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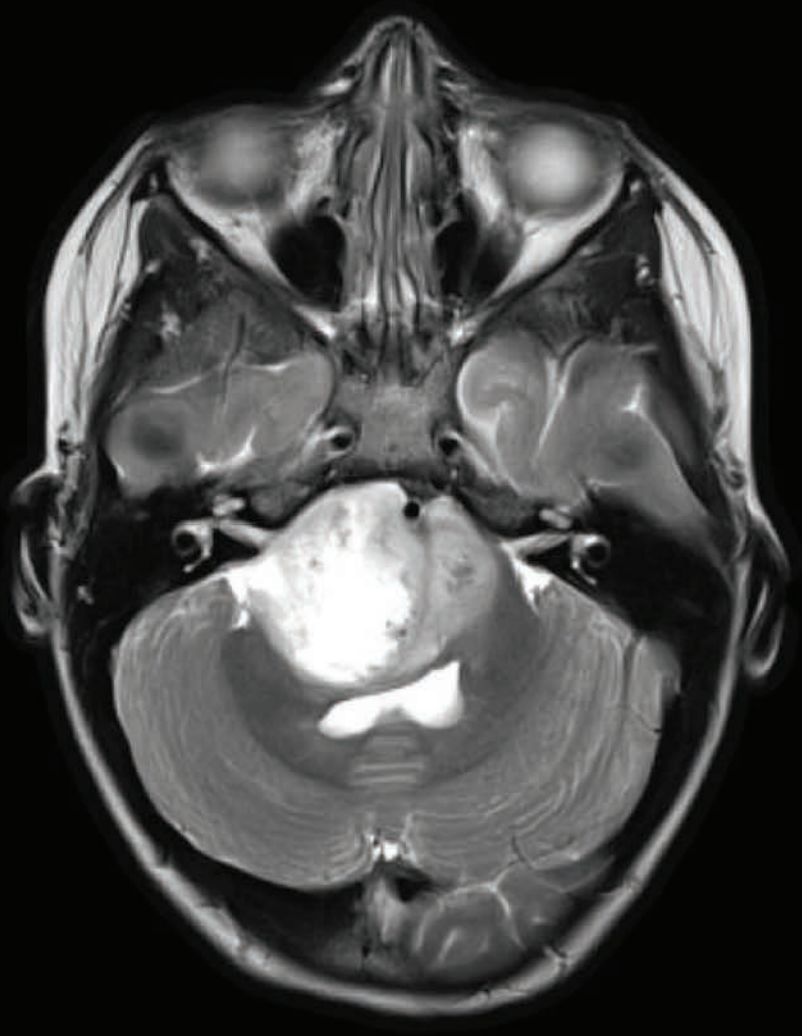
ASBMB TODAY

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



A NEW ANGLE

Discovery of a mutation in a rare pediatric brain tumor gives researchers new targets to go after for a cure

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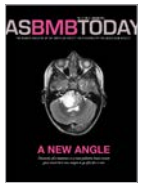
Chief science correspondent Rajendrani Mukhopadhyay reports on an important advance in the study of a pediatric brain cancer that has always been unbeatable.



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ASBMB TODAY
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The straight-jacket of hypothesis-driven research

By Steven McKnight

The advancement of biomedical research requires both leaps of discovery and the steady progress that separates one leap from another. Leaps are universally unanticipated; no one ever wrote them as specific aims in National Institutes of Health grant applications. Gradual transitions are the opposite. They are the essence of what we write as the specific aims of our grant proposals. Gradual transitions fit hand-in-glove with hypothesis-driven research.

I lament that, as presently constructed, the NIH system of funding science is locked into the straight-jacket of hypothesis-driven research. It is understandable that things have evolved in this manner. In times of tight funding, grant reviewers find it easier to evaluate hypothesis-driven research plans than blue-sky proposals. The manner in which the system has evolved has forced scientists to perform contractlike research that grant reviewers judge to be highly likely to succeed. In financially difficult times, more risky scientific endeavors with no safely charted pathway to success often get squeezed out.

We all recognize the formula and nature of hypothesis-driven research; we describe it over and over in the thousands of grant applications we write and submit for review by the NIH each year. But how should we describe the riskier blue-sky research that our granting agencies tend not to favor? I have written about this topic before (1), and I have suggested that this latter kind of research follows the concepts of inductive inquiry (I^2).

Central to the utility of the I^2 form of biomedical research is the definition of a phenomenon. Here is an example of a phenomenon of interest. During hibernation, the core body temperature of ground squirrels goes from 37°C down to 4 – 5°C. Perplexingly, with robust periodicity, hibernating ground squirrels warm back up to 37°C around once every 10 days (2). These brief periods of warming are called interbout arousals. What is the utility to the hibernating ground squirrel to periodically warm up for about a day?

To me, this is a cool phenomenon. Interbout arousals are almost perfectly periodic, and they entail profound changes in body temperature. Instincts tell me something quite important is taking place when hibernating animals warm up briefly like clockwork. As cool as this science is, it is hard to distill it down to a set of measurable, specific aims. Sure, one can say that it would be useful to do some cataloging — measuring metabolite fluctuation as a function of hibernation and entry and exit from interbout arousals. Sure, one might hope then to garner some clues that might lead the way out of the woods But it is hard to say exactly how the science would unfold in the context of the hypothesis-driven form of research we are now forced to perform. As nebulous as it might seem, my predic-

tion is that a talented and dedicated scientist would have a good chance of making cool discoveries if offered the chance to pursue this research for the duration of a typical R01 grant from the NIH.

Were it up to me, and it is clearly not, I would demand that NIH grant applications start with the description of a unique phenomenon. When I say unique, I mean unique to the applicant. The phenomenon may have come from the prior research of the applicant. Alternatively, the phenomenon may have come from the applicant's unique observation of nature, medicine or the expansive literature.

Phenomena abound. One of several that have intrigued me over the past decade is the speed of mouse embryonic cell duplication. Mouse ES cells divide more rapidly than any cancer cell – almost as fast as microbial organisms, such as yeast. Why do ES cells divide so rapidly, and how is hypermitotic drive facilitated? I also find it fascinating that prototrophic strains of yeast (AKA wild type, native or nondomesticated), when grown under nutrient-limiting conditions in a chemostat, enter into an incredibly robust and periodic metabolic cycle. What is the physiologic utility of this metabolic cycle, and what is the underlying regulatory logic controlling it? Finally, the vast majority of newly formed neurons born daily in the adult mouse brain die along the pathway toward differentiation and ultimate wiring into the central nervous system. Why do so many of the cells die, and by what mechanism is neuron death enacted?

I can think of hypotheses with which to begin investigation of these phenomena, but most such hypotheses would be highly biased owing to the extreme limitations of my knowledge of ES cell growth, yeast metabolism or hippocampal neurogenesis. This being the case, it would be folly to submit NIH grant applications in search of funding to support research on these topics. As mentioned above, it is not up to me to guide the NIH on how to spend its funds. On the other hand, we live in a country that is highly protective of freedom of speech. With that in mind, I happily offer the thesis outlined in this essay and close with Albert Einstein's iconic quote: "If we knew what we are doing, it would not be called research."

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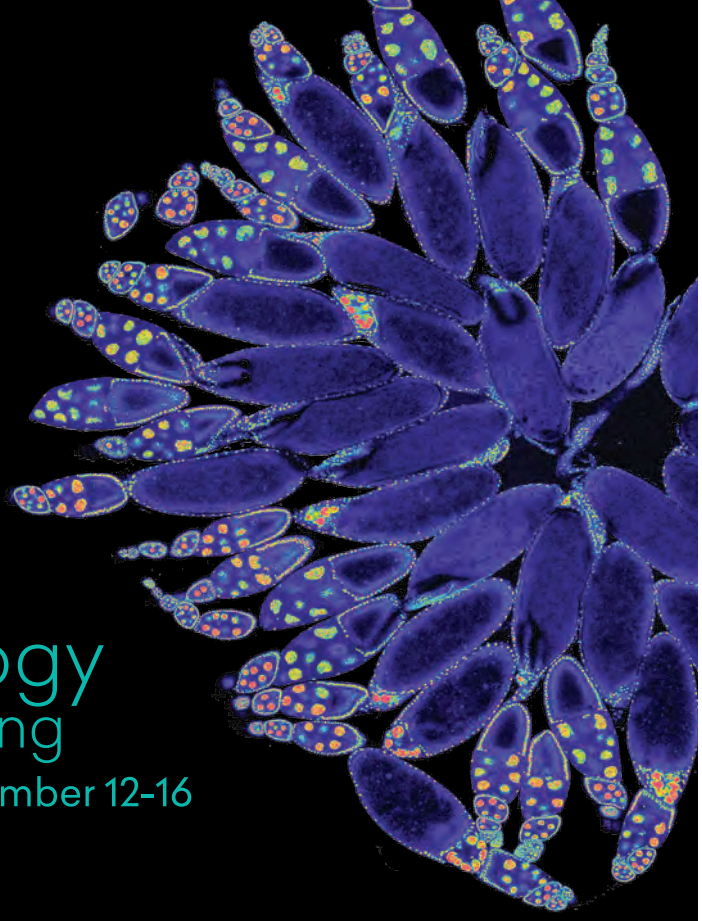
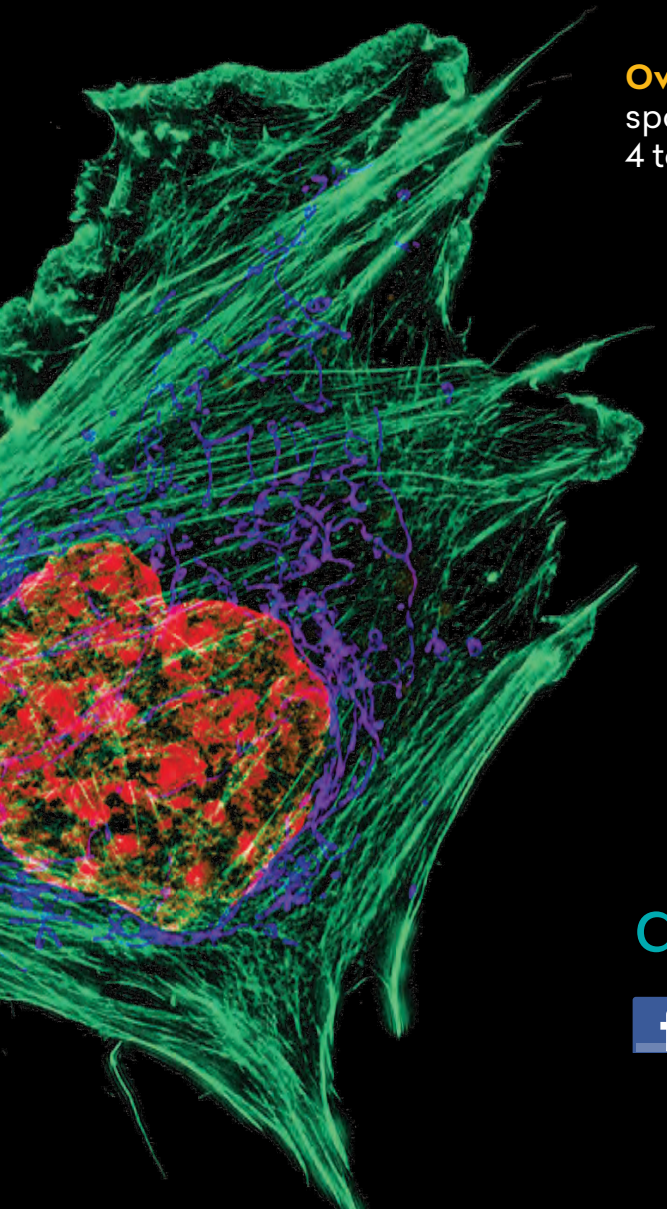
Steven McKnight (steven.mcknight@utsouthwestern.edu) is president of the American Society for Biochemistry and Molecular Biology and chairman of the biochemistry department at the University of Texas-Southwestern Medical Center at Dallas.

SAVE *the* DATE



2015 cell biology
ascb annual meeting
san diego, california · december 12-16



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  (15-minute talk, 5-minute Q&A)
- Minisymposium Lightning Talk
  (5 minute talk, 1-2-minute Q&A)
- Microsymposium Talk
  (5-minute talks with electronic posters)

The meeting's arc will follow the integration of cell biology across diverse fields, scales, and structures into newly relevant scientific disciplines. It's about connecting traditional cell biology questions to new sequencing-based and super high-resolution imaging methods enabled by big data collection and analysis. Present your best and boldest science at this forward-thinking meeting!

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Young scientists advocate on the Hill

By Allison Frick

Young scientists from colleges and universities across the United States arrived on Capitol Hill in June to talk with senators and representatives about the value of biomedical research. For a seventh year, the American Society for Biochemistry and Molecular Biology's Hill Day gave researchers the chance to meet with lawmakers and congressional staffers about the work they are doing.

The undergraduates, graduate students and postdoctoral scholars collaborated with the ASBMB's Public Affairs Advisory Committee to highlight the critical role that federal investments play in supporting the nation's scientific enterprise and how those investments will lead to improvements in the quality of life and well-being of Americans.

Allison Frick (africk@asbmb.org) is the ASBMB's print and digital media specialist.

Kelli Lytle, Jeanette Osterloh and Sharona Gordon at the office of U.S. Sen. Ron Wyden, D-Ore.

Preston Hensley, Jarod Rollins, Torrey Truszkowski, congressional staffer Todd Adams and ASBMB policy fellow Sarah Martin visit the office of U.S. Rep. Jim Langevin, D-R.I.

Torrey Truszkowski, a graduate student at Brown University originally from Providence, R.I., visits with U.S. Sen. Sheldon Whitehouse, D-R.I.

Lynn Ulatowski, a postdoctoral fellow at Case Western Reserve University originally from South Euclid, Ohio, visited with U.S. Sen. Sherrod Brown, D-Ohio.

Melanie Alvarado, Amy Hawkins and Wes Sundquist meet with a staff member in the office of U.S. Sen. Lisa Murkowski, R-Alaska

Participants:

Melanie Alvarado, a graduate student at the University of Alaska Anchorage

Taylor Fuselier, a graduate student at the Tulane University School of Medicine in New Orleans

Tara Gonzalez, a graduate student at the University of Delaware

Amy Hawkins, a postdoctoral fellow at the University of Utah

Aminul Islam, a postdoctoral fellow at Uniformed Services University of the Health Sciences in Maryland

Ryan Kelley, a graduate student at the University of Oklahoma Health Sciences Center

Kelli Lytle, a graduate student at Oregon State University

Joshua Mieher, a graduate student at the University of Alabama at Birmingham

Jeannette Osterloh, a postdoctoral fellow at the Gladstone Institutes in San Francisco

Dakota Pouncey, an undergraduate student at Hendrix College in Arkansas

Jarod Rollins, a postdoctoral fellow at Mount Desert Island Biological Laboratory in Maine

Kimberly Sauls, a graduate student at the Medical University of South Carolina

Megan Sheridan, a graduate student at the University of Missouri–Columbia

Tyler Stanage, a graduate student at the University of Wisconsin–Madison

Jackie Thompson, a graduate student at the University of Kansas Medical Center

Torrey Truszkowski, a graduate student at Brown University

Kristeena Wright, a graduate student at Marshall University

Lynn Ulatowski, a postdoctoral fellow at Case Western Reserve University

Chistopher Yarosh, a graduate student at the University of Pennsylvania

10 members elected to the National Academy of Sciences

The National Academy of Sciences in late April elected 84 new members and 21 new foreign associates. Ten ASBMB members were among those elected. They were:

BRENDA BASS
University of Utah School of Medicine

ALFRED GOLDBERG
Harvard Medical School

ALAN HINNEBUSCH
National Institutes of Health

NANCY IP
Hong Kong University

JEANNIE LEE
Harvard Medical School

JOHN LIS
Cornell University

SHIGEKAZU NAGATA
Kyoto University

RAFAEL RADI
University of the Republic in Uruguay

NAHUM SONENBERG
McGill University

JEREMY THORNER
University of California, Berkeley

6 members named HHMI investigators

The Howard Hughes Medical Institute named 26 researchers HHMI investigators in late May. Six members of the American Society for Biochemistry and Molecular Biology were among them. They were:

SQUIRE J. BOOKER
Pennsylvania State University, University Park

JARED RUTTER
University of Utah School of Medicine

XINZHONG DONG
Johns Hopkins University

REUBEN S. HARRIS
University of Minnesota, Twin Cities

KIM ORTH
University of Texas Southwestern Medical Center

TOBIAS C. WALTHER
Harvard University

Gairdner fund and AACR recognize Cantley

LEWIS CANTLEY

Lewis Cantley is being honored with the 2015 Canada Gairdner International Award for his groundbreaking work in the field of cancer research. The Canada Gairdner International Awards, which come with a 100,000 Canadian dollar prize, recognize biomedical scientists who present novel research toward understanding human biology and disease. The Gairdner Foundation is recognizing Cantley for his discovery of the enzyme phosphoinositide 3-kinase, or PI3K, which has proven vital in understanding cancer. Additionally, the American Association for Cancer Research is recognizing Cantley's outstanding work with the Princess Takamatsu Memorial Lectureship. This award, started in 2007, is given out annually to a scientist whose work makes a profound impact toward understanding and treating cancer. His lecture, entitled "Targeting PI3K for Cancer Therapy," was in April. Cantley is director of the Sandra and Edward Meyer Cancer Center at Weill Cornell Medical College.

Sharp wins Chemical Heritage Foundation's Othmer medal

PHIL SHARP

The Chemical Heritage Foundation is presenting the 2015 Othmer Gold Medal to Phil Sharp. The Othmer Gold Medal was established in 1997 to recognize the achievements of individuals who have made significant contributions to chemical and scientific heritage in a number of key areas, such as research, legislation or entrepreneurship. Sharp's innovative research in the field of genetics has dealt with the molecular biology of gene expression relevant to cancer and the mechanisms of RNA splicing. Sharp, who serves both as Institute Professor at the Massachusetts Institute of Technology and member of the department of biology and the Koch Institute for Integrative Cancer Research, also has founded several biotech companies including Biogen and Alnylam Pharmaceuticals. Sharp is one of three scientists who will get an Othmer Gold Medal at the Heritage Day Awards, the CHF's annual celebration of scientific and technological achievement, this month.

Written by Eric Chaulk

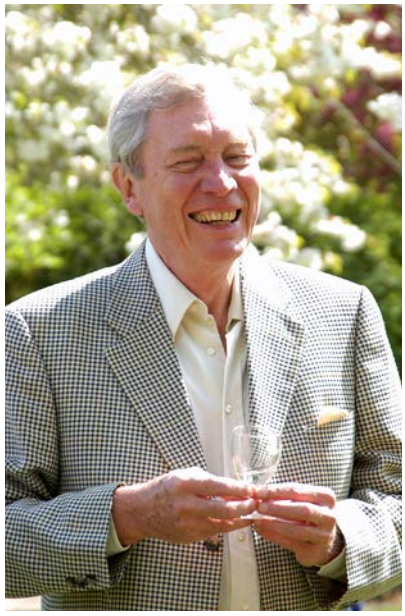
Richard Nelson Perham (1937 – 2015)

By Sheena E. Radford and Nigel S. Scrutton

The world lost one of its most gifted biochemists Feb. 14 with the death of Richard Nelson Perham at the age of 77. An active, renowned member of the academic science community until the very end, Perham was distinguished for his work on the chemistry of proteins and the assembly of giant protein complexes and was a leader in bringing the power of protein-engineering approaches to problems of protein structure and function.

Perham pioneered the development of chemical tools to understand protein structure and function, revealing how enzymes generate energy from glucose (via the remarkable, massive 2-oxoacid dehydrogenase multienzyme complexes) and how viruses assemble capsid coats. Using protein redesign, he was the first to switch the co-enzyme requirement of an enzyme (altering glutathione reductase from using NADPH to NADH for catalysis and lipoamide dehydrogenase from NAD^+ to $NADP^+$). He also made outstanding contributions to our knowledge of the structure and assembly of filamentous bacteriophages and was among the first to use these phages to display foreign peptides on their surface, opening the door to their use for the production of novel vaccines.

Perham was born April 27, 1937, in the London borough of Hounslow West. He went on scholarship to Latymer Upper School, whose liberal outlook and broad curriculum including the arts and sport (both of which remained passions of his for life) inspired and nurtured the budding scientist. In 1955, Perham took the entrance exam for the University of Cambridge. The first of his family to go to university, he was awarded a place at St. John's College.



Richard Nelson Perham

At the time, the field of biochemistry was a hothouse of discovery and achievement. The structure of DNA had been solved in 1953. The first sequence of a protein (insulin) was determined in 1955. And the first three-dimensional structure of a protein (myoglobin/haemoglobin) was established in 1956. A whole new world was opening up.

A Ph.D. with double Nobel Laureate Fred Sanger was Perham's next step. He worked on the structure and mechanism of glyceraldehyde 3-phosphate dehydrogenase under J. Ieuan Harris. Those two identified a key cysteine residue required for protein activity and went on to hold the world record in the mid-1960s for determining the longest amino acid sequence (more than 330 residues) of a protein. This work merited Perham's first major article in Nature, which was published in 1968.

In 1965, Perham became demonstrator in the University of Cambridge Biochemistry department. At the same time, he was awarded a Helen Hay Whitney Fellowship to study at Yale University with Frederic Richards. There he met (over a shared electron microscope) gifted biologist Nancy Lane. The couple returned to Cambridge and married in 1969.

Perham made many significant contributions in his 50 years at Cambridge. In the late 1960s, he uncovered the importance of charge-charge interaction between protein subunits in the self-assembly of tobacco mosaic virus capsids, and later he elucidated the novel mechanism of protein–DNA charge interaction that governs the assembly of filamentous bacteriophage virions. He introduced a number of important techniques in chemical modification of proteins, in particular based on reversible amidination and trifluoroacetylation of lysine residues.

After some 30 years of effort, Perham and his team produced the first complete description of the structure and assembly pathway of the pyruvate dehydrogenase multienzyme complex (whose molecular mass is 10 MDa). He also uncovered a new mechanism of active-site cooperativity distinct

CONTINUED ON PAGE 9

Development of lipids and lipid analogues as potential drugs

By Michael Murray

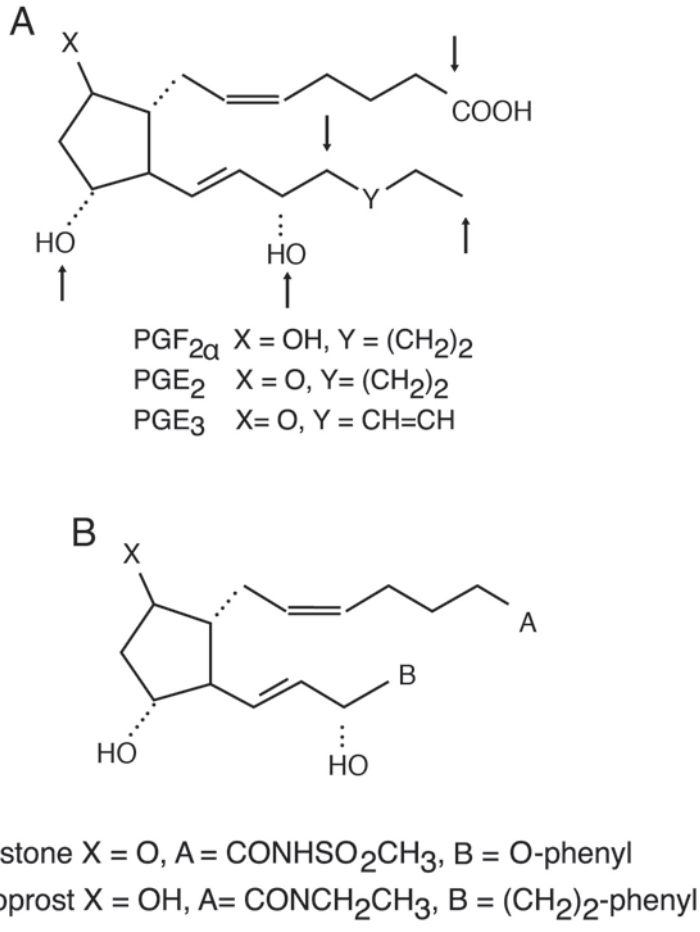
The biological activities of lipids underscore their potential for development as novel therapeutics. To date, the alkyl phospholipids probably have been the most intensively studied lipid-based therapeutics, with miltefosine having value in the treatment of skin cancers and leishmaniasis and perifosine in certain lymphomas. However, the broad roles of many lipids in diverse cellular processes also could detract from their clinical value because of undesired side reactions. In contrast, certain lipid biotransformation products have narrower spectrums of activities that could produce better-targeted drugs.

The 20-carbon ω-6 polyunsaturated fatty acid arachidonic acid undergoes biotransformation mediated by cyclooxygenase, lipoxygenase and cytochrome P450 enzymes to prostaglandins, leukotrienes, epoxides and more complex prostanoids. The analogous biotransformation of ω-3 PUFA, such as eicosapentaenoic acid and docosahexaenoic acid, generates structurally similar but functionally quite different eicosanoids. In cells, these endogenously produced ω-6 and ω-3 PUFA metabolites are extremely potent molecules whose properties could be adapted in novel therapeutics.

A significant problem to overcome in the development of prostanoid-based drugs is their low in vivo stability due to rapid secondary metabolism. Several clinically useful agents that have been developed are prostaglandins that have been modified structurally to stabilize chemical moieties that readily are degraded (1). Important deactivation pathways in prostanoids include oxidation at hydroxyl groups at the ω-end of the molecules or at carbon atoms β to the fatty acid carboxyl group (1).

Incorporation of bulky substituents adjacent to susceptible hydroxyl groups, replacement of the β-carbon with heteroatoms such as oxygen or sulfur, and inclusion of aromatic systems at the ω-end of the fatty-acid chain has produced stabilized prostaglandin analogues suitable for therapy.

For example, stabilization of the



A) Structures of the ω-6 arachidonic acid-derived prostaglandin F2α (PGF2α) and prostaglandin E2 (PGE2) and the ω-3 eicosapentaenoic acid-derived prostaglandin E3 (PGE3). Arrows indicate sites at which biotransformation may occur. B) Structures of the clinically useful prostaglandin analogues sulprostone and bimatoprost.

ω-end of PGE_2 and replacement of the carboxylate with a substituted sulfonamide produced sulprostone (see figure) that has utility in postpartum hemorrhage after childbirth (2). The $PGF_{2\alpha}$ analogue bimatoprost, which carries an N-ethylamide substituent in place of the carboxylate and a phenyl ring at the ω-end (see figure), is favored in primary glaucoma, because it effectively decreases intraocular pressure and has a low incidence of side effects (3). Recently, PGE_3 (see figure) — the cyclooxygenase-derived metabolite of the ω-3 PUFA EPA — has been shown to possess anti-angiogenic properties that could be adapted to cancer chemotherapy (4).

P450-mediated epoxides also have considerable potential as novel therapeutics. ω-6 PUFA epoxides regulate vasoactivity, while the ω-3-17,18-epoxide of EPA, but not its regioisomers, kills tumor cells (5) and DHA epoxides suppress angiogenesis and metastasis (6). Some of these properties have been reproduced in synthetic analogues (7 – 10). Thus, bioisosteric replacement of the epoxide moiety with urea, carbamate, amide or related systems has enabled the retention of the pharmacological activity of the endogenous lipid metabolite precursor (8, 9).

Recently, the in vivo antihypertensive actions of ω-6 PUFA epoxides were replicated in an orally active bioisosteric analogue (10). It may be possible to capture the anticancer activities of EPA and DHA epoxides and other prostanoid metabolites, such as PGE_3, using suitable chemical modifications that inhibit metabolic degradation to facilitate the development of novel anticancer agents.

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Michael Murray (michael.murray@sydney.edu.au) is a professor of pharmacology at the Sydney Medical School.

The work described has been supported by grants from the Australian National Health and Medical Research Council.

RETROSPECTIVE CONTINUED

CONTINUED FROM PAGE 7

from allostery in enzyme activity and elucidated unexpected mechanisms of active-site coupling in his multi-enzyme complexes based on motile protein domains.

Perham was a servant to the scientific community. He served as a councilor and trustee for the Novartis (formerly CIBA) Foundation, chaired the scientific advisory board of the Lister Institute of Preventive Medicine, and sat on the advisory committee and was vice-president of the Fondation Louis-Jeantet de Médicine in Geneva. In 1998, he took the helm of the European Journal of Biochemistry, reinventing it into what is now FEBS J, and served as editor until 2013.

Perham won election to the European Molecular Biology Organisation (1983) and the Academia Europaea (1992). He was a fellow of the Royal Society (1984) and the Academy of Medical Sciences (2005). He won the Max Planck Prize (1993), the Novartis Medal of the Biochemical Society (1998) and the Diplôme d'Honneur from the Federation of European Biochemical Societies (2011).

Perham was a truly exceptional scientist with an impressive knowledge of art, literature, history, sport and all types of music. He was an inspired teacher and mentor, loyal to his students, and passionate about the University of Cambridge and St. John's College. He leaves a legacy of more than 350 scientific papers; an array of well-trained graduate biochemists; and family, friends and the scientific community proud of such a brilliant man.

Sheena E. Radford (s.e.radford@leeds.ac.uk) is a professor at the University of Leeds. Nigel S. Scrutton (Nigel.Scrutton@manchester.ac.uk) is a professor at the University of Manchester.

A longer version of this article appeared in The Biochemist magazine.

Renaming Institute of Medicine

By Erik Maradiaga

The Institute of Medicine has been renamed the National Academy of Medicine. The name change comes as part of an internal reorganization at the National Academies. The new academy will continue as an honorific society and will contribute to and complement the work of the National Academy of Science and the National Academy of Engineering by advising on health matters.

The IOM was founded in 1970 under the congressional charter of the National Academy of Science, which was established in 1863. It is responsible for providing unbiased advice on issues concerning medicine, biomedicine and health.

Victor J. Dzau, who was president of the IOM and is now the first president of the National Academy of Medicine, said: "This change recognizes the important achievements of medicine and health researchers, clinicians and policymakers in improving medicine both nationally and globally. We look forward to expanding our work together with the other academies, and I am confident that this development will enhance our ability to provide evidence-based advice aimed at improving the lives of people everywhere."

Likewise, NAS President Ralph J. Cicerone said the name change is "an acknowledgement of the importance of medicine and related health sciences to today's global research enterprise." He said: "It will also better align us to take a more integrated, multidisciplinary approach to our work, reflecting how science is best done today."

Erik Maradiaga (em3914a@student.american.edu) is an undergraduate at American University.

Upcoming ASBMB events and deadlines

JULY

July 30 – Aug. 2: ASBMB Special Symposium: Transforming Undergraduate Education in Molecular Life Sciences, Saint Joseph, Mo.

AUG

Aug. 1: Early registration deadline for ASBMB Science Communication and Outreach Career Symposium, San Antonio, Texas

Aug. 17: Abstract submission deadline for ASBMB Science Communication and Outreach Career Symposium, San Antonio, Texas

SEPT

Sept. 1: Registration deadline for ASBMB Science Communication and Outreach Career Symposium, San Antonio, Texas

Sept. 17 – 20: ASBMB Special Symposium: Membrane-Anchored Serine Proteases, Potomac, Md.

Sept. 18 – 19: ASBMB Science Communication and Outreach Career Symposium, San Antonio, Texas

Sept. 27 – 30: 14th Human Proteome Organization World Congress (HUPO 2015), Vancouver, Canada, Molecular & Cellular Proteomics booth #413

OCT

Oct. 29 – 31: Society for Advancement of Hispanics/Chicanos and Native Americans in Science (SACNAS) National Conference, Washington, D.C., booth #319

NOV

Nov. 5: Abstract submission deadline for the 2016 ASBMB Annual Meeting, San Diego, Calif.

Nov. 12: Travel award application deadline for the 2016 ASBMB Annual Meeting, San Diego, Calif.

Nov. 11 – 14: Annual Biomedical Research Conference for Minority Students (ABRCMS), Seattle, Wash., booth #900

ASBMB
American Society for Biochemistry and Molecular Biology

All about ELISA

Enzyme-linked immunosorbent assays have widespread use

By Aditi S. Iyengar

What is it?

Antibodies recognize and bind to specific antigens, such as peptides, proteins and hormones. The enzyme-linked immunosorbent assay, better known as ELISA, exploits this antigen–antibody specificity to detect and measure, with the help of enzymes, the presence of proteins in samples of unknown composition and concentrations.

How does it work?

In a plate-based ELISA, researchers immobilize an antigen in a microwell plate. Next, they add antibodies that recognize the antigen at sites called epitopes. These antibodies are special in that they are coupled to specific enzymes. The researchers then treat the antigen–antibody complex with appropriate chromogenic substrates that are catalyzed by the antibody-conjugated enzyme, resulting in a color change. Finally, this color change is read and analyzed by a microplate reader.

Researchers have tinkered with this basic principle of ELISA to develop more sensitive variants. The sandwich ELISA, for example, uses of a pair of antibodies — a capture antibody and an enzyme-linked detector antibody — to recognize two separate epitopes on the same antigen. The antibody pairs in a sandwich ELISA significantly reduce background signals and make antigen detection a lot more specific than a conventional ELISA.

How did it come about?

In 1960, Solomon Berson and Rosalyn Yalow at the Bronx Veterans Administration Medical Center described an immunoassay they developed to measure insulin in human blood plasma. That assay used radioactively labeled antibodies. Yalow went on to win the 1977 Nobel Prize in medicine for the work (Berson died in 1972 and couldn't be awarded the prize posthumously).

The technique garnered much attention, but it was accompanied by concern over the long-term effects of using radiation. The idea of replacing radiation with less hazardous substances was born out of a need to maximize safety while minimizing costs. Though initially met with immense skepticism, the concept of using enzymes as a reporter label started to gain popularity.

In 1971, three groups independently and simultaneously published their work proving the feasibility of ELISA as an alternative to radioactively labeled immunoassays: Eva Engvall and Peter Perlmann in Stockholm University measured immunoglobulins in rabbit serum, Anton Schuurs and Bauke van Weeman from the Organon Pharmaceutical laboratories in the Netherlands quantified human gonadotropin hormone in urine samples, and Stratis Avrameas and Guilbert at the Pasteur Institute in France measured serum immunoglobulin levels.

What are its applications?

In the 1970s, the American pharmaceutical company Abbot Laboratories first developed solid-phase radioimmunoassay kits to detect hepatitis B. Since then, ELISA has become a powerful diagnostic tool and now is used routinely to measure serum antibody concentrations against various toxins and pathogens, such as celiac disease, mycobacterium tuberculosis and the influenza virus.

MOUNT SINAI ARCHIVES

Rosalyn Yalow won the 1977 Nobel prize for work that laid the groundwork for ELISA.

In 1976, Dennis Bidwell and Alister Voller from the Institute of Zoology in London introduced the first sensitive microplate assay to screen for viral infections, including malaria. This microplate format since has been adapted to detect other viruses — with its best-known application being the screening test for human immunodeficiency virus titers in patients.

ELISA also has affected our daily lives in the form of home pregnancy tests, ovulation tests, over-the-counter bacterial infection kits and drug tests.

Aditi S. Iyengar (iyengarsaditi@gmail.com) earned her Ph.D. in cancer biology from Louisiana State University Health Sciences Center at New Orleans and completed her postdoctoral research at Massachusetts General Hospital, Boston.

Let's talk about aphasia

By Indumathi Sridharan

Imagine life without language. For people living with aphasia, that's their reality. Aphasia, which is caused by damage in the language centers of the brain, affects the ability to speak, understand speech, and read or write. There are currently one million Americans with aphasia; 80,000 new cases occur in the U.S. every year. As stroke is the leading cause of aphasia, the American Stroke Association designates June as National Aphasia Awareness Month to increase access to information and support for aphasia patients.

What causes aphasia?

Aphasia occurs when blockage or rupture of a blood vessel cuts off blood supply to the language centers located in the brain's left hemisphere. Without oxygen and nutrients, the neurons die. Neuronal death and missing neural connections result in impaired language abilities. Head injuries, tumors and degenerative diseases also can cause aphasia by damaging the left hemisphere.

What are the types of aphasia?

Broca's aphasia affects the ability to fluently speak in grammatically accurate sentences. Comprehension may be mildly impaired. People with Wernicke's aphasia can construct

sentences, albeit with meaningless or empty words. They also have difficulty comprehending spoken language. Global aphasia affects both speech and comprehension.

Most aphasia patients retain good memory, attention and perception. "A lot of them improve with targeted speech therapy," says Yasmeen Faroqi-Shah at the University of Maryland. She adds, "An important question is how the brain recovers after a stroke or injury." Some studies show that the undamaged parts of the left hemisphere take over language function (1). This ability of the brain to regain function by forming new neural connections is called neural plasticity. The formation of new connections is controlled tightly by positive and negative regulators (2). For example, growth-associated protein 43 helps form cellular projections called neurites that connect one neuron with others. Neurite outgrowth inhibitor A, or Nogo-A, inhibits neural connectivity by blocking neurite outgrowth (3).

Are there biochemical interventions available to improve recovery?

Pharmacological agents, when used along with speech therapy, can improve language recovery in aphasia patients. Piracetam, a γ-aminobutyric acid derivative, is a drug that acts on neurotransmitters like acetylcholine and glutamate. Patients using piracetam have improved comprehension, reading and writing because the drug stimulates cholinergic and glutamatergic neurotransmitter systems. Preclinical studies indicate that administering an anti-Nogo-A antibody or transplanting stem cells at the site of damage to replace dying neurons can boost neural plasticity and help in recovery (4).

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

A look at the Tat system

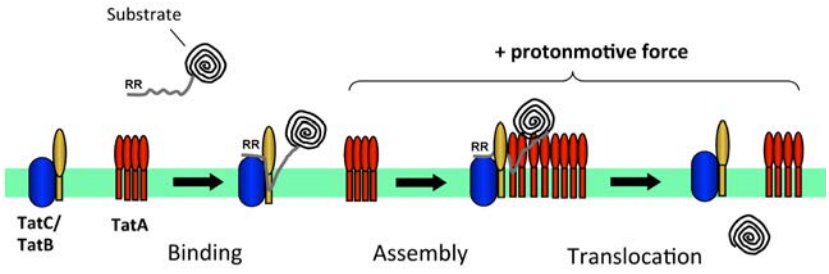
By Alexandra Pantos

In order for most proteins to relocate across membranes, they must unfold, take their journey and then refold upon reaching their destinations. However, in some situations, a protein needs to be translocated while remaining folded. This is the job of the Tat system.

In a recent minireview in the Journal of Biological Chemistry, Kenneth Cline of the University of Florida explores the mechanism of the Tat system. Tat, which stands for twin-arginine translocase, transports a variety of substrates of different sizes and types. The Tat system exists in various organisms and is present in some archaea and some mitochondria. Cline, however, focuses his review on research of the system in the thylakoid membranes of plant chloroplasts and in the cytoplasmic membrane of the E. coli bacterium.

Cline notes that the system has three components in both the thylakoid and in E. coli: TatA, TatB and TatC. The thylakoid orthologs of bacterial TatA and TatB are known as Tha4 and Hcf106 based on their genetic isolation, but the author indicates that the functions of these components are similar enough that this distinction is not necessary. He refers to them as TatA and TatB throughout the review. He also points out that the system's presence in prokaryotes and prokaryote-derived organelles suggests that Tat has been around for quite some time.

The author highlights important steps and players in the mechanism of Tat. He notes that the signal peptide has three parts: an amino proximal N domain, a hydrophobic H domain and a polar C domain that contains the signal peptidase cleavage site. At the N–H junction, however, lies the most important feature: the Arg-Arg (also known as RR) motif. This motif is not the entire consensus sequence, but the rest of the sequence varies among organisms and appears to be less important than the RR motif.



Cyclical mechanism for Tat protein transport. The TatBC receptor complex binds the substrate signal peptide in an energy-independent step. The receptor complex is depicted in the figure as a TatBC heterodimer, but it is actually a multimer estimated to contain up to 8 TatBC units. Signal peptide binding triggers PMF-dependent assembly and oligomerization of TatA. The resulting complex is the translocase. Changes in the TatA oligomer are thought to facilitate protein transport, after which the translocase dissociates.

Once the signal peptide targets the substrate, a cycle of substrate binding, translocase assembly and translocation occurs. The author explains that TatB and TatC are first present in equal amounts as a receptor complex. TatA is separate until the substrate signal peptide binds to the receptor complex, which then "triggers TatA assembly and oligomerization at the substrate-TatBC interface," Cline writes. This complex is known as the translocase. Curiously, the order of the next steps is not known, but the author says they include transportation of the substrate, cleavage of signal peptide and disassembly of the TatA oligomer.

In the rest of the minireview, Cline delves deeper into the roles of TatA, TatB and TatC, and he offers details about how substrates bind and what that binding triggers. The author also goes into some aspects of the research that are not 100 percent certain. He discusses models for TatA-facilitated translocation and notes which model he thinks is best. He includes details about how the oligomeric TatBC structure may enable gated TatA assembly to form the translocase. He says mechanisms for how the protonmotive force and signal peptide binding act as triggers are still speculative.

In fact, Cline emphasizes that much of the information presented in the minireview is preliminary and is based on a single study. He believes that additional approaches will be necessary to create a detailed map of the subunit organization of TatABC and substrate as well as to gain an understanding of the interactions that regulate assembly of the translocase. The author reminds readers that this research is still at a relatively early stage. He goes on to propose some potential approaches for learning more, especially about how TatA assemblies enable passage of the substrate across the membrane, which he views as the core issue.

Alexandra Pantos (apantos@asbmb.org) Alexandra Pantos is an intern at the ASBMB and a senior biology student at the University of Maryland.

Study outlines how inadequate vitamin E can cause brain damage

By David Stauth

Vitamin-E deficiency, it appears, may cause neurological damage by interrupting a supply line of specific nutrients, robbing the brain of the building blocks it needs to maintain the function and integrity of the neural membrane.

New findings on this role of this micronutrient, in National Institutes of Health-supported work done with zebrafish, were published in the **Journal of Lipid Research** by scientists from Oregon State University.

The research showed that zebrafish fed a diet deficient in vitamin E throughout their lives had about 30 percent lower levels of docosahexaenoic acid-containing phosphatidylcholines, or DHA-PC. This major membrane phospholipid species is part of the cellular membrane of every neuron.

In searching for a mechanism of action, scientists examined the level of lysophospholipids, or lyso PLs, that serve as substrates for phospholipid synthesis and as transporters for getting DHA from the plasma into the brain. Once inside, these lyso PLs become the building blocks for neural-membrane maintenance and repair. It was found that brain lyso PL levels are an average of 60 percent lower in fish maintained on the vitamin–E deficient diet.

Why is this important? Because the year-old zebrafish used in this study, and the deficient levels of vitamin E they were given, are equivalent to humans that have eaten a low vitamin E diet for a lifetime. And unfortunately, that's pretty common.

In the United States, 96 percent of adult women and 90 percent of men do not receive adequate levels of vitamin E in their diets. And the new findings about the role of lyso PLs also come after other recent studies showed that low levels of DHA-PC in the blood plasma of humans are a biomarker than can predict a higher risk of developing Alzheimer's disease.

"This research showed that vitamin E is needed to prevent a dramatic loss of a critically important molecule in the brain and helps explain why vitamin E is needed for brain health," said Maret Traber in the College of Public Health and Human Sciences at OSU, and lead author on this research.

"Human brains are very enriched in DHA but they can't make it – they get it from the liver," said Traber, who also is a principal investigator in the Linus Pauling Institute at OSU. "The particular molecules that help carry it there are these lyso PLs, and the amount of those compounds is being greatly reduced when vitamin E intake is insufficient. This sets the stage for cellular membrane damage and neuron death."

DHA, an omega-3 polyunsaturated fatty acid, has been increasingly recognized as one of the most important fatty acids for brain health. It's found in certain omega-3 rich foods, primarily cold-water fish like salmon and mackerel.

DHA is the needed nutrient, Traber said, but it's the lyso PLs that help get it into the brain and ultimately act as the building blocks for maintaining the neural membrane.

This membrane is highly dynamic and is in a constant state of turnover, so an adequate supply of lyso PLs is needed at all times to facilitate normal membrane — and, subsequently, neuron activity.

"You can't build a house without the necessary materials," Traber said. "In a sense, if vitamin E is inadequate, we're cutting by more than half the amount of materials with which we can build and maintain the brain."

In the United States, 96 percent of adult women and 90 percent of men do not receive adequate levels of vitamin E in their diets.

Some other research, Traber said, has shown that the progression of Alzheimer's disease can be slowed by increased intake of vitamin E, including one study published last year in the Journal of the American Medical Association. But that disease is probably a reflection of years of neurological damage that already has been done, she said. The zebrafish diet used in this study was deficient in vitamin E for the whole life of the fish — as is the diet of some humans.

Vitamin E most often is provided by oils, such as olive oil. But the highest levels are often found in foods that don't make the highlight list of an average American diet — almonds, sunflower seeds or avocados.

"There's increasingly clear evidence that vitamin E is associated with brain protection, and now we're starting to better understand some of the underlying mechanisms," Traber said.

David Stauth (david.stauth@oregonstate.edu) is a science writer at Oregon State University.

The promise of personalized nutrition

Studies find that a high-fat, low-carb diet improves cholesterol levels in people with a particular gene variant

By Vivian Tang

An international team of researchers led by Lu Qi at the Harvard School of Public Health recently reported in the **Journal of Lipid Research** that a high-fat, low-carbohydrate diet appears to improve cholesterol levels in obese people with a particular gene variant.

The researchers studied the effects of this diet in a two-year randomized trial called Preventing Overweight Using Novel Dietary Strategies, or POUNDS LOST, involving more than 700 obese individuals. They observed that individuals with a certain variant of the CETP gene ended up with increased levels of high-density lipoprotein (known as HDL or good cholesterol) and decreased levels of triglyceride six months into the trial.

The researchers then did a second independent, two-year randomized trial called the Dietary Intervention Randomized Controlled Trial, or DIRECT, with 171 obese individuals. Again, only those with the specific CETP variant on the high-fat, low-carb diet showed significant improvement in HDL and triglyceride levels.

The results from these trials "indicate that individuals with the CETP rs3764261 CC genotype might be more responsive to low-carbohydrate, high-fat weight-loss diets in raising HDL cholesterol and lowering triglyceride levels compared with those without this genotype," the researchers wrote. "Our findings provide novel information to the development of effective strategies for dietary interventions and supportive evidence for the notion of a personalized dietary intervention based on genetic background."

To understand these results, you have to know a bit about the cholesteryl ester transfer protein — the CETP in the genotype name.

CETP is a glycoprotein that regulates blood lipids by facilitating the transfer of cholesteryl ester and triglycerides between HDL and other lipoproteins. Mutations in the CETP gene affect CETP expression or activity, which affects HDL cholesterol levels. The variant CETP rs3764261 CC is a HDL cholesterol-decreasing mutation.

Previous genomewide-association studies had established that the CETP genetic variant rs3764261 has a stronger association with HDL cholesterol levels than other loci across the human genome. However, investigations exploring the relationship between the CETP genetic variants and dietary fat intake thus far have been mostly short-term studies that detected either no association or associations that could not be replicated. The findings reported in the JLR paper confirm the association and provide the replication that had been lacking.

Qi and co-authors emphasize that they administered the diets under conveniently managed conditions, which facilitated adherence to the regimen by more than 80 percent of the participants throughout the duration of both trials. Also, they noted that study participants either highly restricted their saturated-fat intake or were counseled to avoid foods high in saturated fats.

Weight loss in individuals with the CETP rs3764261 CC genotype was insignificant during the first few months, with most of them regaining weight six months into the trials. The researchers say this indicates that weight loss is only partially dependent on restoration of HDL and triglyceride levels.

Also, they affirmed that even after adjusting for changes in body weight, the restoration of lipid levels remained significant, with the elevated HDL levels persisting throughout the two-year duration of the trials – an indication of the continuous beneficial effect of the high-fat, low-carb dietary intervention even after weight regain.

The team now will explore whether other genetic variants or mechanisms interact with dietary intervention and affect not just lipid levels but also other physiological traits, such as glucose, body fat and blood pressure.

Vivian Tang (victoriousvivian@hotmail.com) is a graduate student at the School of Pathology and Laboratory Medicine at the University of Western Australia.

An unexpected finding in prehistoric bison bones

By Rajendrani Mukhopadhyay

On Oct. 14, 2010, construction workers excavating a site for a reservoir dam near Snowmass Village, Colo., stumbled across bones. The bones belonged to a woolly mammoth. More careful digging revealed close to 5,000 bones from different Ice Age animals. Camels, mastodons and bison were among them. In a recent paper from the journal **Molecular & Cellular Proteomics**, researchers reported the analysis of proteins found in the bones of an extinct species of giant bison from the site. From their analysis, they described an unexpected feature of ancient collagen.

JAMES ST. JOHNS UNDER CREATIVE COMMONS LICENSING

Skeletons of the extinct Bison latifrons.

The bones at the Snowmass Village fossil site (which also is known as the Ziegler reservoir site) were remarkably well-preserved. The high altitude of the site, which was a lake in the Ice Age, kept it at relatively cool temperatures over the past 130,000 to 150,000 years. The cooler temperatures probably contributed to the preservation of the buried materials; even some of the ancient plant material buried at the site was still green at the time of the discovery.

Kirk Hansen at the University of Colorado, Denver, heard of the Snowmass Village discovery in 2010 "while listening to public radio on my way into work." Hansen is a protein biochemist whose expertise is in the extracellular matrix. He called the Denver Museum of Nature & Science, which was directing the excavation of the bones, to see if he could help with analyzing samples.

Hansen's laboratory carries out mass-spectrometry analyses, and he was aware of existing mass-spectrometry work on fossilized proteins. Some studies have suggested that red blood cells can be preserved in ancient bones, but the validity of these interpretations has been questioned. Skeptics also have wondered about inadvertent contamination of ancient samples with modern proteins.

However, Hansen says, "I thought that the methods we were developing to improve characterization of proteins from the extracellular matrix could be used on these well-preserved samples." Hansen knew he would get good-quality samples from the Snowmass Village site when, he says, "one of the scientists described the smell of the bone fossils as 'very organic.'"

Mindful of the issue of contamination, Hansen and colleagues were careful with the samples given to them by the museum. The samples were skull bones from an extinct species of giant-horned bison from the Pleistocene era called Bison latifrons. "We took extra precautions by using new chromatography columns and ensuring the samples were placed in only new vials," he says.

The investigators carried out mass spectrometry on the proteins left in the bison bones. The biggest challenge was in the data analysis. Some of the proteins had degraded as expected of old proteins, producing a

"laddering" effect in the peptides, and numerous peptides were changed by post-translational modifications.

But the investigators sorted through the data and identified extracellular matrix proteins and plasma proteins. Thirty-three of the ancient bison proteins mapped over to modern bovine proteins, showing the evolutionary kinship.

In particular, Hansen and colleagues sequenced in detail the collagen from the bison samples. The extracellular matrix protein, which forms a fibrous, ropelike structure, bore modifications seen in other studies of ancient collagen, such as proline hydroxylation.

But one modification was new and unexpected — hydroxylysine glucosylgalactosylation. "This was the first discovery of a preserved glycan, to the best of my knowledge," says Hansen. "Finding it in a sample that is over 100,000 years old was surprising."

Bioarcheologist Matthew Collins at the University of York in the U.K., who specializes in studying ancient collagen, is most impressed with the finding of the hydroxylysine glucosylgalactosylated residue. Glycosylation is a key structural feature of collagen, crosslinking chains together to stablilize its ropelike structure. But it was assumed the seemingly labile glycosylated residues would not withstand the test of time.

"You'd imagine, over this period of time, you would have lost the sugars. That's one of the reasons why we never bothered to look for them: We didn't expect to find them. This work elegantly shows that I was wrong!" says Collins. "We're now going back and looking at our samples for glycosylated residues."

As Hansen and colleagues were working on the bison samples, data came from a young Siberian woolly mammoth called Lyuba. Her proteins bore similar modifications to those of the bison. "Finding these modifications in modern tissue samples usually requires some form of enrichment," says Hansen. But with these two fossils, "the modifications were relatively easy to find." He says the discoveries suggest that collagen with hydroxylysine glucosylgalactosylation might be enriched over time because it creates a stable complex.

Hansen and his team's next aim is to study the relationships between collagen modifications and collagen fiber architecture. The ramifications of the work will go beyond the study of ancient proteins. As Hansen explains, "Once we make progress in this area, we will have a better understanding of the microenvironment's role in tumor progression and the ability to rationally design biomaterials for tissue engineering applications."

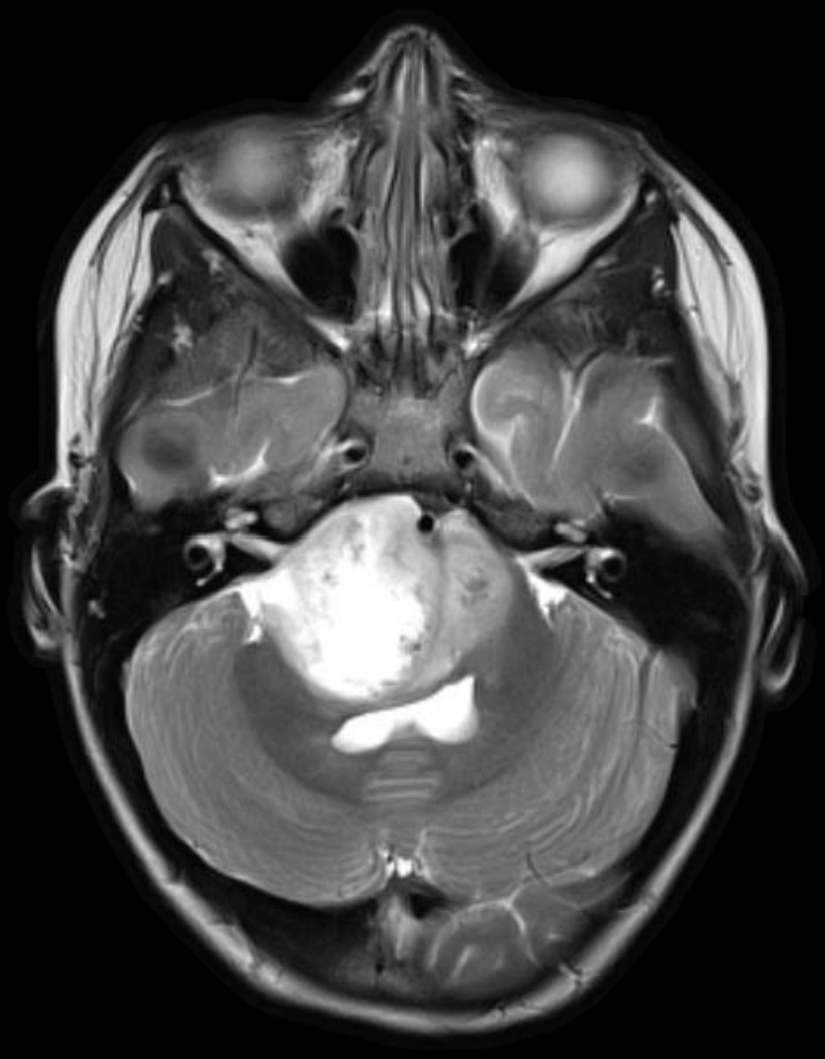
KIRK HANSEN

Cranial bone sample from Bison latifrons that shows connective tissue.

Rajendrani Mukhopadhyay (rmukhopadhyay@asbmb.org) is the chief science correspondent for ASBMB. Follow her on Twitter at twitter.com/rajmukhop, and read her blog at wildtypes.asbmb.org.

A NEW ANGLE

Discovery of a mutation in a rare pediatric brain tumor gives researchers new targets to investigate for a cure



By Rajendrani Mukhopadhyay

"Some of these cancers affect thousands of people. Others affect few. But, regardless of magnitude, the lessons we may learn may cure us all"

– BROOKE AND KEITH DESSERICH IN "NOTES LEFT BEHIND."

Denise Downing remembers feeling incredulous and frightened as she sat with her husband, Jeff, in a doctor's office on a January day in 2012. They just had heard a pediatric neuro-oncologist tell them that their daughter, 4-year-old Caitlin, had a rare brain tumor.

The doctor had diagnosed Caitlin with diffuse intrinsic pontine glioma, or DIPG. Denise Downing asked the specialist how many children had survived the disease and Caitlin's chances of beating it.

The doctor said, "Zero." Bewildered, Downing remembers asking, "Zero what?"

The doctor clarified: There were no survivors of DIPG.

Caitlin Downing died on November 11, 2012, nine months after her diagnosis. She was 5 years old.

Each year in North America, DIPG kills between 250 and 300 children. Knowledge of the tumor stretches back a century, but a treatment, much less a cure, has been elusive. "There's not a single approved drug," says pediatric oncologist Oren Becher at Duke University.

Historically, many clinicians shied away from studying DIPG. "There was a huge disincentive for focusing on the disease. It's rare. Funding was nonexistent. The outcome is dismal. Your chances of succeeding were horribly low," says pediatric neurosurgeon Mark Souweidane of Weill Cornell Medical College.

That's what the Downings discovered: Because DIPG is a rare disease, not much was known about it. Not much funding had gone toward studying it. There wasn't much to do about it.

The pain and anger of having no recourse still ring in Downing's voice. "We live in an age where we spend billions of dollars to send satellites into space, and we don't even get upset when they get lost!" she says. "But 250 children die every year from a brain tumor, and we allow that to go on."

But the tide is turning. Shortly after Caitlin was diagnosed, two scientific papers described the sequences of DNA from DIPG and other pediatric brain tumors. Researchers found mutations in the most unlikely location: histone genes.

Misregulation of proteins such as kinases and cell-cycle regulators is known to promote tumor growth. But not histones. "No one, absolutely no one, in their wildest dreams would have expected this," says C. David Allis of The Rockefeller University, who studies these proteins around which a cell's DNA winds like thread.

Since this unexpected finding, says Souweidane, the nearly nonexistent field of DIPG research has "exploded." Molecular biologists like Allis suddenly are discovering that their curiosity-driven explorations of the genome's packaging material have clinical implications.

'We are going to help you enjoy your child'

The disease affects both girls and boys, usually between the ages of 4 and 11. Children with DIPG typically die within 12 months of their diagnosis.

The tumor sprouts out of a structure in the brainstem known as the pons. The pons is involved in eye movement, balance, hearing, facial expressions and other functions.

Caitlin's first symptom was uncoordinated eye movement. It was the

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DENISE DOWNING

In 2012, Caitlin Downing died at age 5 from a rare pediatric tumor.

WEILL CORNELL MEDICAL COLLEGE

Photo on opposite page shows an image of a child's brain with a tumor.

Some foundations dedicated to DIPG research

Fly a Kite Foundation (*flyakitefoundation.org*), in memory of Zachary Bernstein, age 11

Hope for Caroline Foundation (*hopeforcaroline.org*), in memory of Caroline Cronk, age 5

Jeffrey Thomas Hayden Foundation (*jthf.org*), in memory of Jeffrey Hayden, age 12

Julian Boivin Courage for Cures Foundation *(courageforcures.org*), in memory of Julian Boivin, age 5

The Cristian Rivera Foundation (*cristianriverafoundation.org*), in memory of Cristian Rivera, age 6

The Cure Starts Now (*thecurestartsnow.org*), in memory of Elena Desserich, age 6

The McKenna Claire Foundation (*mckennaclairefoundation.org*), in memory of McKenna Claire Wetzel, age 7

Reflections of Grace Foundation (*reflectionsofgrace.org*), in memory of Grace Elizabeth Ekis, age 6

Children's Brain Tumor Family Foundation (*cbtff.org*), a consortium of families brought together by pediatric brain tumors

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Sunday after Christmas 2011. The Downing family had gathered around the dining table. Denise Downing looked at her third child, whom she describes as a "girly-girl" who loved cheerleading, dancing, gymnastics and dolls all heavily doused in pink. The iris of the preschooler's eye was drifting toward her nose.

Downing has relatives with lazy eye, so she offhandedly asked her husband Jeff, a family practice physician, if lazy eye is genetic. He said it was, and Downing thought no more of it. The next day, she noticed Caitlin's eyes cross several times and that the child was holding her head oddly. Sure she was making something out of nothing, Downing carried on.

By Wednesday, it was clear to both Downing and Caitlin's preschool teacher that the little girl was holding her head almost to the side. Still thinking lazy eye, Downing made an appointment with an ophthalmologist for the next day. The ophthalmologist assured Downing there was nothing wrong with Caitlin.

But something gnawed at Downing, and she decided to keep Caitlin with her that Thursday. Her daughter begged to go back to preschool, but Downing told her that she was going to have a fun day with Mommy with a trip to the mall and a McDonalds' Happy Meal. "I watched her," says Downing. "Every hour, she seemed to be getting worse."

Later in the day, Downing was home with her four children and talking to her oldest daughter, Courtney. Caitlin got up from in front of the television and tried to walk toward Downing. But she ran smack into Courtney and fell down. As she picked herself up, Caitlin, who Downing describes as sweet-tempered, yelled in anger at her sister for deliberately getting in her way. Both Courtney and Downing stared at her in shock. Courtney hadn't budged. Caitlin couldn't tell where Courtney was standing.

Downing's unease turned into panic. When her husband got home late that night, she told him that, without a doubt, something was wrong with their daughter. They took Caitlin to the pediatrician first thing on Friday morning. The pediatrician sent them to the Arnold Palmer Children's Hospital in Orlando, Fla., where Caitlin got an MRI scan. The Downings got the DIPG diagnosis on Friday, January 13, 2012.

Caitlin's symptoms were typical. Parents of DIPG patients report uncoordinated eye movement, uncharacteristic clumsiness, inexplicable mood swings and muscle weakness. The change from a healthy, vibrant child to one stricken with these symptoms happens in a matter of days.

"They progressively lose their ability to move, swallow, smile, talk," says pediatric neuro-oncologist Michelle Monje at Stanford University. "But kids stay very cognitively alert throughout the course of the disease. They are aware of everything happening to them."

She pauses. Then she says, with a catch in her voice, "It's awful."

Downing, a certified bereavement counselor, says, "There is nothing that can prepare you for when a doctor sits across from you and says, 'Your child's got a brain tumor.' Then the second blow comes when I ask, 'How do we treat that?' She says, 'There is no treatment, Mrs. Downing. You have a maximum of 15 months. We are going to help you enjoy your child.'"

No progress

In DIPG, the cancerous tissue is rooted so intricately into the bed of healthy tissue that it's impossible to know how far the tumor spreads and where it ends. Surgeons have attempted to biopsy and cut out the tumor, but because of its vise-like grip on healthy tissue, they never have been able to remove the tumor safely.

With the advent of MRI scanners

in the 1980s, radiologists found they could diagnose the tumor noninvasively. "There was a kind of moratorium, where it felt inappropriate to biopsy the tumors," explains pediatric neuro-oncologist Mark Kieran of Dana-Farber/Boston Children's Cancer and Blood Disorders Center. "The only thing worse than dying of DIPG was to be damaged by the biopsy before you got to die of the DIPG."

Without biopsies, there weren't any DIPG tissue samples to study. Clinicians tried to make do with another cancer, adult glioblastoma multiforme. That brain tumor strikes adults and is thought to be similar to DIPG because the two tumors seem to resemble each other under an optical microscope. Any clinical trial to test potential therapies for DIPG was based on what was known about adult glioblastoma. "We've done that now for 30 to 40 years and unfortunately made no progress in the disease whatsoever," states Kieran.

All doctors can offer to DIPG patients is radiation treatment. Downing and another mother of a DIPG patient, Kristine Wetzel, both mention Neil Armstrong's family. The first man to walk on the moon had a daughter with DIPG. Karen Armstrong died when she was 3 years old in January 1962. Her treatment of cobalt-based radiation wasn't drastically different from the radiation treatment offered to children with DIPG today. In James R. Hansen's authorized biography of the astronaut, "First Man: The Life of Neil A. Armstrong," sources speculate that Armstrong channeled his profound grief over his daughter's death into becoming an astronaut.

Radiation temporarily shrinks the tumor and gives the children a temporary reprieve, known as the honeymoon period, when they can resume their normal activities. But the tumor comes back within months, more aggressive than before, after which there is nothing left to be done.

The most unexpected finding

In 2007, a group of French neurosurgeons safely performed biopsies of 24 children with DIPG. Kieran, who had been arguing unsuccessfully for the need to biopsy DIPG patients to advance the field, says the French demonstration provided perfect leverage: "We had to argue that either the French neurosurgeons were infinitely more capable than American neurosurgeons or it was time to allow us to start to move forward."

Getting actual DIPG samples was a major step forward for the field. Another was that the parents of patients with pediatric brain tumors were growing increasingly vocal in advocating for more research and allowing their children to be autopsied.

Indeed, it was with autopsy samples that researchers took an important step in understanding the molecular biology of pediatric brain tumors. In 2012, two groups of researchers, one led by pediatric oncologist Nada Jabado at McGill University and the other by developmental neurobiologist Suzanne Baker at St. Jude's Children's Hospital, published data from autopsied pediatric brain tumors. Independently, the groups had sequenced the DNA extracted from the tumors, including DIPG, and discovered mutations in histones.

In the cell's nucleus, histone proteins form a series of complexes around which DNA wraps. Histone complexes undergo a slew of post-translational modifications — methylation, acetylation, ubiquitination — to dictate how tightly or loosely DNA wraps around them. The complicated pattern of post-translational modifications influences whether or not genes around the histones are transcribed.

Four types of proteins make up a histone complex. One is called histone H3. It is one of the most conserved and fundamental components

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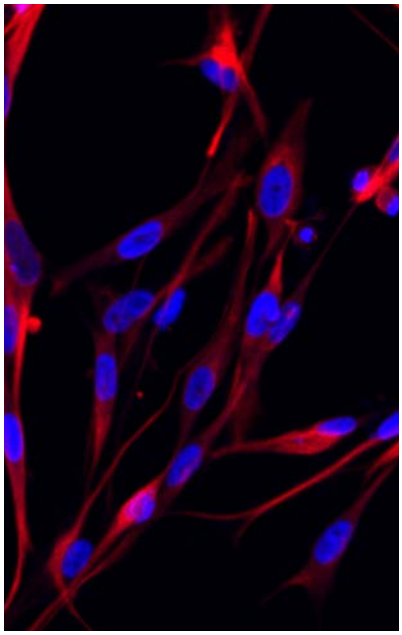

MICHELLE MONJE

Fluorescent images of cells taken from a DIPG sample.

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of the histone complexes, and it has three variants, H3.1, H3.2 and H3.3.

In the non-DIPG tumors in the brain's cerebral cortex, investigators found a mutation in H3.1 that changed the code for a glycine residue called G34 into the code for a valine or arginine residue. This mutation had a ripple effect: A lysine two residues down from G34, called K36, became improperly methylated.

In about 80 percent of the DIPG tumors, investigators discovered a different mutation in histones. This mutation took place in the genetic code for a specific lysine residue called K27. The mutation changed the lysine to a methionine. The mutation is known as K27M. Three-quarters of the DIPG tumors with histone gene mutations had the K27M mutation in H3.3; the remaining quarter had the glycine mutation in H3.1.

The genome contains multiple copies of H3.1 and H3.3. But these mutations turned up only once in a single copy of each gene. Other copies of the genes were normal. The genes "are so redundant that it was unexpected a single one of those genes would be a hotspot" for mutations, says Baker.

Not only does K27M prevent methylation, says histone-expert Allis, but it also looks like the mutation poisons the enzymes that add on the methyl groups, causing methylation to go awry across the genome.

A year after the Jadabo and Baker groups published their results, histone mutations were implicated in other pediatric diseases. Researchers found that H3 gene mutations now are present in more than 90 percent of two types of pediatric bone cancers.

Histone mutations are some of the hottest targets in oncologic drug development. Earlier, scientists had targeted enzymes that modified histone proteins, and several phase I clinical trials are under way to test small molecules against those histone-modifying enzymes. But until the mutations were found in DIPG and other pediatric cancers, no one thought to target the histones themselves.

Researchers have found additional mutations that may affect the progress of DIPG. Last year, investigators found mutations in a gene called ACVR1 that accompany the mutations in H3.1. Unlike the histone-gene mutations, the ACVR1 gene has been implicated in fibrodysplasia ossificans progressiva, another rare

Deciding to donate

The decision to allow a child's tissues to be used for research stirs up conflicting emotions. Kristine Wetzel and her husband, Dave, decided to donate their daughter McKenna's brain and spinal cord when she died from DIPG four years ago. A friend and neighbor of the Wetzels, Lisa Roberts, was the one to suggest tissue donation.

Wetzel says the decision to donate came easily as McKenna reached her final hours on July 21, 2011, two weeks shy of her eighth birthday. "It was our way of fighting back," says Wetzel. "I wanted her life to have meaning, and I wanted her death to have meaning as well."

When McKenna died, Roberts made the arrangements to have McKenna's organs sent to Michelle Monje's laboratory at Stanford. Since then, the Monje lab has established a cell line from her tumor.

But the decision brought up pain. Wetzel, a high-school history and English teacher, says that the first time she held a Petri dish of DIPG cells in the Monje lab was the worst moment of her life after losing McKenna. All she could think was, "This is what is left of my daughter – the thing that killed her is the only thing that is still alive."

But with the discoveries coming out of the DIPG field, Wetzel has come to see the power of tissue donation. She also finds comfort in the idea that even in a laboratory setting, McKenna lives on as the name of the cell line.

disease. In that disease, patients slowly accumulate abnormal bony tissue; the illness sometimes is referred to as 'stone man disease.' Connective tissue starts to turn to bone, and patients soon can't breathe.

While these breakthroughs are exciting, they have left researchers with many questions. How can a mutation in a single copy of a histone gene be so potent as to cause cancer? How do these mutations promote tumor growth? And why do these mutations cause only pediatric forms of brain and bone tumors? There are hints that the spatiotemporal expression of these genes explains why DIPG happens in children only in a certain time frame.

What is obvious, says Becher, is that pediatric cancers are distinctly different from adult cancers. Pediatric cancers are products of developmental pathways gone awry. Adult cancers are manifestations of misregulation of the cell cycle.

The fresh research into what causes pediatric brain cancers is exactly what Keith Desserich, a founder of The Cure Starts Now, wants to see. His 6-year-old daughter Elena, whom Desserich describes as a perfect little lady, died from DIPG in 2007. In Desserich's view, cancer research has been far too dependent on the trifecta of surgery, radiation and standard chemotherapy.

"For the last 80 years, we focused on the same three tenets and tweaked our way to treatments," says Desserich. "You can't make monumental advances through incremental science. You need to change the way you think about everything if you're going to try to find a cure."

No more double blows

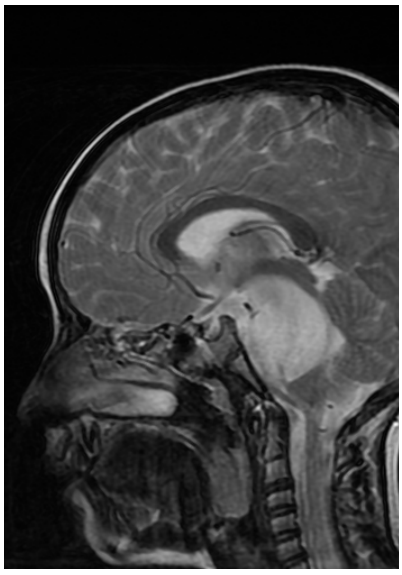
Researchers are unanimous when they say that the parents of patients have changed the landscape of DIPG research in the past decade by allowing biopsies and autopsies of their children and raising money for research (see "Deciding to donate"). With these resources in hand, researchers are developing appropriate cell lines and animal models that more accurately reflect DIPG as well as carrying out better-informed clinical trials. Today, there are 37 ongoing clinical trials targeting DIPG.

Parents of DIPG patients talk about balancing making sure their children live full lives in their last few months and going all-out to fight for more time. The Downings, after spending hours combing through the scientific literature, decided to enroll Caitlin in a clinical trial headed up by Souweidane in New York City.

Caitlin was the first child to be enrolled in the trial, which is still ongoing. It is exploring the targeted delivery of a radioactive monoclonal antibody directly into the tumor through a catheter. The Downings had to make several trips between New York City and Orlando, with Caitlin eager to see her beloved "Dr. Mark." Two weeks after she underwent surgery to embed the catheter into the tumor, Caitlin celebrated her fifth birthday dressed in a resplendently pink Hello Kitty outfit accented with fake pink hair.

When Caitlin died six months later, the Downings donated Caitlin's brain and spinal cord to Souweidane's research group. Denise Downing, like every other parent of a child stricken with DIPG, has become a vocal advocate and supporter of more research: "I hope the outcome of doing the science is that someday, that pediatric neuro-oncologist is going to sit across from a set of parents and she's going to hand them that first blow. She's going to say, 'Your child has a brain tumor.' Those parents are going to panic," says Downing. "But she's not going to deliver the second blow, because she's not going to say, 'We don't know how to treat that.' Instead, she will say, 'We know how to cure that.'"

With her voice breaking, Downing says, "I know that the day will come."



WEILL-CORNELL MEDICAL COLLEGE

MRI of a DIPG tumor. The tumor is the diffuse white mass at the top of the spiral cord.

Rajendrani Mukhopadhyay (rmukhopadhyay@asbmb.org) is the chief science correspondent for ASBMB. Follow her on Twitter at twitter.com/rajmukhop, and read her blog at wildtypes.asbmb.org.

Meet Svetlana Lutsenko

An associate editor of the Journal of Biological Chemistry

By Mollie Rappe

Svetlana Lutsenko at The Johns Hopkins University joined the ranks of the associate editors at the Journal of Biological Chemistry in February 2014. Her laboratory focuses on copper homeostasis. The interview has been edited for length and clarity.

Would you briefly explain what your research group is studying?

We work on human copper metabolism. We are very interested in it, because copper is an essential metal for human growth and development, and disruption of copper homeostasis causes a wide spectrum of pathologies. As an essential enzyme cofactor, copper is important for respiration, for formation of vascular tissue and for brain development. Enzymes that require copper as a cofactor produce catecholamines, so whether we are happy, sad or depressed very much depends on whether we have sufficient copper.

There are two well-described human diseases that have been known for almost a hundred years that are caused by copper imbalance. Menkes disease is an X-linked chromosomal disorder affecting boys. They invariably die because they are deficient in copper absorption in the gut and copper delivery in the brain. The other disease is Wilson's disease, which is a disease of copper overload.

In the past two decades, copper research has progressed significantly. Starting from having only cDNAs of genes and no experimental information about copper transport across various membranes, we and others have gained a lot of insights into how transporters work and how they are regulated in a cell.

Using genetically engineered mice to study Wilson's disease helped us to uncover new metabolic links between copper homeostasis and lipid metabolism. We have characterized a mouse model for Wilson's disease that is now used by a lot of people. My mice, I tell people, are better traveled than I am. Right now, we are trying to generate a comprehensive picture of how transporters work in human cells and how they are regulated — and also what happens in disease.

The more I learn, the more interesting it becomes, because we now

know that copper intersects with many metabolic pathways. We have discovered there is a very tight connection with lipid metabolism, and right now we are really very excited about learning more about the role of copper in adipocyte maturation. Also, we are very interested in neuronal degeneration and how copper contributes to CNS development and function.

Tell us about your academic background and research training.

I received my undergraduate degree at Moscow State University; I was born in Moscow. I was really torn initially between chemistry and biology, because I really like chemistry; but I also like furry and fuzzy things, and biology seemed appealing.

I was always interested in membrane transporters. I'm just really fascinated. What's going on in the membrane? How do cells talk to each other? How do they get stuff in? Out? When I was an undergraduate student, I decided to do my undergraduate research working on the Na^+/K^+-ATPase and the Ca^{2+} ATPase.

I did my Ph.D. in membrane biology working on the Na^+/K^+-ATPase, trying again to understand how this transporter works. The institute where I did my Ph.D. is the Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry. Their strength is in membrane biology, so it was very good for membrane biology and biochemistry of membranes.

After that, I realized it would be really nice to have advanced postdoctoral training, and fortunately or unfortunately the Soviet Union was starting to fall apart … so I had an opportunity to go abroad and do a postdoc. I did my postdoctoral studies at the University of Pennsylvania in the physiology department. I continued to be interested in membrane transporters and expanded my studies to look at the functional role of the beta subunit of the Na^+/K^+-ATPase and conformational changes associated with the transport cycle.

While I was at Penn, I became interested in copper. Then I moved to Oregon Health & Sciences University. I was hired there as an assistant professor. I went through the ranks at OHSU and established my independent lab, and then I came to Hopkins in 2009 as a full professor.

Hopkins is really great because people are so interested in science here and we can work with clinicians. We have very good collaborators in the department of medicine, so we can actually start translating our findings. We are still in the early stages, but we have started treating animals with drugs and we have had certain small successes at improving liver function in the Wilson's disease animal model.

Did anything occur, in a milestone sort of way, that made you choose science as a career?

I have always wanted to investigate something. As an 8-year-old girl — I think this was unusual — I wanted to be a detective.

My parents are both scientists. My mom spent most of her time teaching, and my father was a scientist. I just wanted to learn how everything works.

What does it mean to you, on a personal level, to be an associate editor for JBC? What was your reaction when you were asked to be an associate editor?

Oh, I was delighted! I was really

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delighted, because I remember JBC being my favorite journal as a graduate student.

I was in Russia. At that time — it is funny how things change — we couldn't check magazines out of the library without permission. Everything was so controlled, all the information. We could make a Xerox copy only after filing a request and getting signed permission for every page. So I was carrying this big green JBC magazine back and forth, and because I wanted to read quite a few of them and they were very thick at the time, it was a lot of exercise just to carry the JBC to the Xerox copier and back.

Scientific journals were the only way you could get knowledge of what was going on (in the West). The first time I came to the United States in '89 and saw all these people who published these papers, it was wonderful. Then becoming an associate editor of the journal that I used to go and get permission to copy from the library — it was really very nice.

What do you think is the most exciting thing about science these days?

I remember I would go to a cell biology meeting and many studies were fascinating but rather descriptive, and I would go to biophysical meetings and though that technology is great, the questions were far from real biology.

Now, we have this synergy where there are great technologies that are finally coming to the stage where we can apply technology and really address, mechanistically, fascinating questions about development, about cell programming, about regulation. The most fascinating aspect of science right now is that it is easier to study fascinating biological questions mechanistically. Like for real, with tools, and technology, and resolution, and numbers.

For scientists in training, do you have any words of wisdom or a favorite motto?

What I tell people in my lab is this: As long as you're interested in what you do, things will fall the right way. I believe it is very important to do not necessarily what is fashionable today but what you feel excited about, because fashions change. Of course there are ups and downs, and there always are, and things are sometimes harder, sometimes easier. Some fields are sexier than others, and they are somewhat easier, maybe, in terms of funding, but there's also more competition. I think the way to have a good time is actually to like what you do.

Mollie Rappe (mrappe@asbmb.org) is a Ph.D. candidate in biophysics at Johns Hopkins University and a former intern at ASBMB Today.

Observing Father's Day

Visit the online version of this issue to see snapshots of ASBMB members with their dads and kids: *asbmb.org/asbmbtoday*

Visit our chief science correspondent's blog, Wild Types, to read about Journal of Biological Chemistry Associate Editor Henrik Dohlman (right) and his father, prominent vision researcher Claes Dohlman: *wildtypes.asbmb.org*

DEFYING STEREOTYPES:

"So, a biochemist walks into a comedy club …"

Stand-up comedian Joe Wong traded in his lab tools for a microphone

By Rajendrani Mukhopadhyay & Geoffrey Hunt

Many people have poked fun at Vice President Joe Biden. But at the 2010 Radio and Television Correspondents Association Dinner in Washington, D.C., there was something decidedly unique about the person roasting Biden.

"I actually read your autobiography," comedian Joe Wong told Biden. "Today, I see you. I think the book is much better."

It wasn't the jokes or the straitlaced delivery that stood out but rather the fact that Wong isn't your typical comedian. He has an advanced degree in biochemistry, something that none of the previous hosts of the swanky black-tie event, including Wayne Brady and Don Imus, can lay claim to.

How did a Chinese immigrant who once studied neurotransmitters in fruit flies wind up on stage telling jokes at the expense of the second-highest ranking U.S. official? According to Wong, delivering jokes and getting data have more in common than one would think.

"In science, you have to fail so many times," he says. "I've learned to deal with failure. That's very important. A lot of people try stand-up comedy. They do a bunch of jokes, and if things didn't work out, they get really frustrated. They give up."

That's the other commonality between science and comedy — perseverance. "In science, you don't always make great discoveries. There's a lot of frustration. You just have to keep doing it," notes Wong. "It's the same with comedy. Nobody can guarantee you're going to write a great joke tomorrow, but you just have to keep trying."

Wong readily acknowledges that the transition from biochemist to comedian is "not very direct." Growing up in mainland China, Wong says, "I grasped American humor early for some reason." He counted Woody Allen and George Carlin among his comedy idols.

While in college in China, Wong says, "Some of my classmates were trying to read jokes off Reader's Digest. They understood every word in the jokes. But they didn't understand why it was so funny. I had to explain to them why this joke was funny."

Though his adeptness at American humor may have set him apart from his Chinese peers, Wong stuck to a more traditional career path at first.

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IMAGES PRODVIDED BY JOE WONG

Former biochemist Joe Wong is now a larger-than-life comedian.

JOE WONG

Wong has performed on American talk shows and hosts his own TV show in China.

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He enrolled at the Chinese Academy of Sciences to study molecular biology and in 1994 moved to the U.S. as a graduate student at Rice University. After earning his Ph.D. in 2000, Wong joined a startup company that didn't survive long, so he next moved to Boston for a job at Sanofi Aventis.

The change of scenery gave Wong the chance to "explore different things and hobbies," as he puts it. "I played a little golf. Then I took a stand-up comedy class." With that class, a change in careers began. Wong fine-tuned his routines in clubs around Boston, struggling to get noticed. "After you do this for about seven or eight years, gradually, you know your own style, and at that point, it's a little bit easier," he says.

His perseverance paid off in 2010 when Wong was named Boston Comedian of the Year and won recognition at the Great American Comedy Festival.

Catapulted to stardom, Wong has made numerous memorable appearances, including ones on "The Ellen DeGeneres Show" and "The Late Show with David Letterman," along with his gig at the correspondents' dinner, which he considers a career highlight.

"Growing up, I could never imagine comedy could be used to talk about so many different topics, from philosophy to politics," says Wong. "In China, you can't joke about political leaders, that's for sure."

The ability Wong showed in adroitly tweaking Biden that night is a good example of how engrained he has become in American culture and society, something he chalks up to effort. Even as a graduate student, he says, he worked hard to be plugged into mainstream America, reading novels while experiments ran "to get to know the American society a little bit better."

Such in-depth knowledge of how America functions has been important for Wong, because audiences in the U.S. and China latch onto different things as funny. "Every country has different rules," he says. "You have to know how people live." In the U.S., Wong stays away from jokes about public transportation, because most people drive their own cars. But in China, "jokes about the subway are really popular," he says.

Wong keeps his scientific training hidden during his routines and sticks to more general topics. "As soon as people know I have a degree in biochemistry, they tune out," he says. But Wong notes with some satisfaction that he once managed to get a joke about nitric oxide out on Letterman.

Nowadays, Wong is busy doing gigs around Beijing and hosting his own show on Chinese television called "Is It True?" Watched by 5 million to 7 million viewers each week, the show offers a smorgasbord of comedy and investigative reporting and is, according to Wong, the highest rated one for the network that carries it. He also makes guest appearances in plays or other TV shows and does comedy routines at corporate events, schools and comedy clubs. His wife, who used to be a financial manager at Fidelity Investments in the U.S., now manages his career.

Having left a relatively tame scientific career for the roller-coaster life of a comedian, Wong emphasizes that "it's important for people who want to do something slightly different in science" not to be afraid to take a chance. For once, he isn't joking.

Rajendrani Mukhopadhyay (rmukhopadhyay@asbmb.org) is the chief science correspondent for ASBMB. Follow her on Twitter at twitter.com/rajmukhop, and read her blog at wildtypes.asbmb.org. Geoffrey Hunt (ghunt@asbmb.org) is the ASBMB's public outreach coordinator. Follow him on Twitter at twitter.com/thegeoffhunt. Both writers contribute equally in creating and developing the profiles for the "Defying Stereotypes" series.

Temptation

By Najla Arshad

December 7, 2004

It's three in the afternoon,
full stomach,
shaded, cool bedroom,

the soft teddy bears call,
the bed looks inviting —
It's siesta time, after all

Cool pillow to lay my head,
the gentle whirr of the fan —
Oh, to snuggle up in bed!

Across the room, a stark reminder —
my cluttered table —
of exams round the corner

The fingers bleed from paper cuts,
from sifting through notes
stuck in that student's rut …

of inky hands, notes awry,
and books piled
precariously high

As sleep with sweet dreams tries to lure,
my wake-up call
is my Lehninger crashing to the floor

Wearily, I try to study,
to stay awake
and make my dreams a reality!

Then

Now

December 17, 2014

In the lab close to midnight,
the lack of sleep
is blurring my sight

One more wash to go
to develop my blot —
ten minutes more

I've stayed so late
to know this result
Nervously, I wait

The film emerges —
a failed experiment!
My heart submerges

Around every corner, failure lurks,
but our tenacity tells us,
"Next time, it will work!"

Indeed there is still hope and joy,
for the other has repeated (thrice!)
and serves as my heart's buoy

We've uncovered another piece
of Nature's puzzle,
so tonight I sleep in peace

Research may seem
a nightmare,
but I'm living my dream.

Najla Arshad (najla.arshad@gmail.com) graduated from the Indian Institute of Science in Bangalore, India. She is currently a postdoc at Yale University School of Medicine. Photos courtesy of Arshad.

The truth goes only so far

Scientists need to do more to increase scientific literacy in their communities

By Leonardo Valdivieso–Torres

Science impacts all of us, and knowledge of it should not be exclusive to scientists. I think this is the perfect time to build more and stronger bridges between scientists and their communities. We scientists must reach out and help our neighbors understand the facts, the scientific process, and the risks and rewards of technologies. We must talk to our family members and friends about the everyday discoveries that lead to improvements to our quality of life and that should not be taken for granted.

Why do I say this?

The volume of scientific knowledge is growing to the point that sometimes even scientists within the same discipline need to fill big gaps of knowledge to understand each other. How many of us have gone to a presentation that we cannot get much out of (sometimes nothing) — not because it is hard to understand but because we are not familiar with the techniques or vocabulary?

The same thing happens with the public and our politicians. Despite an overwhelming amount of research by the scientific community confirming the safety of drugs, vaccines, antibiotics and genetically modified organisms, many people have doubts about these advancements.

I asked Bruce M. Chassy, a professor emeritus at the University of Illinois who runs a website (academicsreview.org) intended to demystify controversial science, why he thought sound science isn't necessarily the prime driver of public attitudes. "There's plenty of good information out there for someone who cares to dig for it and can understand it," he said.

Scientists often think that the truth will gain the public's trust, but this is not always the case. Unfortunately, a lot of misinformation is published on the Internet and broadcast on TV, two of the public's major sources of information. And with scientists making up less than 1 percent of the world's population, it is very unlikely that a member of the public will meet a scientist in his or her life.

I worry we scientists are not doing enough to clarify misconceptions among the general population. Herein, I offer three ways to do more.

Hold informational seminars

Organize short seminars for faculty members and students from other university departments and invite the public to attend. Universities often have conferences on different topics, but the great majority, if not all, are designed to be understood by scientists and not the general public.

At Rutgers University, we have Rutgers Day, at which time the university is open to the public and many activities are performed for kids and adults. Science clubs and departments often have booths for performing DNA extractions and other science activities. Local families and members of the Rutgers community enjoy these activities while learning key science concepts and about the university. It would be great if we could add seminars on science misconceptions on the evening of this event. This is one example of an existing activity that we can take advantage of.

Join an outreach program

Formal science-outreach programs also can clear up misconceptions among the public. There are many scientific societies through which you can get involved in outreach. Sometimes you can even get paid for it.

At Rutgers, we have the Rutgers Science Explorer Bus, which is an ambulatory science laboratory that travels to K – 12 schools. Student participants perform basic experiments and learn science concepts while being supervised by scientists.

I volunteer with the Rutgers University and Robert Wood Johnson Bio Links program. It pairs a postdoc or graduate student with a teacher in a public school to assist with teaching science once a week. I have had the opportunity and flexibility to come up with my own ideas and implement them in the classroom. I have touched upon science misconceptions and taught with hands-on experiments how science positively affects

SHANNON ALBERS

The author, Leonardo Valdivieso–Torres, talks to David Tribe (left), a professor at the Melbourne University, during the 2015 Biotechnology Literacy Project Boot Camp at the University of California, Davis, in June. At the three-day event, undergraduate students, graduate students and postdoctoral fellows learned more about and practiced engaging the public in discussions about biotechnology, nutrition and agriculture.

our everyday lives. I know it might sound like a lot of work, and it's definitely not easy, but the smiles of those kids when they learn and enjoy the activity easily can make it seem like a hobby instead of a burden.

The University of Hawaii at Manoa offers another good example of formal science outreach. The GENE-ius Day Program exposes students in first grade through eighth grade to hands-on biotechnology experiments, organizes field trips, and holds talks on the relationship between science and the food we eat. GENE-ius leader Ania Wieczorek also started Bio-Tech in Focus, a website that publishes, twice a month, a bulletin addressing biotechnology concerns. We need outreach activities like these that focus on vaccines and global warming, for example, with support from experts in those fields.

The benefits of doing formal science outreach far outweigh the burdens. Scientists and science students who get involved gain teaching experience that can enhance their repertoire of skills. I personally have had to become more creative to engage kids and make sure I do not lose their focus. And to my satisfaction, 10 kids have gotten to meet a scientist, something that otherwise probably would not have happened.

Donate to nonprofits to support science outreach

Donations to scientific nonprofits are often tax deductible, and this is perhaps the easiest way for us to contribute.

As Donna Kridelbaugh noted in her article "The giving list: supporting science with annual donations" for ASBMB Today, we all can make a giving list to support science with annual donations and promote a philanthropic culture. There are plenty of nonprofits that promote science literacy for adults, put scientists in K – 12 classrooms and perform hands-on activities in public places. These organizations often need money.

Finally, I know it is easy to get lost in the details of the everyday work of a scientist – troubleshooting, writing, reading and even taking a little time to think and dream. However, we always should keep in mind the big picture and the great advances we all have achieved as a community. Let's share these goodies through science outreach.

Leonardo Valdivieso–Torres (valdivieso.leonardo@gmail.com) is a Ph.D. candidate in biochemistry and molecular biology at Robert Wood Johnson Medical School at Rutgers University.

Donate your time and money

Check out these resources:
American Society for Biochemistry and Molecular Biology (*asbmb.org/Outreach*)
Genetic Literacy Project (*geneticliteracyproject.org*)
Academics Review (*academicsreview.org*)
Science Cafes (*sciencecafes.org*)

Find a program that's right for you:
Volunteer Match (*volunteermatch.org*)
All for Good (*allforgood.org*)
Association for Science-Technology Centers (*astc.org*)

Connect with local venues:
Nature centers and gardens
Museums
Science centers
Park authorities
Science and engineering fairs
Community centers
Fitness centers
Science and engineering clubs

Something is fishy in the dean's office!

By Samarpita Sengupta

Mark Schmitt is the dean of the College of Graduate Studies at Upstate Medical University in the State University of New York. His passions in life include the endoribonuclease RNase MRP and a 120-gallon saltwater reef fish tank containing a variety of fish and coral.

A blog post by his institution described the biochemistry and molecular biology professor's tank as "home to more than 30 kinds of live coral and seven colorful fish – a purple tang and a hippo tang (think Dory from Disney), a pair of clownfish (Nemo), a coral beauty, a royal gramma and a very shy Mandarin that is rarely seen."

Schmitt says: "There's a lot of science involved in maintaining the whole reef tank, so, being a scientist, I find it to be very fascinating."

Schmitt feeds the fish three times a week and says the tank, which is an ecosystem on its own, containing fancy equipment such as an ultraviolet sterilizer, a protein skimmer, a sump filter, a bioreactor and special lights, has a calming effect when the stress of grant deadlines and paper submissions begins to take its toll.

Schmitt has been an American Society for Biochemistry and Molecular Biology member for 21 years.

Samarpita Sengupta (samarpita.sengupta@utsouthwestern.edu) is a postdoctoral fellow in the pharmacology and neuroscience departments at the University of Texas-Southwestern Medical Center at Dallas.

WILLIAM MUELLER/UPSTATE MEDICAL UNIVERSITY

Playing games to learn

By Paul Sirajuddin

A cute yet determined blue monster hobbles across an alien, planetlike surface toward a green haystack of pulsating rods, gobbling them up with an audible and satisfactory "Mmmm." With a jovial grin on his face, the monster pats his stomach in glee, having finished his feast.

You might think this is a scene from the newest Pixar animated short. In fact, it's the college-level, science-themed video game ImmuneQuest, in which users direct the movements of a macrophage seeking out and eating up harmful bacteria colonies infecting a host (1).

The Electronic Software Association estimates that in 2014, 59 percent of Americans played video games on their smartphones, personal computers or game consoles. As technology and gadgets extend their reach into nearly every aspect of society, educators increasingly are using these new mediums to teach complex concepts.

Syandus Inc., the maker of ImmuneQuest, is just one of several developers that are aiming to take this opportunity to the next level and partnering with scientists. In ImmuneQuest, players take control of the immune system by directing an arsenal of colorful 3-D animations of macrophages and neutrophils, among others, to fight off infections. It is a strategy combat game akin to blockbuster videogames like Starcraft and Civilization. It even stars the voice actors in those high-profile videogames.

While the idea of such games may have seemed far-fetched years ago, there is now considerable support for them. Syandus, for example, has received several funding awards, including a grant from the National Science Foundation, to allow its team of scientists, game developers and engineers to bring the product to maturity. Other developers have created games in which players fold proteins and even build RNA chains.

Public engagement

Each year, upwards of 350,000 children, students and curious participants attend the Science and Engineering Festival in Washington, D.C., a multiday exhibition and celebration of science, technology, engineering and mathematics, collectively known as STEM. Though this seems like a great number of attendees, sustained public interest in STEM has been difficult to garner. A constant challenge for scientists is broadly communicating their ideas and engaging the public in a manner that enables them to take a more active role in science.

At the D.C. science festival in 2014, it was clear that scientists have to move beyond using static textbooks to engage the public, as evidenced by flashy projection screens and interactive demos on tablets. As an attendee at this conference, I was struck by how the interactive games about science were a hit.

No force-feeding

Using science-themed video games as an outreach medium is starting to pay off. Many of these games are now pilot testing in high-school and college-level classrooms.

As important as it is to make an attractive and engaging game, developers are careful not to overwhelm players with science all at once. Take ImmuneQuest as an example: As students progress through the game, they unlock more components of the immune system to use to combat enemy bacteria and viruses. Knowing which components of the immune system work best for each enemy scenario is essential to completing each mission. Windows pop up on the screen with text explaining the science behind the cute characters that fight pathogens in the body, teaching users how the immune system works as the game moves along.

Players get upgrades based on how well they understand the material and answer questions correctly in a quiz-like format. The playing and learning are integrated seamlessly so that it never feels like the science is being force fed, something that has been a peril of past so-called edutainment products.

The collective power of gamers

Multiplayer games harness the power of pulling individuals together for a common cause. When news of the Ebola outbreak in West Africa gripped the public this past summer, there was a real fear of a global pandemic but also an urgency to develop a vaccine to treat Ebola, one of the deadliest diseases in recent times, for which no cure exists. A group of scientists from the University of Washington joined the fight against Ebola with their collaborative massively multiplayer protein-folding puzzle game, Foldit (2).

In Foldit, players bend, pull and fold squiggly green lines that represent amino acids and assemble them into proteins in a 3-D space based on the rules of physics and molecular

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charges, all while competing with one another to find the highest-scoring protein structures. Though solving 3-D structures of proteins historically has been done using powerful computers and complex computer algorithms, the scientists found that human players often were more resourceful and, in some cases, quicker at solving protein structures than computers.

This crowdsourcing of brain power made headlines in 2011 when Foldit gamers, in just three weeks, solved the structure of an enzyme that dictates how HIV replicates, a puzzle that had baffled scientists for more than a decade. More recently, Foldit programmers released an Ebola challenge that tasked its 200,000 users worldwide to discover protein conformations that essentially can gum up the Ebola virus and halt it from propagating.

The real power in this game, however, is what happens after players complete the challenges and put down their keyboards and mice. Findings from the game can be extrapolated to a wet lab and tested in the real world, which has the potential to translate into new cures that never would have been found otherwise or would have taken years longer to find.

Similar to Foldit is Stanford University and Carnegie Mellon's RNA-building, browser-based game EteRNA (3). In that game, which is supported by a National Science Foundation grant, players build RNA sequences that self-assemble and fold into functional biological models.

EteRNA's puzzles have drawn tens of thousands of users. Results from EteRNA have been published in the Proceedings of the National Academy of Science, where the gamers were acknowledged alongside the medical researchers as co-authors of the papers.

Given the success of these examples, it's clear that videogames and science have a synergistic future ahead of them. Science outreach is changing: It's becoming digital and interactive. It may not be uncommon to see more classrooms use these products as teaching tools. Instead of killing zombies late at night, the next generation of students might stay up late killing virtual pathogens to give them a leg up on their homework.

REFERENCES

1. *http://immunequest.com/*
2. *https://fold.it/portal/*
3. *http://eterna.cmu.edu/web/*

Paul Sirajuddin (psiraju1@jhmi.edu) is a radiation oncology postdoctoral fellow at The Johns Hopkins School of Medicine.

Science? There's an app for that!

Immune Defense

In each and every person, a war has been raging far longer than any in the history of civilization: the war of the immune system. The game Immune Defense is the brainchild of Melanie Stegman of Molecular Jig Games. It blends a classic tower-defense strategy with the dynamic world of immunology by teaching players how to use neutrophils and macrophages to destroy bacteria, not unlike what is happening inside the players' bodies at all times. Stegman has said she aims to use the game to increase awareness and interest in science. The result is an entertaining and educational experience for students from middle school to college.
Website: *molecularjig.com/immune-defense-game*
Platforms: PC, iOS

Doctor Mole

Summer is a time for having fun, relaxing and going to the beach. However, warnings are plentiful urging people to apply ample sunscreen to avoid getting melanoma, a skin cancer that originates in the pigment-producing melanocytes on the skin in the form of moles. Doctors have devised a system, the ABCD system (which stands for asymmetry, borders, color and diameter), to detect the warning signs that a mole might be turning malignant. But now people can take the doctor with them to the beach in the form of an app called Doctor Mole. A user can take a photo of his or her moles, and this app will analyze it using the classic ABCD signs that physicians use. It then rates each category on a scale and even gives the user photos of examples to educate him or her on what is normal and abnormal.
Website: *doctormole.com*
Platforms: iOS, Android

3D Brain

This app puts the whole brain in the palm of your hand. Cold Spring Harbor Laboratory created this simple yet informative app for medical students, neuroscience majors or anyone with an interest in the brain. Users can touch a smartphone or tablet to rotate, zoom and see details and names of 28 structures of the brain. Touching the different sections reveals more detailed information including functions, disorders, case studies and links to recent research.
Website: *itunes.apple.com/us/app/3d-brain/id331399332?mt=8*
Platforms: iOS, Android

Empty bench syndrome

Here's to all the undergrad research mentors who said goodbye to great students and felt that little pang of sadness as they cleared the bench for a new researcher

By P. H. Grey

In May, an undergrad who spent three years in our lab finished her last experiment and made the last update in her lab notebook. It was a bittersweet day.

Madi joined the lab the summer after her first year of college. Like most undergrads I work with, she was unfamiliar with the concepts and inexperienced with the skills of molecular research. In her first summer, Madi put in 30 hours a week at the bench learning how to pipette, pour agarose gels, perform cloning reactions, safely run the autoclave, keep a proper notebook, troubleshoot techniques and interpret results. She learned, practiced and refined core techniques that she would use for her projects over the next three years.

Throughout her time in the lab, Madi, a microbiology major and premed student, worked hard. She optimized protein expression of several clones, completed actin assays on the confocal microscope and analyzed the data using the statistical programming language known as R. She used her expertise to help train other undergrads and always stepped up to take on extra responsibility.

The Monday after she left, when I glanced at the empty bench across from me, I felt a pang of sadness. Training, advising and mentoring Madi hadn't been my job as much as it had been my privilege – as is often the case.

As a full-time research scientist and mentor in David Oppenheimer's lab at the University of Florida, I think it's important to get to know my undergrads so that I can help them reach both their personal and professional goals. It's also important so I can direct them to specific opportunities that will help them get the most out of their college experiences.

P. H. GREY

When the bench is empty, a mentor should feel proud for giving an undergrad the tools and confidence to thrive in the research world.

For example, I encouraged Madi to apply to the Frost Scholarship Programme, which funds science, technology, engineering and math students to pursue a master's degree at the University of Oxford. Because I had taken the time to get to know Madi, I knew she was a perfect fit. When she was accepted to Oxford on a full scholarship, the entire lab celebrated.

By the time any undergrad's research experience comes to an end, I've been proud of his or her accomplishments many times over – and not just because of poster presentations, fellowships or research awards. It's also the little things, such as when an undergrad finds the self-discipline to master a difficult technique or says to me, "Of my two options for the next research step, I think I should choose No. 1 because …" or when an undergrad analyzes a result and, before I've even weighed in, realizes the next question that should be asked.

What I want students to know is this: As an undergrad in the lab, the impact you make might be more than the results and data you contribute. The bigger the impact your research mentor makes on you, well, the bigger the impact you're probably making on her.

P. H. Grey (phgrey@ufl.edu) works as a molecular biologist and is co-creator of undergradinthelab.com

Re: "Funding decisions: the HHMI method," President's Message by Steven McKnight, May issue

In the March issue of ASBMB Today, Steve McKnight explained the Howard Hughes Medical Institute method for funding decisions and provided some explanations for its great success. But he did not mention that the task of the HHMI selection committee (i.e., to select and retain individuals who have the potential to make significant contributions to science) is just about the easiest job on Earth. This committee could not go wrong since it is already dealing with a highly selected pool of overachievers who are destined to succeed anyway. It is the same as asking somebody to predict who is going to win a Wimbledon tennis tournament in five years. The answer is likely those who won the junior title the past five years or the last year's winner. McKnight also did not speculate as to whom from the list of the Nobel laureates was going to win the prize anyway, irrespective of HHMI support. I suspect most of them.

The job of picking future stars in science is not difficult, if you know their accomplishments as independent juniors. The daunting task is to select among 100,000 applicants (old and new) those 5 percent to 10 percent who have the so-called "best" projects. Most winners and losers are separated by very few points. I wish I had a solution, and I speculate that the HHMI selection committee does not have one either. As we say in science, in the end, this is a stochastic (good or bad luck) approach. – Eleftherios P. Diamandis, Mount Sinai Hospital, University Health Network, University of Toronto

Re: "The reality that dare not speak its name," essay by Andrew Hollenbach, April issue

I completely agree with Andrew Hollenbach about the fairness of being able to obtain a research grant these days. Only a fraction of applications are now getting funded, and it depends on whom you know rather than the degree of creativity and excitement of your hypothesis. Funding now depends on buzz words, hype, "study-section think," confirmation of previously published boring data, and fundability — rather than the possibility of taking a risk that might make an important breakthrough contribution to advance a field of study.

Study-section issues and discrepancies notwithstanding, another big problem is the fact that the amount of federal funding for basic research is dwindling compared with the expanding number of aspiring young principal investigators. Also, more National Institutes of Health money is being moved from the pot of funding R01 and R21 grants to that of funding large centers, consortiums and infrastructure, which leaves out the PI who wishes to maintain a small lab and do hands-on, wet-bench research combined with proper mentoring. Another very serious problem cannot be ignored: The federal government currently spends about $3 billion each day beyond its budget. Someday, our exploding national debt, soon to reach $20 trillion, must be curtailed by serious budgetary cuts (and/or massively increased taxes); when this happens, one can only hope that scientific research funds will not be severely slashed.

Hollenbach described having had a small lab, trying to be an outstanding mentor and failing to acquire additional research funding after having co-authored fewer than two dozen papers. An even more impressive example came from my own lab: a senior postdoc who became a research assistant and then tenure-track assistant professor. In the third year of his five-year R01, he saw the writing on the wall and chose to leave academia to become a house-husband — caring for his two kids, brewing his own beer, volunteer-teaching science and music at local middle and high schools. Now he's sleeping better at night. He left academia with more than six dozen publications. – Daniel W. Nebert, professor emeritus at the University of Cincinnati College of Medicine and Cincinnati Children's Hospital

Clarification

Further analysis of the 2014 ASBMB graduation survey revealed that four schools may have reported incorrect numbers of American Indian or Alaskan Native graduates. As ASBMB Today has no means of independently validating their self-reported answers, it is possible that fewer American Indian or Alaskan Native students received biochemistry and/or molecular biology degrees in 2014 than was reported.

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