eliminated? For using his platform and office to raise these issues, I thank McKnight.

– CURT CORUM

First, I will echo the comments of others: The quality of young scientists is a direct result of the recruitment and training of older scientists. Introspection rather than condemnation might be valuable. As for the broad training, individual inquiry and perseverance of scientists in the days of yore, that was a product of the time. As time passes, the scientific endeavor, by nature, is dealing with ever more complicated and intricate problems. The training of the past certainly had virtue, but it is foolish to think the same style of training will perennially produce results. … Times change, and the way people must react also changes. To think otherwise is obtuse at best and more likely shows a nostalgia and disconnect from reality ill-suited for a society president. Lamenting the inevitability of change does not invalidate it; it simply marks the speaker as out of touch.

– "SCIENCE"

HEY, RESEARCHER! LEAVE THAT BLOT ALONE!

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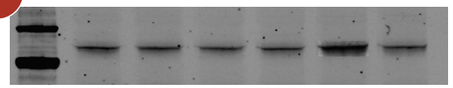

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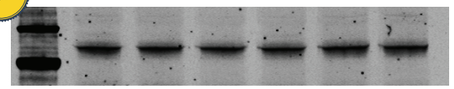

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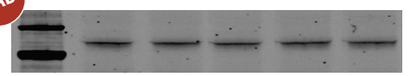

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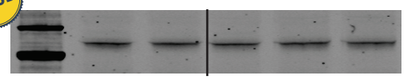

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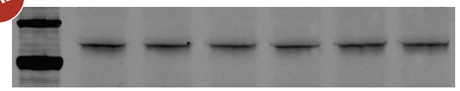

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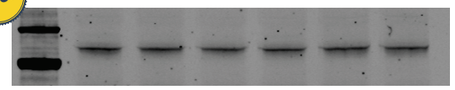

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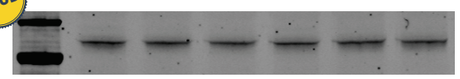

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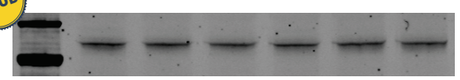

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We know that a life in science can be grueling. We also know that some of you have very interesting or unusual ways of blowing off steam or finding your Zen. We would like to feature your essays, poems, artwork or multimedia reflecting on scientists' pastimes. We welcome all creative interpretations of the theme. You could send us a photo of you shooting hoops or jumping out of an airplane. You could send us a video of you jamming with your band. You could send us a poem about a childhood hobby or otherwise abandoned escapes. You could write about a hobby enjoyed by someone else — perhaps a figure in science history or one of your mentors. And you could send us a rant about how you don't have time for such frivolity.

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