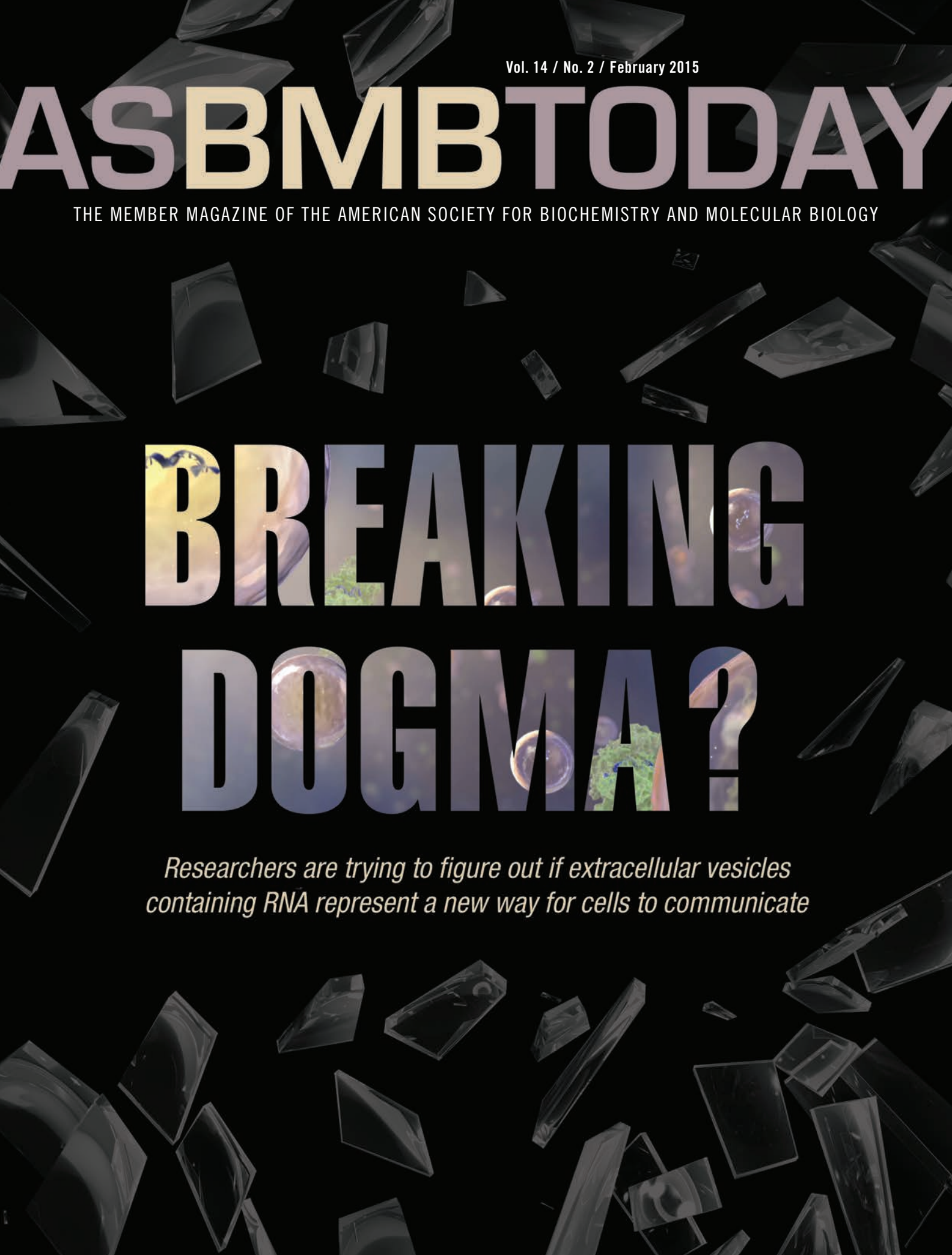
Vol. 14 / No. 2 / February 2015

ASBMBTODAY

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



BREAKING DOGMA?

Researchers are trying to figure out if extracellular vesicles containing RNA represent a new way for cells to communicate

CONTENTS

NEWS

2
PRESIDENT'S MESSAGE
Why meet?

4
NEWS FROM THE HILL
The Department of Defense wants you!

5
MEMBER UPDATE

6
RETROSPECTIVE
Donald F. Steiner, 1930 – 2014

8
JOURNAL NEWS
8 JBC: New Tabor Young Investigator Award winner
8 JBC: A connection between blindness and Parkinson's disease
10 JBC: 'The rewards were gratifying': Jackie Corbin reflects on his scientific career
12 JLR: Molecular insights and potential therapies for Niemann–Pick C disease
13 MCP: Making mouse psoriasis relevant

14
NEWS
Matters of the heart

15
NIH UPDATE
NIGMS to pilot grant program

17
LIPID NEWS
The promise of unknown unknowns

FEATURES

20
BREAKING DOGMA?

25
SCIENCE IN SIGN LANGUAGE

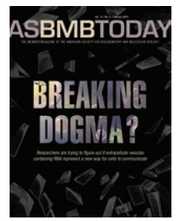
28
BEYOND THE FINISH LINE

25

28

20

Science writer Rajendrani Mukhopadhyay explores the mysterious world of extracellular RNA.



PERSPECTIVES

30
GENERATIONS
Regeneration of a transgenic mouse model

31
HOBBIES
31 Arrowhead hunting with Jackie Corbin
33 Break it down again

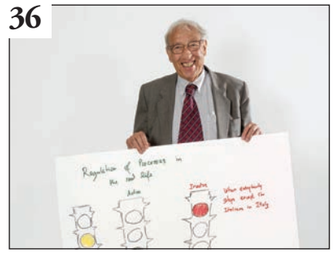
34
OUTREACH
Impact by design

36
OPEN CHANNELS
Colorful characters

30

31

36



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

www.asbmb.org/asbmbtoday
PRINT ISSN 2372-0409

Why meet?

By Steven McKnight

Next month, the American Society for Biochemistry and Molecular Biology will convene its annual meeting in Boston. Thousands of scientists, young and old, will attend. Scientific communication ranging from plenary talks to poster presentations will allow both members and guests to share their science.

What is the value of our large annual meeting, and why is it important that ASBMB members participate?

In thinking about how to address these questions, I go back 39 years to the first scientific meeting I ever attended. It was the annual meeting of the American Society for Cell Biology held in San Juan, Puerto Rico, in the fall of 1976. I was then a second-year graduate student working under the mentorship of Oscar Miller in the University of Virginia's biology department.

For weeks, I assembled my poster presentation, and I can remember as if it were yesterday when Joe Gall came to grill me on the electron micrographs I had taken of active genes being transcribed from early embryos of the fruit fly, Drosophila melanogaster. That an esteemed cell biologist and member of the National Academy of Sciences would take the time to investigate what I had to contribute represented the single most inspirational moment of my early career.

I attended ASCB scientific sessions small and large and was enthralled to hear George Palade consider the enigma of how membrane-invested organelles could be born only from existing organelles, challenging the audience to think about how mysterious it was for life forms to have accomplished compartmentalization of biological complexity when life first evolved on our planet. I recall the raucous laughter when Lewis Tilney told us about the acrosome reaction elicited by sperm activation, when a huge reservoir of soluble actin is triggered to polymerize — terming the poised, soluble actin pro-filamentous actin, or "profilactin." I had no idea what David Baltimore or Joan Steitz would even look like.

My contemporaries might have gotten the same rush by attending a rock 'n' roll concert to hear Elton John, Bob Marley or Van Morrison. But I was far more keen to see and hear — in the flesh — the biochemists, molecular biologists and cell biologists whom I placed on the highest of pedestals.

Fast-forward almost four decades, and let's consider how the meeting enterprise has evolved. Instead of being limited to the large ASBMB, ASCB and Society for Neuroscience annual meetings, we now have access to an almost limitless number of smaller meetings. What are the characteristics of these postmillennial venues for the dissemination of new scientific information?

More and more, we have access to destination meetings convened at fancy resorts. Unlike our societal meetings, many conferences today are narrowly focused on a single topic or subdiscipline. Finally, participation by graduate students and postdoctoral fellows tends to be significantly limited relative to established, principal investigators.

I argue that the large annual meetings convened by scientific societies remain instrumental as inaugural venues where budding scientists are able to display their wares and to hear directly from the mouths of established scientists whose work helped create the foundation of our knowledge.

Participation in the ASBMB annual meeting is open to undergraduate students, graduate students, postdoctoral scholars, technicians and independent investigators. Ample opportunities offer young scientists the chance to present their science in poster sessions, and exemplary abstract submissions are chosen for oral platform presentations associated with specific symposium events. Bottom line: Our annual meeting offers exceptionally liberal access for trainee participation. Beyond science, the ASBMB annual meeting gives us opportunities to hear about developments at ASBMB journals, advocacy efforts for basic research, the diversity of our workforce, educational initiatives and science-outreach activities.

As president of the ASBMB, I have chosen to focus on two aspects of our annual meeting that are of particular importance to me. First, I hope to expand participation of trainees and will strive to enhance all aspects of the meeting that may be of benefit to young scientists. Second, I have helped increase the number of plenary lecturers at the Boston meeting — to include Rachael Klevit, David Allis, James Chen, Bonnie Bassler and Ian Wilson. Together with our ASBMB award recipients, these plenary lecturers help carry the torch such that our membership — and particularly trainees — might be inspired in the manner I was nearly 40 years ago.

The health of our organization will be put to test at the upcoming meeting. Here is what I will be looking for. Are the plenary and award lectures overflowing? Are the smaller sessions also filled to the brim, especially with young scientists? Finally, will the poster sessions be lively and well attended not just by the young presenters but also by our more established ASBMB members?

All of us will be able to measure the pulse of our organization in Boston. Afterward, the society will ask all of us to weigh in by completing a post-meeting survey. Please keep tabs on all aspects of the meeting so that you can participate in an informed way. The ASBMB is our organization; let's collectively pitch in at the Boston meeting to make it as healthy as possible!

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.

BECKETT

ROBERTS

GEILING

The efforts of particularly dedicated ASBMB members lead, each year, to a meeting program that covers a wide distribution of the science and activities most relevant to our society. The efforts of Dorothy Beckett of the University of Maryland and Mary Roberts of Boston College have been instrumental in the organization of our 2015 annual meeting. Working with dozens of field-leading scientists, Dorothy and Mary have organized a meeting overflowing with fantastic venues.

Aside from ASBMB volunteers, significant efforts are demanded of our ASBMB staff in preparation for the annual meeting. We are particularly indebted to the ASBMB's meetings director, Joan Geiling. Joan's efforts devoted to the Boston meeting began more than 18 months ago and will continue to consume her attention until things wrap up on April Fools' Day!

The Department of Defense wants you!

By Benjamin Corb

Last fall, members of the American Society for Biochemistry and Molecular Biology Public Affairs Advisory Committee traversed the Washington, D.C., metropolitan region to meet with research-funding agencies. We met with representatives not only of the old standbys, the National Institutes of Health and the National Science Foundation, but also with funders that we typically have fewer conversations with. We met with officials at the Department of Veterans Affairs, the Department of Energy's Office of Science and the Army's Congressionally Directed Medical Research Programs.

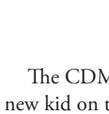
Since its inception in 1992, the CDMRP has administered more than $8.5 billion in federal appropriations, funding more than 12,000 grants (out of 90,000 applications) for research around the country and the world. The CDMRP is different in a couple of ways from the NIH. First, the overwhelming majority of the research CDMRP funds focuses on disease, which may make it difficult at first to see a connection for many ASBMB members looking to diversify their funding portfolios.

"(M)ost of our cancer and specific disease programs have awarded over half of their portfolio to basic research in areas of cell biology, genetics and molecular biology, endocrinology, pathobiology, and immunology," explains Col. Wanda L. Salzer, CDMRP's director. "For example, the (Department of Defense) Breast Cancer Research Program's portfolio from fiscal 1992 to FY12 shows that over half of the 6,400 funded awards are in basic research areas."

Also, grants funded by the CDMRP go through a two-tier review process. The first step is a rather typical peer-review process, of which you are keenly aware. After peer review, however, grants then are reviewed based on programmatic and community need. This second review is not a rubber stamp for those grants that scored highest in peer review. The applications that have the highest potential to help achieve the vision and goals of the respective program (programmatic relevance, relative innovation and impact respective to the award mechanism, portfolio balance and adherence to the intent of the mechanism) win funding.

The CDMRP, while a relatively new kid on the block in terms of funding research, already has had some major successes in its first 20 years of funding biomedical science. The CDMRP notes that its funded investigators have affected significantly the standards for care provided to patients with breast cancer, neurofibromitosis, ovarian cancer, prostate cancer and spinal cord injuries.

For those interested in the program or funding opportunities, the ASBMB has been told that comprehensive program announcements will be released in March for the FY15 cycle. The program announcements will include detailed descriptions of funding mechanisms, evaluation criteria, submission requirements and deadlines. Each program announcement will be available at Grants.gov and the CDMRP website (http://cdmrp.army.mil).



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

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Lindquist, Walter win Vallee Visiting Professorships

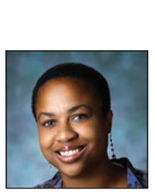
SUSAN LINDQUIST

PETER WALTER

Two American Society for Biochemistry and Molecular Biology members – Susan Lindquist of the Whitehead Institute in Cambridge, Mass., and Peter Walter of the University of California, San Francisco – received 2015 Vallee Visiting Professorships from the Vallee Foundation. The purpose of the program is to bring outstanding scientists and premier biomedical research institutes together in an informal arrangement that promotes scientific exchanges and fosters new partnerships in biomedical research. In 2009, Lindquist received the President's National Medal of Science, and Walter received the 2014 Lasker Award for Basic Research, popularly known as the "American Nobel." Both scientists are Howard Hughes Medical Institute investigators and study protein synthesis, protein folding and protein quality control as they relate to human diseases.

Two members win awards from ASPET

HAMM



BUMPUS

The American Society for Pharmacology and Experimental Therapeutics will recognize two ASBMB members, Heidi Hamm and Namandje Bumpus, at the Experimental Biology meeting in Boston in March. Hamm, a professor of pharmacology at the Vanderbilt University Medical Center and a former ASBMB president, will receive the 2015 Robert R. Ruffolo Career Achievement Award in Pharmacology. Hamm's primary research focus is the structure–function relationship of GTP binding proteins and G-protein–coupled signal transduction mechanisms. Established in 2011, the award recognizes the achievements of scientists who have made significant contributions to pharmacology. Bumpus, an assistant professor at the Johns Hopkins University School of Medicine, will receive the 2015 Division for Drug Metabolism Early Career Achievement Award. Her research focuses on adverse effects associated with non-nucleoside reverse transcriptase inhibitors in HIV.

Raushel receives ACS Southwest Regional Award

RAUSHEL

The American Chemical Society recognized Frank Raushel's contributions in enzymology and biological chemistry and honored him with the organization's Southwest Regional Award in November. Raushel received the award, which included a $2,000 cash prize and a commemorative plaque, at the Dallas–Fort Worth chapter. Raushel is a distinguished professor of chemistry at Texas A&M University, where he has worked since 1980. He is also a fellow of the ACS and the American Association for the Advancement of Science. Raushel is recognized internationally for his research on the structure and function of enzymes and their mechanisms. More recently, his group is focusing on newly discovered enzymes, such as nonspecific carboxylate esterase and cyclic phosphodiesterase.

IN MEMORIAM: Bhupendra P. Doctor

Bhupendra P. Doctor, the former director of the biochemistry division at the Walter Reed Army Institute of Research in Silver Spring, Md., died in November. He was 84. After receiving a B.S. degree from the University of Bombay (India) in 1952, Doctor came to the U.S. and earned his Ph.D. in biochemistry at the University of Maryland in 1959. He worked at the Walter Reed Army Institute of Research between 1960 and 2007, during which time he focused on developing enzymes as bioscavengers for cholinesterase-inhibiting organophosphorus compounds, such as soman. Doctor won three Presidential Rank Service Awards and the Order of Military Medical Merit for his research.

Written by Alok Upadhyay

Donald F. Steiner, 1930 – 2014

By Robert Roskoski Jr.

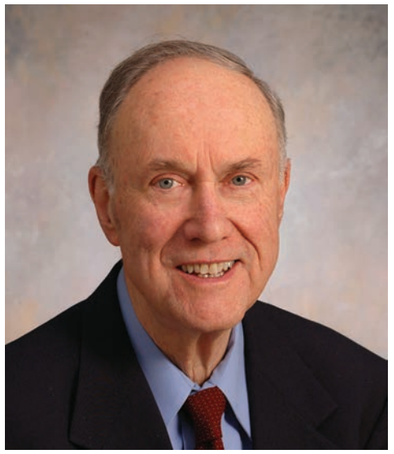
Donald F. Steiner, the distinguished professor emeritus at the University of Chicago who elucidated the mechanism of biosynthesis of insulin from proinsulin, died Nov. 11 at age 84.

Insulin is a small and beautifully organized protein with a unique two-chain structure. It was the first protein to be sequenced, which led to Fred Sanger's first Nobel prize in chemistry.

There was much speculation about how the two chains were assembled, but the mystery was solved after the discovery of proinsulin. Proinsulin was the first of the prohormones (including proglucagon, proparathyroid hormone and proopiomelanocortin) and proproteins such as proalbumin.

Diabetes mellitus is an increasingly common disease that results from inadequate insulin production (Type I) or inadequate insulin signaling (Type II), and Steiner's work led to a better understanding of these disorders and to their improved treatment.

After graduating from the University of Cincinnati with his bachelor's in chemistry and zoology, Steiner earned a master's degree and medical degree at the University of Chicago School of Medicine in 1956. As a medical student, he worked with Herbert S. Anker in the biochemistry department and studied the biosynthesis of antibodies in rabbit spleen explants, for which Steiner received his master's degree. This work was published in the Proceedings of the National Academy of Sciences, with Steiner as first author, a harbinger of his scientific acumen. He then did an internship at the University of Washington and spent three years in the laboratory of Robert H. Williams, an endocrinologist who was also the chairman of the department of medicine. Steiner's work centered on the mechanism of action of oral hypoglycemic agents.



Earl A. Evans Jr., the chairman of the biochemistry department at the University of Chicago, offered Steiner the position of assistant professor in 1960. Steiner had not applied for the position, and the offer came out of the blue. The starting salary of $9,000 ($71,000 in today's dollars) was much more that he could have made as a medical resident or a postdoctoral associate, which Evans emphasized as an inducement (if one were needed). To add perspective, tuition at the University of Chicago School of Medicine was $999 in 1960 ($7,900 in today's dollars), which contrasts with today's tuition of $47,673 for three quarters. Steiner began his new job in September 1960.

Steiner initiated his own studies on the action of insulin on carbohydrate metabolism and glycogen biosynthesis at Chicago. His work demonstrated that insulin led to dramatic increases in glycogen content, RNA synthesis and protein synthesis in diabetic rats. His work in the early 1960s showed that insulin regulates the rate of synthesis of several proteins involved in glycolysis and gluconeogenesis in vivo.

Before moving to a high-rise apartment on Chicago's Gold Coast, Steiner lived in an apartment near the university. At a chance meeting at an elevator with a medical student who lived in the same building (Nicholas A. Vick), Steiner asked to be alerted if a patient with an insulin-secreting adenoma was admitted to Billings Hospital. Serendipity intervened several months later: Such a patient was admitted, and Steiner retrieved about half of a one-gram tumor and incubated portions of it with [3H]-leucine and [3H]-phenylalanine.

Steiner commented later that he had no preconceptions about how this work would develop. He had no grant for these studies and no working hypotheses to test. Because he had no experience in this line of experimentation, he knew that he would not have been funded initially for such experiments. After acid/ethanol extraction of the pancreatic tumor, gel-filtration chromatography revealed radioactive a, b, and c peaks. Component a included high-molecular-weight material, and component c was insulin. There were no lower-molecular-weight peaks corresponding to the two chains of insulin. Component b was a protein of high specific activity that reacted with insulin antisera and was readily converted into insulin after treatment with trypsin. Component b was the biosynthetic precursor of insulin, and it was named proinsulin.

Proinsulin begins with the B-chain, followed by the connecting peptide, and ends with the A-chain. Proinsulin is processed in the trans-Golgi, yielding the connecting peptide and insulin with its A- and B-chains attached by two disulfide bonds. In response to glucose and other agents, insulin and connecting peptide are co-released from pancreatic β-cells. Arthur H. Rubenstein (formerly dean of medicine at Mount Sinai School of Medicine and the University of Pennsylvania) and Kenneth S. Polonsky (currently dean of medicine at the University of Chicago) were early collaborators who studied the secretion of connecting peptide along with insulin under a variety of clinical conditions.

The identification of the physiological enzymes involved in the conversion of proinsulin to insulin required more than 20 years of effort from many laboratories. This work started in the 1970s with the discovery that Kex2p in yeast is required for the production of α-mating factor. This eventually led to the discovery of the kexin/subtilisin-like prohormone convertases 1/3 and 2 as participants in the proteolysis at paired basic amino acid residues that led to the cleavage of the connecting peptide. This is followed by the action of carboxypeptidase E to eliminate basic amino acids, yielding mature insulin with its A- and B-chains.

Steiner made significant contributions in deciphering the physiology of insulin biosynthesis as well as in the pathology of diabetes, a disease that affects some 29 million Americans. Frederick Banting and Charles Best discovered insulin in canine pancreas in Toronto in 1921. Insulin extracts from bovine or porcine pancreas treated diabetes for more than 60 years. A new era began in the 1980s when human insulin was synthesized for therapeutic use. In 1982, recombinant A- and B-chains were expressed in E. coli and combined chemically to produce molecular insulin. Since 1986, human insulin has been prepared from recombinant proinsulin followed by treatment with trypsin and carboxypeptidase B. This is the form of insulin that is prescribed in the United States today, and the methodology for its preparation is a direct consequence of Steiner's work.

I joined Steiner's laboratory in 1961 as an M.D./Ph.D. student and left in July 1966 to work in the U.S. Air Force Medical Corps; unfortunately, I did not participate in the proinsulin saga. I wrote my dissertation and returned to the university in 1968 to defend my work and receive the Ph.D. Steiner was an exacting mentor who thought that any dissertation should undergo the review and scrutiny of a paper (or papers) submitted to the Journal of Biological Chemistry. After extensive discussions and rewrites to obtain his endorsement, gaining the approval of the dissertation committee (Herbert S. Anker, Eugene Goldwasser and Wolfgang Epstein) was a cakewalk.

At first, Steiner's career developed slowly. After six years as an assistant professor, he was promoted to associate professor in 1965. Just a year later, he was promoted to professor after the discovery of proinsulin (even though the dust had not yet settled concerning the validity of this biosynthetic process). A promotion after such a short time was and is very unusual. Evans most likely did not want to lose Steiner to Harvard University as he had lost Konrad Bloch and Eugene P. Kennedy. Steiner received many offers for positions elsewhere, but he valued his colleagues and chose to remain at Chicago for his entire professional career. Evans emphasized research for both graduate students and faculty members, and he held course work for both to a minimum, an educational and scientific strategy with which Steiner agreed. This tradition has held since its earliest days, when Maude L. Menten received her biochemistry doctorate in the department.

Steiner was soft-spoken, and his outlines for lectures or seminars contained the directions "speak louder" interspersed throughout. He was a person of even disposition who never raised his voice under circumstances that would readily elicit expletives from others. He was an efficient and prolific worker who also had time for activities in the arts, especially music.

In 1964, a National Institutes of Health site visit team reviewed the application of Lloyd M. Kozloff, whose laboratory was two doors away. In the afternoon, Kozloff gave the visitors a tour of the department. They entered the main lab, where I was working with Judith King, a superb technician who was co-author on several Steiner papers. Then they walked into Steiner's office, where he was kneeling on the floor fabricating a harpsichord. Kozloff won the grant despite this encounter.

Steiner received the University of Chicago's Alumni Award in June. This is the highest award that the university gives. For anyone interested in a more complete description of the proinsulin story including numerous blind alleys and technical difficulties, see Steiner's "Reflections" article ("Adventures with insulin in the Islets of Langerhans") in the JBC (1).

Robert Roskoski Jr. (rrj@brimr.org) is the scientific director at the Blue Ridge Institute for Medical Research in North Carolina.

REFERENCE

1. http://metabolism.jbc.org/content/jbc/286/20/17399.full.pdf

New Tabor Young Investigator Award winner

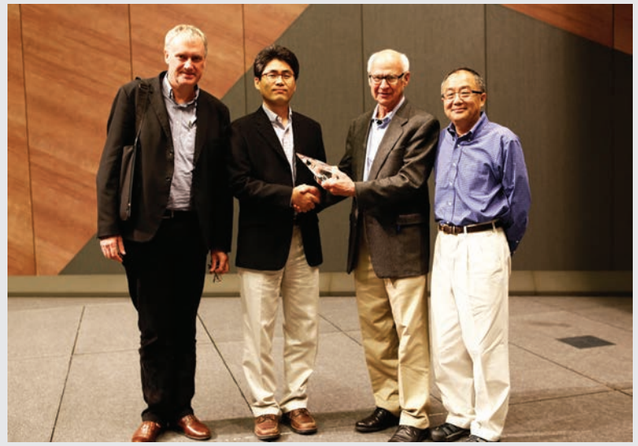
By Caitlin Hanlon

Yeonseok Chung, an assistant professor at Seoul National University, is the recipient of the **Journal of Biological Chemistry**/Herb Tabor Young Investigator Award for his ongoing work on immune responses.

Chung began his work on the immune response while completing his master's and doctoral research in the laboratory of Chang-Yuil Kang at Seoul National University. His studies focused on the mucosal immune system and its crosstalk with the gut immune system. Chung also worked on potential therapeutics for cancer while completing his doctorate.

During his postdoctoral work in the laboratory of Chen Dong at the University of Texas MD Anderson Cancer Center in Houston, Chung further diversified his studies by investigating the differentiation of naive T cells into the specific Th17 cell lineage. Chung discovered that interleukin-1 signaling is crucial for this commitment. He also discovered the follicular regulatory T cell as a novel subset of regulatory T cells specialized for controlling germinal center reactions.

Chung then established his own laboratory, first at UT and then at Seoul National University. He has continued to delve deeper into research involving the immune response. Currently, Chung and his lab are studying the interplay of lipids in the immune response and related diseases. He also is focusing on immune response in the lung, asking why the lung preferentially triggers only specific helper T cell responses. While his work uncovers the fundamental pathways and players in the immune response, Chung said that he is hopeful that his work will lead to new therapies for treating immune disorders in humans.



Yeongseok Chung won the Tabor award in late October at the International Cytokine and Interferon Meeting in Melbourne, Australia. Charles Samuel, a JBC associate editor, issued the award. Also in attendance were associate editors Luke O'Neill (left) and Xiao-Fan Wang.

Caitlin Hanlon (chanlon3@jhmi.edu) earned a B.S. from Ursinus College and is pursuing a Ph.D. in the cell biology department at the Johns Hopkins School of Medicine.

A connection between blindness and Parkinson's disease

By Martina Efeyini

A research team led by Paulo A. Ferreira at Duke University Medical Center and collaborators at Cleveland Clinic led by Neal Peachey has found a promising genetic link between blindness and Parkinson's disease. This discovery, the researchers say, opens doors for new treatments of age-related disorders. The team's study was published in the **Journal of Biological Chemistry**.

The researchers set out to understand better the role of Ran-binding protein 2, or Ranbp2, in the retinal pigment epithelium, a tissue that lines the back of the eye. The retinal pigment epithelium, or RPE, is a critical component of the blood–retinal barrier, which helps to maintain the homeostasis of the neuroretina. Aging, toxic environmental insults and genetics lead to age-related macular degeneration and retinitis pigmentosa, and these diseases ultimately lead to blindness. In addition, the RPE produces L-DOPA, an intermediate chemical compound required for dopamine production. Dopamine is crucial for communication of dopaminergic neurons. When these dopaminergic neurons begin to die widely for reasons that are not well understood yet, patients develop Parkinson's disease.

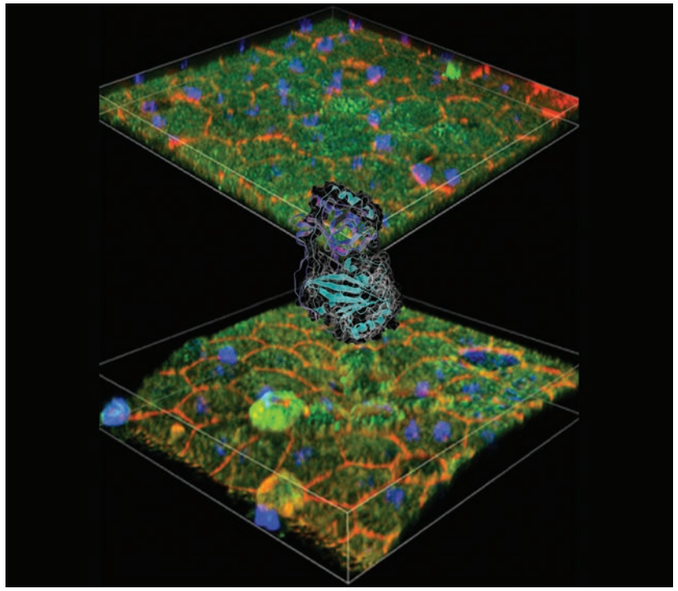
Ferreira's interest in neurodegenerative diseases goes back to his graduate and postdoctoral work, when he was searching for proteins with chaperone activity in neurons of the retina. He discovered a large and multimodular protein, Ranbp2, and then set out to gain a better understanding of its partners and find out the biological and physiological functions of the interactions between Ranbp2 and its partners.

Ferreira's new study in the JBC reports that mice with overall functional deficits in Ranbp2 develop degeneration of the RPE and secondary breakdown of the blood–retinal barrier. This loss of Ranbp2 in the RPE has features that resemble those of a severe form of age-related macular degeneration, wet AMD, which is characterized by abnormal blood vessels and bleeding in the back of the eye. Further, the researchers pinpointed a selective biochemical activity of Ranbp2 that, when lost, sufficed to recapitulate the degeneration of the RPE. This Ranbp2 activity is implicated in controlling nucleocytoplasmic trafficking of selective substrates.

Ferreira's team also found that the mice that lacked overall Ranbp2 activities also developed robust juvenile Parkinsonian tremors. Interestingly, loss of the biochemical activity of Ranbp2 that controls nucleocytoplasmic trafficking and causes RPE degeneration did not promote Parkinson's in mice. The observation that loss of Ranbp2 causes Parkinsonism in mice did not come as a complete surprise to the Ferreira laboratory, because they knew that mice with reduced levels of Ranbp2 are predisposed to toxicity for the Parkinsonian neurotoxin, MPTP, which is highly damaging to dopaminergic neurons of the midbrain and retina. In addition, other groups had found that Ranbp2 is a substrate for degradation by Parkin, a ubiquitin-ligase whose impairment causes familial and sporadic Parkinson's disease or multisite oncogenesis.

Based on the results of their study, Ferreira and co-workers concluded that (1) distinct mechanisms and functions of Ranbp2 promote RPE degeneration and Parkinsonism and (2) Parkinsonism is controlled by Ranbp2 and other genetic modifiers, because not all mice lacking Ranbp2 develop Parkinson's, but mice with Parkinson's must have loss of Ranbp2 function. Understanding the connections between blindness and Parkinson's and factors determining the development of these diseases is crucial, because it will help in the development of much-needed therapeutic strategies with multiple clinical applications in neurodegenerative conditions.

"This (study) is a classical example of twists and turns of science and an example of what Louis Pasteur once said: 'Chance favors only the prepared mind,'" Ferreira said. The study provides "an excellent basis to help us understand the development of novel therapeutic approaches toward multiple diseases."



3-D-confocal images of RPE of wild-type mice (top) and knock-out Ranbp2 mice with extrusion of degenerating RPE cells (bottom). Ribbon representation of the structure of the binary complex of a Ran-binding domain of Ranbp2 with Ran-GTP (middle).

Martina Efeyini (mefeyini@gmail.com) is a toxicologist and freelance writer. Read her blog at mademoisellescientist.wordpress.com. She also writes for the National Society of Black Engineers and ScientistaFoundation.com.

‘The rewards were gratifying’

Jackie Corbin reflects on his scientific career

By Maggie Kuo

A football game does not air without at least one commercial for an erectile-dysfunction drug. Considering the treatments that were available before them — psychotherapy, implants, vacuum constriction devices, direct injection, surgery — being able to take a pill truly revolutionized the field. The discovery of these drugs, though, is also a success story for basic research.

Viagra, Cialis and Levitra are all inhibitors of phosphodiesterase 5, an enzyme that breaks down cyclic guanosine monophosphate, which is important for increasing blood flow. The idea to use PDE5 inhibitors to promote blood flow came out of the work of Jackie Corbin, an emeritus professor of molecular physiology and biophysics at Vanderbilt University. Corbin spent his career understanding how cyclic nucleotides control physiological processes, and in his recent “Reflections” article in the **Journal of Biological Chemistry**, he wrote about how his career demonstrates the importance of basic research in developing new treatments.

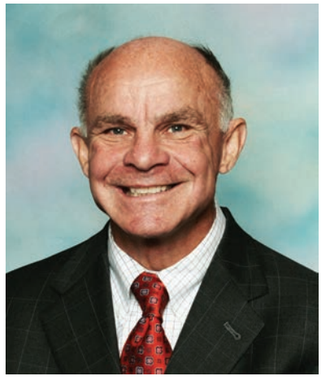
When I chatted with him about his article and his research, I came away with another theme: camaraderie. Corbin’s remarks on going through science as a team and helping the greater good reminded me of an aspect of science that is often forgotten: Science is a group effort, working toward the broader goal of improving people’s health.

Corbin is recognized as a leader in the cyclic nucleotide field. He spent his early career studying cyclic adenosine monophosphate signaling and his later career studying cGMP. Corbin attributes his success with cGMP to his longtime collaborator, Sharron Francis. “Sharron was much more precise than I was,” says Corbin. “I was more general, and she corrected me more than I corrected her. I think to have her involvement and to have all the scientific discussions we had, there’s no question that I never could have achieved anywhere near what I did without her.” He adds, “I like to think I probably helped her a little bit as well.”

Corbin started collaborating with Francis in 1977. He and his postdoctoral fellow had discovered a protein that bound to cGMP, and Francis joined them to elucidate their new protein. Together, they identified the protein as a phosphodiesterase, a member of a class of enzymes that breaks down cyclic nucleotides. They further defined how this phosphodiesterase, which later was named phosphodiesterase 5, interacted with cGMP to regulate and degrade it.

Many health conditions, including erectile dysfunction, result from the arteries not being able to dilate adequately, reducing blood flow and the amount of blood in the region. The diameter of the artery is controlled by smooth muscle cells that make up the walls of blood vessels. When the smooth muscle cells relax, the artery dilates.

Several studies at that time had shown that raising the level of cGMP caused smooth muscle cells to relax, suggesting that cGMP could be important in regulating blood flow. Corbin and Francis established that cGMP caused arterial dilation through the enzyme cGMP-dependent kinase, or PKG. cGMP activates PKG, and PKG proceeds to turn on the cellular machinery that results in the smooth muscle cells relaxing and the artery dilating.



After identifying that pathway, Corbin writes that he and his team came up with the idea that impaired arterial dilation could be treated by elevating cGMP with “a drug such as a PDE5-resistant cGMP analog that would serve as a dual-acting compound to activate PKG and inhibit PDE5.”

Corbin and Francis decided to work toward making cGMP analogs to activate PKG and received a three-year grant in 1989 from the pharmaceutical company Glaxo to pursue their project. In the last year of the grant period, Glaxo recommended that they focus on developing PDE5 inhibitors instead of PKG activators, because PKG activators broke down in the digestive system and could not be used as orally administered drugs.

From what they had learned from creating cGMP analogs, Corbin, Francis and their postdoctoral fellow, Sekhar “Raja” Konjeti, came up with the structure for a PDE5 inhibitor that would be more powerful than what was available commercially. They synthesized and tested several candidate compounds and showed that one “was much better than any known inhibitor of the enzyme at that time,” Corbin recounts.

After reading a study that reported that an elevated cGMP level mediated penile erection in rabbits, Corbin and his team believed that their PDE5 inhibitor could be used to treat erectile dysfunction. They shared their idea with the department of technology transfer at Vanderbilt University. “To our knowledge,” Corbin writes in his Reflections article, “this was the first written mention that PDE5 inhibitors could be used to treat this condition.”

Corbin also told Glaxo their idea. Glaxo encouraged them to submit a new research proposal and detail their experimental design. They did so, received another grant in 1991 and continued working on PDE5 inhibitors, passing along their results and materials to the scientists at Glaxo.

What they did not know, Corbin says, was that at the same time, Glaxo was synthesizing and testing compounds that were similar to the structure he and his team had described. One of these compounds would eventually become tadalafil, which is currently marketed commercially as Cialis.

They did not become aware of Glaxo’s actions until 2003, Corbin says, after the results of tadalafil were published. “We planned to synthesize Cialis to do some research with the compound,” says Corbin. “Raja looked up the structure and came to me and said he noticed the structure was similar to what we had suggested way back. The structure of Cialis is very different from that of Viagra or Levitra; it’s a little bit unique.”

Having actively collaborated with the scientists at Glaxo and having given them their compounds and materials to do the synthesis, Corbin and his team felt that Glaxo was able to develop tadalafil because of their work and assistance. They approached the technology transfer department at Vanderbilt, wondering about their rights. In 2005, Vanderbilt filed a civil action lawsuit against the company, seeking to have Corbin, Francis and Konjeti added to the tadalafil patent as joint inventors.

The litigation lasted five years and went through two courts. Both courts ruled against Corbin and his team. “I guess the major thing the judges ruled was that we did a lot to help and we did provide a lot of information and materials, but that it was not enough,” says Corbin. “In science, we feel that the original ideas and what leads up to the final product is important.” However, Corbin reflects, “the legal system rules that whoever comes up with the final product is most important.” The case was brought to the Supreme Court, but the court declined to hear it, ending their legal quest in 2011.

Although they did not receive the credit they felt they deserved, Corbin would not advise colleagues against collaborating with industry. University technology-transfer offices now are much more aggressive in protecting their researchers’ interests, Corbin says. But he also adds that the broader impacts stemming from university discoveries are fulfilling in themselves. “So what if we don’t get any financial rewards?” he says. “Discoveries move on and are applied. People are better off with the medications, so that works and that’s OK.”

Corbin is semiretired now and does very little research. He leaves two pieces of advice for the next generation of scientists. To junior scientists, Corbin strongly recommends they consider working with a partner. “To have around every day someone to talk to about the results and plan the next experiments, talk about the students in the lab, write grants and papers together — no question that is a good way to do it,” he says.

To potential scientists, he writes, “I urge young people to adopt a scientific career. You will be appropriately challenged; you will meet many interesting people from diverse cultures; you will feel the ecstasy of discovery; you will contribute to the improvement of the health and welfare of all living things.”

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HOBBIES

Jackie Corbin reflects on the joys of arrowhead hunting, his favorite pastime, in this month’s installment of the “Hobbies” series, ***page 31***

Molecular insights and potential therapies for Niemann–Pick C disease

By David B. Iaea

A recent thematic review in the **Journal of Lipid Research** from Jean E. Vance and Barbara Karten summarizes the molecular mechanisms that underlie the lysosomal storage disease Niemann–Pick C and discusses the development of therapies for patients with this disorder.

NPC disease is a progressive, inherited disease that affects about one in 150,000 births. In NPC disease, unesterified cholesterol accumulates in late endosomes/lysosomes, called LE/Ly for short, of all cells. This accumulation occurs in all tissues but most notably affects the brain, liver, spleen and lungs, resulting in neurodegeneration as well as liver and lung dysfunction.

The authors discuss NPC1, a transmembrane protein in the limiting membrane of LE/Ly, and NPC2, a soluble protein in the LE/Ly lumen, and how mutations of these proteins result in NPC disease. The authors point out that about 95 percent of NPC patients have mutations in NPC1, while the remaining cases are caused by mutations in NPC2. Mutations in either of these proteins result in reduced egress of low-density lipoprotein-derived cholesterol from LE/Ly.

In normal physiology, NPC2 binds unesterified cholesterol that is generated from endocytosed lipoproteins and transfers the cholesterol to the cholesterol-binding domain of NPC1. Cholesterol is then exported from LE/Ly to other destinations in the cell by unknown mechanisms. Mutations in either NPC1 or NPC2 result in cholesterol sequestration in LE/Ly and dysregulation of multiple cellular processes that lead to organ dysfunction.

The authors discuss the development of models used to study NPC disease and explain how NPC deficiency affects cells of the brain. Several cellular and animal models are available for studying NPC disease. The most widely used models are mice in which either NPC1 mutants are expressed or amounts of NPC1 or NPC2 proteins are reduced. These models have shown that, as in human NPC patients, one of the most dramatic consequences of mutation or reduction of NPC proteins is loss of Purkinje neurons in the cerebellum. However, the authors point out that the reason Purkinje neurons are particularly sensitive to defects in NPC1/NPC2 and the mechanisms underlying the neuropathology characteristic of NPC disease remain unclear.

Currently, no effective treatment is available for NPC disease. The glucosylceramide synthase inhibitor miglustat produces modest improvements in disease phenotypes in animal models. Also, a histone deacetylase inhibitor reduces cholesterol accumulation in NPC-deficient cells but has not yet been tested in animals.

The authors of the JLR review focus on the cholesterol-binding agent 2-hydroxypropyl-β-cyclodextrin, or CYCLO, that markedly delays neurodegeneration and extends the lifespan of NPC-deficient animals with minimal toxicity. Interestingly, for reduction of cholesterol accumulation in cellular models of NPC disease, CYCLO must be taken into the cell and delivered to LE/Ly, thereby bypassing the functional need for both NPC1 and NPC2.

Vance and Karten note that this

very exciting finding from John Dietschy's lab at the University of Texas Southwestern Medical Center at Dallas has led to a promising NPC treatment approach for which a clinical trial is underway.

The authors also consider the limitations of using cyclodextrins, such as CYCLO, as a therapy for NPC disease. One major limitation is poor penetration of CYCLO across the blood-brain barrier. To circumvent this problem, researchers are working to improve CYCLO delivery in cellular and animal models. As the authors note, while the identification and validation of CYCLO as a potential NPC therapy is encouraging, there is still work to be done to determine whether or not CYCLO will be effective.

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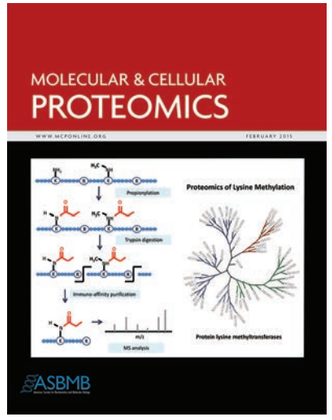
Making mouse psoriasis relevant

By Maggie Kuo

The red scaly patches that are the hallmark of psoriasis can be unsightly and quite irritating. Although psoriasis is a common skin condition that results from an overactive immune system, researchers still do not understand its exact causes. Treatments exist, but none is a cure. Moreover, the most potent therapies have the most serious side effects, and psoriasis can become resistant to treatments.

Scientists are researching new signaling pathways in psoriasis to find new drug targets. A research group at Case Western Reserve University led by Nicole Ward and Mark Chance recently reported in **Molecular & Cellular Proteomics** four proteins that are promising.

The researchers harvested skin samples from genetically modified mice



that develop a skin condition similar to psoriasis. Using proteomics analysis and gene-expression measurement techniques, the researchers discovered and validated four proteins that were significantly higher in the psoriasis mice: SerpinB1; kallikrein-related peptidase 6, or KLK6; Cystatin A; and solute carrier family 25 (mitochondrial carrier; adenine nucleotide translocator) member 5, or Slc25a5.

The investigators next took skin samples from psoriasis patients and measured the expression levels of these proteins along with Ras-related protein Rab18, a protein that they found did not change in the psoriasis mice. Consistent with the mice, the psoriasis patient skin samples had higher expression of the four proteins, while Rab18 was unchanged, demonstrating that these proteins are relevant in humans and that the mouse is a good model for human psoriasis.

Ward says of the study's findings: "When we talk about translational biology, this is what we're talking about: going from the bench in the lab — the mouse model, identifying something new, then going back to the patient and validating that what we found in the research lab actually matters to patients."

The investigators now are defining the roles of their proteins in psoriasis. Ward admits that she is not sure if the proteins can be viable drug targets but "maybe something downstream in terms of what they affect or how they change inflammation" will be, she says.

"This is just the first step," Ward continues. "Now that we have a list of proteins that we know may be important, we're going to try to study what they're actually doing at the biological level."

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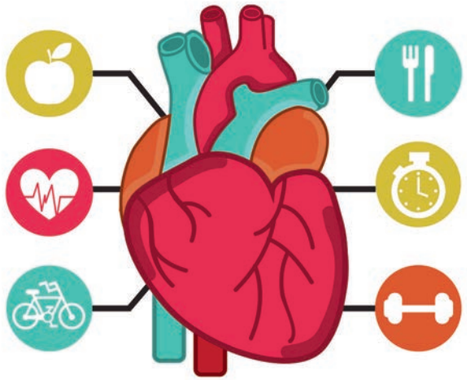
Learn how the psoriasis mouse came to be in this month's installment of the "Generations" series, ***page 30***

Matters of the heart

By Indumathi Sridharan

It is February, and all things red — from roses to dresses — once again are en vogue for Valentine's Day. But there is another reason to go red this month. The American Heart Association marks it as American Heart Month.

According to the National Heart, Lung and Blood Institute, coronary heart disease is the No. 1 killer in the U.S (1). The American Heart Association reports that coronary heart disease imposes the highest economic burden of all cardiovascular diseases, coming in at a cost of about $109 billion in treatments, medications and lost productivity each year (2).



Common symptoms are chest pain, heart palpitations and heart attacks.

What is coronary heart disease?

The coronary artery supplies nutrients to the heart. Coronary heart disease is the result of atherosclerosis, which is a process of plaque buildup on the coronary artery wall. The plaque, which narrows and hardens the artery, consists of cholesterol, calcium and cellular debris. Obesity, high cholesterol levels (in particular low-density lipoprotein cholesterol), family medical history, smoking and high blood pressure are risk factors.

How does atherosclerosis cause coronary heart disease?

Saturated fats in diet and obesity-related insulin resistance increase the deposition of LDL-cholesterol molecules on the endothelial lining of the artery wall. Smoking and high blood pressure exacerbate the damage to the endothelium, which secretes pro-inflammatory cytokines to recruit immune cells to scavenge the lipoproteins at the plaque site. The immune cells may get trapped within the plaque and contribute to hardening of the artery. As the blood flow drops, the heart receives less nutrition and cannot pump properly. This causes chest pain or heart palpitations. In extreme cases, the T lymphocytes and macrophages rupture the plaque via collagen-degrading enzymes. The ruptured plaque generates blood clots that block blood flow and cause heart attacks.

What are the recent breakthroughs in atherosclerosis treatment?

A clinical trial called Dual Antiplatelet Therapy proved that prescribing two anti-blood-clotting drugs, thienopyridine (an ADP receptor inhibitor) and aspirin (a prostaglandin inhibitor), for 30 months, rather than one year, lowered the incidence of blood clots in patients who had drug-eluting stents implanted in them. IMPROVE-IT, which stands for "improved reduction of outcomes: vytorin efficacy international trial," demonstrated that a combination of ezetimibe, a cholesterol-absorption inhibitor, and simvastatin, an inhibitor of cholesterol production, reduced LDL-cholesterol levels and prevented heart attacks more effectively than simvastatin alone. These studies were presented at the American Heart Association meeting held in November (3, 4).

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NIGMS to pilot grant program

By Erica Siebrasse

When Jon Lorsch became the director of the National Institute of General Medical Sciences in August 2013, he had a vision for a new type of research-funding mechanism – funding research programs instead of individual projects. The pilot program for Lorsch's idea, Maximizing Investigators' Research Award, or MIRA, will begin in the summer.

LORSCH

An interview about the program, Lorsch said he believes grants that fund individual projects (i.e., R01s) are inefficient and discourage researchers from proposing innovative, creative projects due to the potential instability of their funding in the long term. "Having a system be as unstable as it is, with investigators constantly worried they're going to go from being funded to having no funding at all, causes a certain conservatism in the system both in terms of the types of projects investigators will take on and the way the review panels view the science," Lorsch said.

Furthermore, R01 applications require defined experiments proposed in advance, leaving little room for investigators to follow new research directions within the grant's cycle. Lorsch is also concerned that the time spent writing grants is increasingly burdensome.

The MIRA program, developed by Lorsch and other NIGMS leaders, will fund renewable five-year grants of up to $750,000 for direct costs each year. Applications for MIRA awards, which the NIGMS hopes to begin accepting in the summer, do not require specific aims. Instead, applicants must describe the overall questions they are interested in exploring and will be evaluated based on the importance of the proposed research and their track records. Applicants also must discuss the efficiency, rigor and reproducibility of their past work. MIRA awardees will not be eligible to apply for most other types of NIGMS grants and must dedicate 51 percent of their research effort to the MIRA-funded work. Finally, NIGMS will be able to scale MIRA awards (up or down) depending on renewal reviews instead of abruptly terminating them.

The first pilot cohort of awardees will be established investigators with two or more NIGMS R01 awards or a single R01 award of more than $400,000 in direct costs. Applications are expected to be due in the summer. The second pilot cohort will include early-stage investigators. If the initial pilots are successful, the NIGMS plans to broaden eligibility to include all investigators working in areas relevant to the institute's mission.

Lorsch said he believes the flexibility and stability of MIRA awards will give investigators the freedom to explore new avenues of inquiry and will allow the maximum return on taxpayer investments through a broad, diverse NIGMS research portfolio.

"We hope that by creating the stability for investigators, we can really empower them to be more ambitious and more creative in their research," he said. "We also hope to increase the flexibility for investigators to follow new ideas and new research directions as they arise during the course of their work. If they discover something very interesting … they'll be able to follow that."

There already has been interest from other leaders within the National Institutes of Health who are awaiting results from the MIRA pilot.

Concerns from the science community

The NIGMS solicited comments from the research community about the program in July. The response was overwhelmingly favorable, Lorsch said, with positive comments from 80 percent of 300 respondents.

Lorsch indicated the two main concerns raised by respondents were somewhat contradictory. First, some were worried that funds would be unevenly distributed. Joseph Haywood, president of the Federation of American Societies for Experimental Biology, echoed that sentiment in a public letter in August to Lorsch. "We are concerned about the possibility that (NIH) funding will become concentrated among a small number of (investigators) or institutions," Haywood wrote.

However, Lorsch insists that one of the program's goals is to broaden the NIGMS portfolio by increasing the total number of investigators and number of research areas and preventing funds from being concentrated in the hands of a small number of elite researchers. "It is impossible to know in advance where the next breakthroughs will arise. Having a broad and diverse research portfolio should maximize the number of important discoveries that emerge from the

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science we support," Lorsch wrote in a NIGMS Feedback Loop blog post in January.

Second, some respondents indicated the cap on funds – $750,000 – would not be enough for some investigators who have large labs with many employees, trainees and projects and who are used to receiving more money. Lorsch said he hopes the stability of the program and the desire on the part of principal investigators to write fewer grants will be incentives.

Lorsch also said he believes concentrating the limited funds in only a few hands is inefficient and that several studies, including a 2010 analysis by the NIGMS, have shown that large research budgets usually do not give the best return on investment.

"These and other lines of evidence indicate that funding smaller, more efficient research groups will increase the net impact of fundamental biomedical research: valuable scientific output per taxpayer dollar invested," Lorsch wrote in January on his blog. In addition, he wrote, the tight funding environment often means that funding a single investigator with multiple R01s precludes funding other researchers at all.

Lorsch said that the NIGMS is developing an evaluation plan for the MIRA pilot, and he indicated that it will include feedback from both reviewers and grantees. It also will determine whether grantees altered their original research plans based on new data and whether MIRA allowed for a more diverse NIGMS portfolio.

While most in the science community feel that MIRA is a promising program, there are still a number of unknowns.

Benjamin Corb, public affairs director for the American Society for Biochemistry and Molecular Biology, ticked off a list of questions that he and others have: "What will be the buy-in from the community? How will reviewers adapt to the different review guidelines? What will the final evaluation plan look like? For most of these questions, we won't know the answer until the experiment (the MIRA pilot) is complete, but I am looking forward to seeing the results."

Erica Siebrasse is the education and professional development manager for ASBMB. Follow her on Twitter at twitter.com/ericasieb.

The promise of unknown unknowns

By John Browse

"There are also unknown unknowns — the ones we don't know we don't know. And if one looks throughout the history of our country and other free countries, it is the latter category that tend to be the difficult ones."

– DONALD RUMSFELD

For soldiers and politicians, it is indeed the unknown unknowns that are difficult. However, as researchers, we can rejoice that, despite the difficulty, these are what make our chosen pursuit worthwhile.

Two essential fatty acids derived from plants are linoleic (18:2) and alpha-linolenic (18:3) acids. These dietary fatty acids are precursors of the omega-6 and omega-3 fatty acids popularized in the press. In addition to their importance for human health (1), these lipids also compromise oxidative stability of vegetable oils, and removing them results in the production of undesirable (and now banned) trans fats. Given the importance of these lipids, their synthesis in plants has gained considerable attention.

In oil-accumulating cells of plant seeds, linoleic and alpha-linolenic acids (referred to here on out as 18:2 and 18:3, respectively) are generated by the desaturation of oleic acid (18:1) catalyzed by fatty acid desaturase, or FAD, enzymes FAD2 and FAD3 (2, 3). For FAD2 and FAD3 to work, oleic acid must be incorporated into the membrane lipid phosphatidylcholine. How 18:1 is incorporated into phosphatidylcholine has been debated.

In earlier models, 18:1 was known to be incorporated into phosphatidylcholine by one of two routes: direct incorporation from 18:1-CoA catalyzed by acyl-CoA:lyso-phosphatidylcholine acyltransferase, known as LPCAT for short (4), or incorporation into diacylglycerol followed by conversion into phosphatidylcholine by CDP-choline:diacylglycerol cholinephosphotransferase, or CPT (5). It also has been proposed that reversibility of the CPT reaction would provide one mechanism for the production of polyunsaturated diacylglycerol for the synthesis of triacylglycerols containing 18:2 and 18:3.

During our earlier studies, we isolated a mutant of the model plant Arabidopsis with increased total levels of 18:1 and reduced total levels 18:2 and 18:3 in its seed oil (6). This mutant, rod1 (short for reduced oleate desaturation 1), had substantially reduced levels of 18:2 and 18:3 in both triacylglycerol and the immediate precursor diacylglycerol relative to wild-type Arabidopsis.

Surprisingly, however, phosphatidylcholine in the mutants contained increased 18:2 and 18:3. These data suggested to us that the rod1 mutation reduces transfer of 18:1 into phosphatidylcholine for desaturation but not the desaturation reaction itself. The known unknowns, lyso-PC acyltransferase and CPT, were eliminated from consideration by ^{14}C-glycerol radiolabeling experiments and by sequencing the two CPT genes from rod1 and wild-type plants.

So what is ROD1? When the Arabidopsis genome sequence was completed in 2000 (7), the puzzle of ROD1's identity seemed to become a manageable task of identifying the gene locus by map-based cloning. However, when we completed this task and identified ROD1 as At3g15820, the encoded protein was annotated as a phosphatidic acid phosphatase-related protein. This made no sense in the context of our knowledge of the pathways of triacylglycerol synthesis or the fatty acid composition of rod1 seeds. Furthermore, assays of recombinant ROD1 protein found no detectable phosphatidic acid phosphatase activity.

Time for a Hail Mary pass? The geneticist's equivalent of this desperate football strategy is a position-specific iterative basic local alignment search tool, or PSI-BLAST, search of protein databases. As in football, this approach most likely will get you in a mess, but there is always the chance that it will produce a winning touchdown.

Far down in the fourth iteration of our PSI-BLAST search (at entry No. 67) was a weak hit to a mammalian phosphatidylcholine:ceramide cholinephosphotransferase. This enzyme catalyzes transfer of the phosphocholine headgroup from phosphati-

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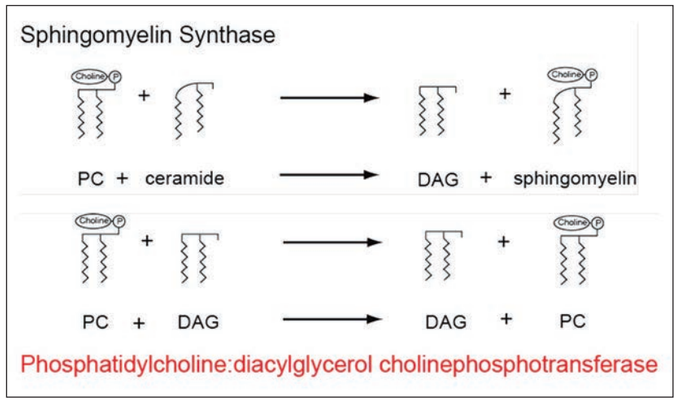
dylcholine to ceramide, generating sphingomyelin and diacylglycerol.

Plants do not contain sphingomyelin, but the structure of ceramide is analogous in some respects to that of diacylglycerol, suggesting to us that ROD1 might catalyze the transfer of phosphocholine from 18:2/18:3-containing phosphatidylcholine to 18:1-containing diacylglycerol (see figure).

Indeed, assays of recombinant ROD1 confirmed this activity (8), revealing our discovery of a new enzyme of lipid metabolism, phosphatidylcholine:diacylglycerol cholinephosphotransferase. Called PDCT for short, this enzyme is required for efficient synthesis of 18:2 and 18:3, as well as some other fatty acids (9), during triacylglycerol accumulation in seeds. ROD1 also is expressed in vegetative tissues of plants.



The known reaction between phosphatidylcholine and ceramide (top) provided the clue to identify a novel reaction in lipid synthesis (bottom) catalyzed by phosphatidylcholine:diacylglycerol cholinephosphotransferase.

Although the rod1 mutation does not result in substantial changes in root or leaf fatty-acid composition, it is possible that PDCT has a role in lipid homeostasis or remodeling of membrane lipids in response to temperature changes or other environmental perturbations.

ROD1 homologues are present in many plants, but no readily identifiable homologues are present in animals; however, the family of human proteins related to sphingomyelin synthase includes eight proteins of unknown function. Thus, it remains possible that PDCT will be found to play a role in lipid metabolism in animals as well.

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Upcoming ASBMB events and deadlines

FEBRUARY

Feb. 6: Accreditation webinar

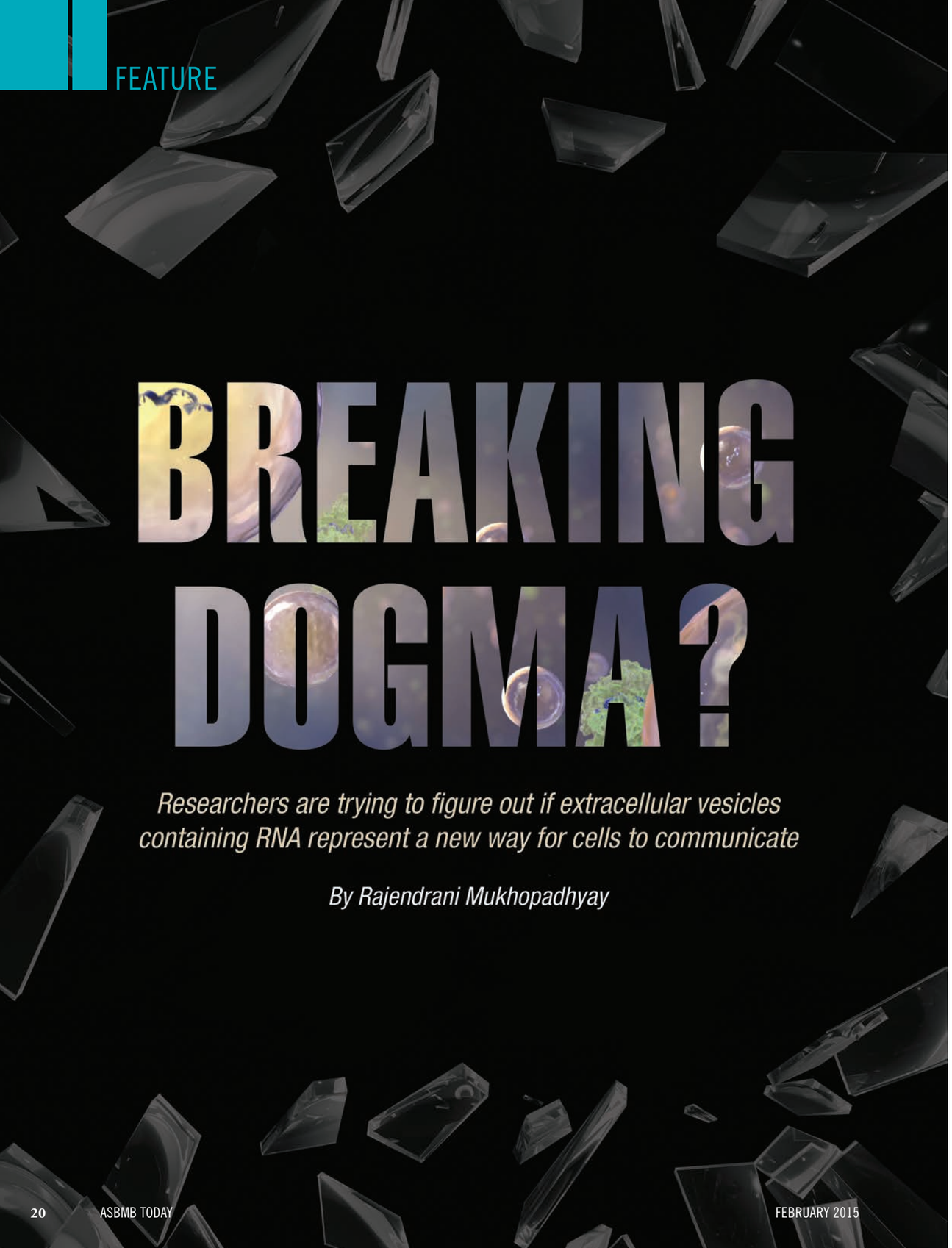
Feb. 23: 2015 ASBMB annual meeting housing deadline

MARCH

Mar. 3 – 5: ASBMB is a sponsor at the Deuel Conference

Mar. 15: Accreditation deadline

Mar. 28 – Apr. 1: ASBMB annual meeting



BREAKING DOGMA?

Researchers are trying to figure out if extracellular vesicles containing RNA represent a new way for cells to communicate

By Rajendrani Mukhopadhyay

When a molecular entity comes along that appears to affect cancer biology, immunology and neurobiology – as well as turn conventional molecular biology wisdom on its head – people tend to sit up and notice. They start thinking up ways to exploit the molecular entity for diagnostic and therapeutic purposes. They may even put forward $17 million to investigate this molecular entity, as did officials at the National Institutes of Health's Common Fund program in 2013.

That's what is happening with extracellular vesicles that carry RNA. RNA long has been thought to be a molecule imprisoned within a cell. Proteins, like hormones, always have been thought to be the ones to do long-distance communications. If more research confirms that RNA is transferred from one cell to another through extracellular vesicles and causes the recipient cell to change its behavior, this phenomenon will represent a paradigm shift in biology.

Researchers have documented RNA-containing extracellular vesicles triggered by environmental stimuli coming off brain tumor cells, inflammatory cells and neurons. They don't contain a random jumble of RNA: Specific types of RNA are found in the vesicles. They tend to be small, noncoding RNAs as well as microRNAs. The assortment of RNAs hints that the process of making these vesicles is highly regulated.

The vesicles can be found in every body fluid, such as blood, urine and semen, so researchers can envision using extracellular vesicles as diagnostic and therapeutic agents. Collecting the body fluids and using the vesicles in them to diagnose diseases and illnesses is a tantalizing idea, because it's easier to do than more invasive procedures.

"It's a very exciting field right now," says Johan Skog at Exosome Diagnostics. "But we have to be careful to not get too carried away." Michiel Pegtel at VU University in The Netherlands concurs. "You want to think big when talking about these small vesicles," he says. "But you want to be very cautious."

The skepticism is warranted, because "the functionality of these RNAs in recipient cells is a question for debate," acknowledges Xandra Breakefield at the Massachusetts General Hospital. "Right now, there is very little conclusive data in that area. It's just the idea that wouldn't it be amazing if RNA could actually communicate?"

"Anything is possible now"

If RNA does manipulate far-flung cells through extracellular vesicles, the implications for cell biology are profound. "The dogma was (that) we have genetic information in multicellular organisms, like ourselves, as DNA. It's inside the nucleus, and it's nicely protected there," says Pegtel. Any movement of genetic information happened within the confines of the cells in multicellular organisms using RNA.

"Bacteria might do all kinds of weird things to exchange genetic information with each other, but we, higher organisms, didn't do that," says Pegtel. "That was the dogma." Now, with the discovery of these extracellular vesicles containing RNA, Pegtel adds, "it's a paradigm shift in how we think multicellular organisms function. That's where the excitement comes from."

One exciting idea is that microbial and plant-based foods come into our bodies with their own baggage of extracellular vesicles. The issue of cross-species interactions is "an extremely interesting and important question to ask," says Pegtel. "For instance, do we communicate with our commensal bacteria in the gut, and does our genome have an effect on the genomes of bacteria? This is

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one of the reasons why there is so much skepticism – because, potentially, anything is possible now."

Making them work

Besides remodeling our understanding of cell-cell communications, researchers think extracellular vesicles can do some work for them. For example, these extracellular vesicles could be used as biomarkers. Louise Laurent at the University of California, San Diego, says genetic testing on fetal DNA found in maternal blood opens up the possibility to look for fetal RNA in extracellular vesicles floating in maternal blood. "RNA is much more dynamic than DNA," she says. With DNA, "we usually use it to check if there's a genetic abnormality, but RNA, we reason, could change with different complications of pregnancy. They might even change prior to the onset of signs or symptoms that we could clinically identify."

Relying on extracellular-vesicle cargo as diagnostic biomarkers will be a reality shortly. Exosome Diagnostics, where Skog works, is gearing up to release a prostate cancer test that detects RNA in vesicles found in urine. The timeline for having the diagnostic test on the market is "months," says Skog.

Researchers also are looking to exploit these vesicles for therapeutic purposes. Therapeutics based on vesicles with RNA is a very appealing idea, because the vesicles might be made to target specific cells carrying RNA with a particular set of instructions. Using nanoscale lipid vesicles as carriers for drugs is not a new idea, but the discovery of naturally occurring vesicles that target certain cell types gives researchers a new form of vesicles that come endowed with the bells and whistles needed for targeting and delivery of cargo. Richard Kraig at The University of Chicago Medical Center rattles off the attributes of the vesicles: They are nontoxic, conserved among species, targeted for specific cells and carry potent signaling molecules.

However, therapeutic applications of these vesicles are a longer way off, say experts. "Five years away from therapeutics – that's my dream," says Kraig. For his work, Kraig is using naturally occurring exosomes to encourage myelination in animal models of neurodegenerative disorders, such as multiple sclerosis.

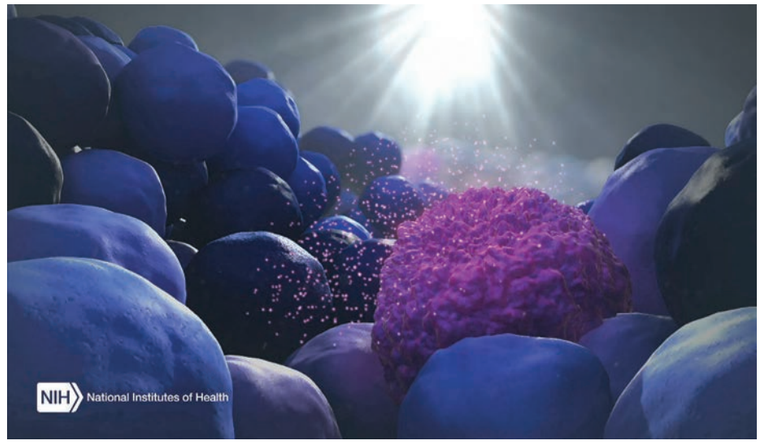
What are we talking about?

To understand why caution must temper the enthusiasm over extracellular vesicles, simply consider the fact that researchers in the field are still trying to agree on a name for what they are studying. "The terminology has not been sorted out yet," says Breakefield.

The problem is that the field is young and still riddled with fundamental questions. It was only in 2007 that researchers were able to demonstrate that extracellular vesicles contained RNA. So the questions began: Why do cells bundle RNA into lipid vesicles? Are all vesicles created the same? How are they targeted to receiving cells?

Extracellular vesicles are among a cadre of other vesicles found in the body, so it's critical to be clear exactly which kind of vesicle is being discussed. Right now, Skog says, the vesicles "have different names depending on what the (research) group is working on. Everyone thinks they are their favorite vesicles, but it's really a mixed bag of vesicles from different origins, and there's no way now of knowing where they are coming from after they have left the cell."

Several different names, such as "exosomes" or "microvesicles," have been used in the literature to describe the lipid-encapsulated particles. These days, most researchers in the field of vesicles call the RNA-containing vesicles "exosomes." But the waters remain murky, because different



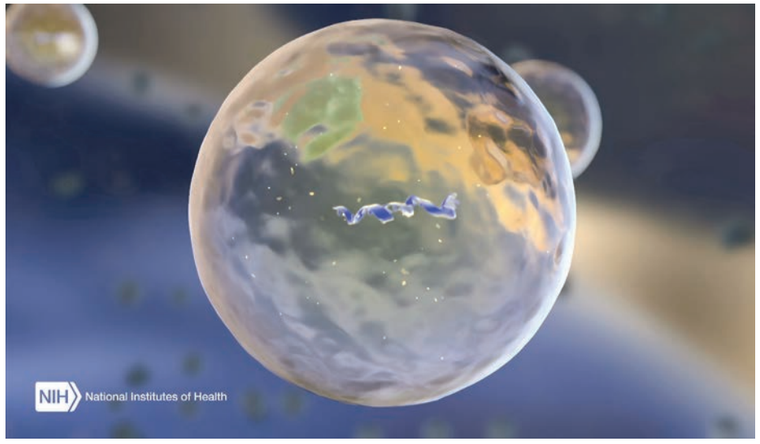
If research confirms RNA molecules are transferred via vesicles between cells, the phenomenon will represent a paradigm shift in molecular biology.

people give different rationales for calling their vesicles exosomes.

One popular naming procedure relies on the molecular mechanism: Label vesicles coming from the endosomes as exosomes and those vesicles blebbing off the plasma membrane as microvesicles. But this definition runs into problems, because the mechanisms by which these vesicles are made still remain to be elucidated unequivocally. Fans of the mechanistic form for naming vesicles say that the exosomes and microvesicles can be distinguished from one another by different protein markers on the surfaces. Exosomes are the vesicles coming from the multivesicular pathways that bear tetraspanin proteins like CD9, CD81 and CD63. Microvesicles supposedly don't have these markers, because they bleb from the cell surface.

"We know that's not true," counters Douglas Taylor at Exosome Sciences. "Almost any vesicle that comes from a tumor cell has a tetraspanin, whether it's blebbed from the surface or if it comes from the endocytic pathway. So that's not really a good definition."

Furthermore, "there is no data that demonstrates that the mechanism of vesicle budding at the plasma membrane is mechanistically different from that which occurs in the endosome," adds Stephen Gould at Johns Hopkins University. "They might be simply



two ends of the same spectrum."

Some researchers want to use size as the defining factor. Exosomes are vesicles that are smaller than 200 nanometers, and microvesicles are lipid bodies that are 500 nanometers and bigger, they say. But the size has no bearing on the biological effect elicited by the vesicles.

Until there's a better understanding of the biology, some researchers, like Breakefield and Gould, suggest that the best course of action for now is to use the more generic term – extracellular vesicles. "In lieu of having good, strong experimental data and detailed

CONTINUED ON PAGE 24

CONTINUED FROM PAGE 23

mechanistic hypotheses tested rigorously by multiple labs, the models are mostly imaginations of what we think is probably going on rather than empirically derived, well-accepted scientific facts," says Gould, who is the president of the American Society for Exosomes and Microvesicles.

What are you looking at?

Besides coming up with a name, researchers also have to figure out how to ensure they are looking at the same entities. "There are a large number of papers where people demonstrate some biological functions of exosomes. But it's very hard to compare them, because there are no standards for workflows," says Alexander "Sasha" Vlassov at Thermo Fisher Scientific, whose group is involved in developing tools to study extracellular vesicles. "It's still the wild West."

Indeed, trying to compare results is a problem. "One of the things impeding the advancement in this field is that not only there isn't well-defined terminology or nomenclature, but there's also no well-established protocols that people can agree on" for isolating, purifying and analyzing extracellular vesicles, says Danilo Tagle of the National Center for Advancing Translational Sciences at the National Institutes of Health.

The conventional tools for isolating extracellular vesicles are ultracentrifugation and density gradient separations. But companies have jumped in with kits. "There are a zillion different types of kits that try to isolate vesicles from different cell supernatants with different types of antibodies or even with polyethylene glycol," says Jan Lötvall at Gothenburg University in Sweden, who is the president of the International Society of Extracellular Vesicles.

Tagle says one way in which the NIH Common Fund program in extracellular RNA is hoping to help the field move forward is to "come out with a best set of recommendations" for analyzing extracellular vesicles.

Lots of questions

A looming issue is that no one is sure yet how to demonstrate the scale of importance of extracellular vesicles. "We still don't really know how to block the secretion of exosomes without disrupting the whole cell. It might not even be possible," says Pegtel.

He gives the example of mitochondria. "You can't prove the importance of mitochondria by saying, 'I'm going to knock out mitochondria in cells and then show that they are important.' It's a little bit of a catch-22," he notes.

Lötvall's group has seen "the translation of mouse proteins in the recipient human cells. It didn't change the phenotype of the recipient cell, but it showed that the RNA was actually transferred in an intact form and was functional in the recipient cell. It wasn't destroyed during the uptake process." But Lötvall says he hasn't seen evidence that proves that a mixture of RNAs in an extracellular vesicle elicits a change in the recipient cells within the same organism. He says, "The killer experiment, to prove or disprove the importance of extracellular RNA in normal physiology, still remains to be done."

Experts keep returning to the fact that they have more questions than answers at this point. Where are the vesicles made inside the cell? How do certain RNAs get packaged into them? How often are the vesicles made? What aspect of the pathway goes wrong in different diseases? "There is an insane amount of questions at the cell biological level that we still need to answer," says Pegtel.

And the biggest question of all is whether the buzz surrounding extracellular vesicles will hold up when one question in particular gets scrutiny. As Pegtel put it: "How big is the role of exosomes, and how useful are they?"

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Science in sign language

How deaf scientists navigate the hearing scientific community

By Maggie Kuo

I sit across from Dan Lundberg in his office on a rainy, late-fall afternoon. He tells me about his scientific career, his eyes lit and his demeanor enthusiastic, radiating brightness against the grayness coming in through the window. But only through the interpreter can I hear his words and the energy in his voice. Lundberg, a professor of chemistry at Gallaudet University, is deaf and communicates using American Sign Language.

Lundberg's path to professorship was not particularly unusual. As an undergraduate at Gallaudet University, the nation's only university for the deaf and hard of hearing, he planned on continuing on to medical school. He explored different fields, though, through summer internships with the National Forest Service and labs at James Madison University and Duke University. By the end of his undergraduate studies, he had lost all interest in a career in medicine but was intrigued by pharmacology. He then met Peter Blumberg, an investigator at the National Cancer Institute of the National Institutes of Health in Bethesda, Md., who had post-baccalaureate fellow positions open.

Blumberg is a leading authority in diacylglycerol signaling and investigates the potential of downstream targets to treat cancer and pain. Blumberg's lab was appealing to Lundberg, because it had two deaf scientists working there at the time. Blumberg is not deaf but has been providing research opportunities for deaf students and scientists for 10 years. "How successful people are, in my experience, isn't related to whether they are deaf or not," Blumberg tells me. "It's related to their ability to do the sort of science we do, pay attention to detail, how hard they work – things of that sort."

Bridging the gap

How does a principal investigator facilitate communication among deaf and hearing colleagues? Moreover, how are the large number of field-specific technical terms adopted and communicated in sign language? These communication differences are not notably challenging to work around, those I talked to say.

Blumberg taught himself American Sign Language and has interpreters stationed in the lab during the day. For lab meetings, journal clubs and research seminars, he has two interpreters present to tag-team signing. Costs for the interpreters are covered by the NIH's Office of Research Services. The only learning curve that he experienced, Blumberg says, was realizing he needed more interpreters. Before, when he had one deaf student, he could carry out the interpreting. As more deaf fellows joined, Blumberg sought full-time

CONTINUED ON PAGE 26

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interpreters for help.

Having interpreters around all day is not necessary though. "In general, interpreters are only needed during the day if we're having lab meeting, classes, important functions or events, or presentations – poster presentations, student presentations, guest presentations from other scientists," Lundberg says. "The rest of the day, I do not need an interpreter, because I'm in lab and it's independent work."

During his Ph.D. at the University of Minnesota, Lundberg used online chat platforms to speak with his adviser and colleagues. Or he wrote on a whiteboard, scratch paper, or paper towels. His adviser later suggested that he keep the scraps of paper, which "was really good advice," Lundberg says, "because they were really good notes."

The best way to arrange the most suitable accommodations for deaf individuals is to ask them what they need, says Derek Braun, a former postdoctoral fellow with Blumberg and currently a professor of biology at Gallaudet University. One of his ongoing projects is a collaboration with Blumberg and Lundberg to investigate the role of Ras guanyl nucleotide-releasing proteins, a downstream target of diacylglycerol, in cancer. "Not all deaf people sign," Braun says. "Some are oral. Really, we come in every flavor imaginable. The best judge of what that person needs is usually the person."

Signing scientific terms is not unusually challenging either. While no standardized set of signs for technical words exists, colleagues working in the same lab develop their own signs for the terms they frequently use. If each lab develops signs independently, what happens when members of different labs meet?

Larry Pearce, a technician in Blumberg's lab who is deaf, explains to me, "It's really not that difficult, because when an individual does not understand a sign we use, they'll ask for clarifications and I'll finger-spell. I'll spell it out. They will tell me what their sign is, and I'll tell them what our sign is. If I like their sign better, I might adopt it and use it every day, or vice-versa, and eventually it becomes more universal."

Artificial barriers

According to the report prepared from the Workshop for Emerging Deaf and Hard of Hearing Scientists in 2012, deaf and hard of hearing college students are as likely to study science and engineering as college students of the general population.

However, less than 1 percent of science and engineering deaf and hard of hearing students continue on to Ph.D. programs compared with the 11 percent to 15 percent of students in the general population. If the daily logistics of conducting lab research are not taxing to solve, why is the attrition between undergraduate to graduate school so high?

Blumberg posits that scientists may hesitate to take in a deaf candidate because accommodating comes across as a new challenge and more work for the lab. He finds the reluctance puzzling because "in science, all the time we're doing new things," he says.

For Braun, the resistance seems to come from misconceptions about deaf people. "There's a common attitude that deaf people are less educable," Braun says. While at a meeting held by the American Society for Human Genetics in October, Braun said he stood out because he had an interpreter with him. "After one of the sessions, a geneticist came up to me," Braun recounts, "and said he had a deaf son who wanted to become a scientist, but he, the father, didn't realize that deaf people could become scientists."

How the accommodations are paid for can also promote reluctance. "When an institution tries to have it come out of a departmental budget, which is smaller, the department becomes resistant to providing accommodations," Braun says. "The best setup is when accommodations are paid for out of a central budget for the institution."

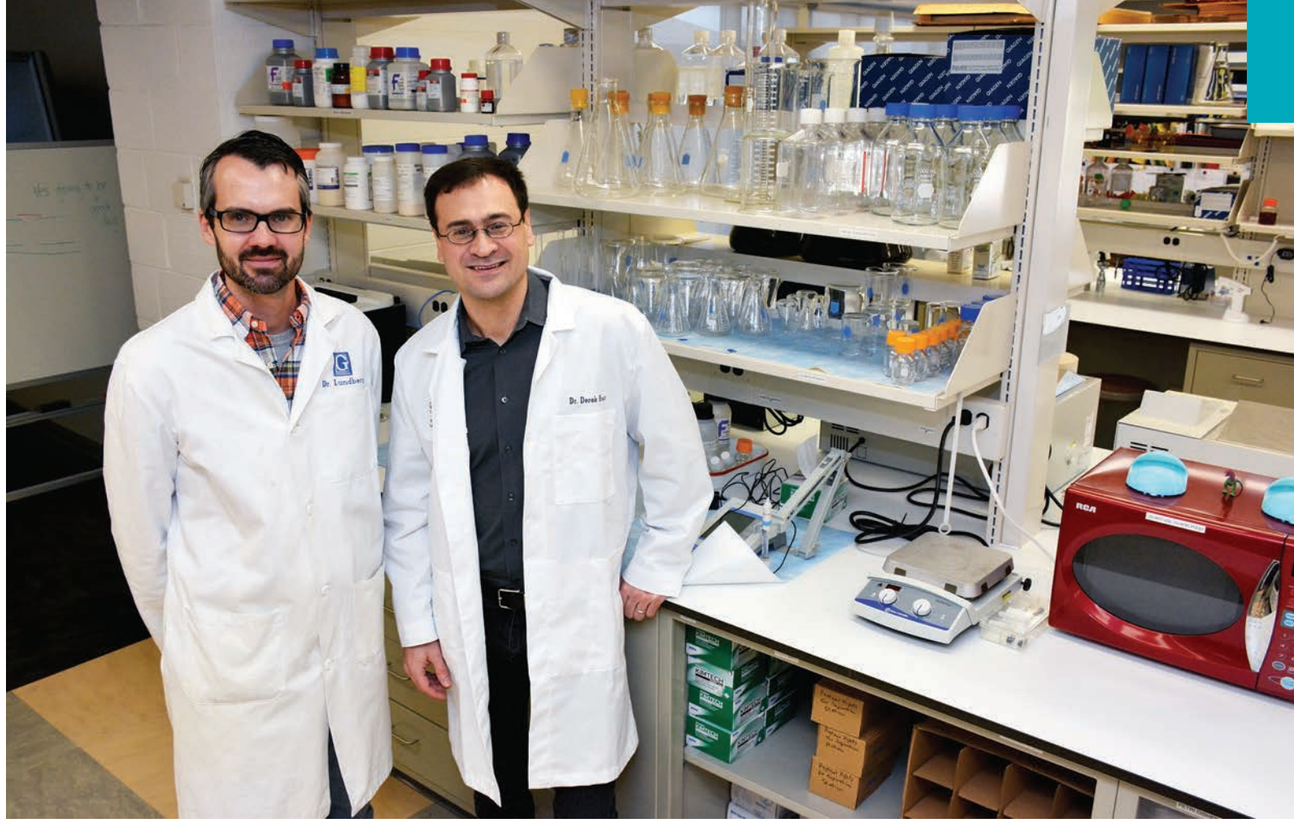

IMAGE COURTESY OF GALLAUDET UNIVERSITY

Daniel Lundberg (left) and Derek Braun.

Lundberg hesitates to call the resistance he has encountered prejudice. He says he prefers to think of it in terms of "people being exposed to new experiences." Most people, Lundberg feels, "are very open and willing. They just need to be oriented with how things go. Like, interpreters are not needed all the time, because that is the first thing they think."

Moving forward

After completing his Ph.D., Lundberg landed an assistant-professor position at Gallaudet and received tenure seven years later, last summer. Besides the project with Blumberg and Braun investigating RasGRP in cancer, Lundberg is expanding into environmental science and is starting a project on pharmaceutical waste in fresh water sources.

Blumberg believes that considering the deaf and hard of hearing disabled negatively skews the public perception of their abilities. "I always feel awkward when someone cites me for efforts to provide training opportunities for the disabled," Blumberg said in his acceptance speech when he received the American Society for Biochemistry and Molecular Biology's Ruth Kirchstein Diversity in Science Award in 2013 for his outreach activities. "The reality is that I do not consider that I have any disabled people in my group. I have a group of individuals who are defined by what they can do and who they are, not by some job-unrelated characteristic."

Blumberg says he hopes that the productivity and success of his deaf mentees persuade other scientists to reach out. He has published 61 papers from the work of his deaf mentees. To investigators who want to encourage diversity at their institutions, Blumberg's advice is straightforward: "None of it is tough. Go ahead and do it."

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DEFYING STEREOTYPES:

Beyond the finish line

A background in biochemistry taught Olympic track and field athlete Nick Symmonds how to succeed on and off of the track

By Geoffrey Hunt and Rajendrani Mukhopadhyay

If any moment symbolizes Olympic runner Nick Symmonds' career, it is a roundtable with his fellow chemistry majors during his senior year at Willamette University to discuss their future plans. "At least 80 percent of my class was going on to pursue a Ph.D. in chemistry or a M.D.," remembers Symmonds. "When they got to me, I said I was gonna stop everything and train for the 2008 Olympics."

The snickering and eye rolls from his classmates didn't deter Symmonds. "I knew even if I never made the team, I had to take the risk, or I wouldn't be able to look back and have been proud of myself for not at least trying," he says.

The risk turned out to be worth it, as Symmonds has become one of the most successful American runners of his generation. Yet the lessons he learned as a biochemistry major have been an integral part of his success.

Growing up, Symmonds always expected to become a surgeon like his father. "The reason why I was a biochemistry major was because it had the best success rate of getting people into medical school, and that's what I wanted to do," he says.

But he found something that attracted him even more than medicine: running. Symmonds had started running competitively in middle school. By the time he graduated high school, Symmonds had won state championships in the 800-, 1600- and 3200-meter races, along with the 4x400-meter relay race.

He decided to enroll at Willamette University, a small liberal-arts school in Salem, Ore. As he writes in his autobiography, "Life Outside the Oval Office," the track coaches at Willamette insisted that he would "be a student-athlete, not the other way around."

At first, Symmonds devoted equal effort to his coursework and athletics. (He won the national championship in the 800 for each of his four years at Willamette.) But as Symmonds' running aspirations grew, the rigors of a science major became too burdensome. "My senior year, I decided that if I was going to have a push for the 2008 Olympics, I really had to reevaluate my priorities," he says.

That meant his academic performance had to suffer. "I had terrible grades my senior year," he remembers. But Symmonds says he doesn't regret taking on the demanding workload of a challenging major like biochemistry, pointing out that "chipping away piece by piece and ultimately coming to the right answer taught me even the most insurmountable challenges can be broken down and tackled eventually."

Willamette's faculty noted Symmonds' ability to put his nose to the grindstone. "I think Nick would have made a very good biochemist," states Todd Silverstein, Symmonds' adviser in the chemistry department. "His level of understanding and his work ethic were quite good." In fact, Silverstein points out, Symmonds "accomplished more on our ongoing enzyme inhibition project than any other previous student, with perhaps one exception."

IMAGE COURTESY OF KIRBY LEE IMAGE OF SPORT

Nick Symmonds

IMAGE COURTESY OF JOHN JEFFERSON

Symmonds says the demanding workload of a biochemistry major taught him how to overcome challenges.

Such determination and dedication served Symmonds well on the track, where he became the second-ranked American runner at 800 meters during his senior year in college. His achievements caught the attention of Nike, which signed him to a sponsorship deal that allowed him to focus all of his energy on training after he graduated in 2006. He won the 800 meters at the 2008 U.S. Olympic Trials, earning his ticket to the Olympics.

In Beijing, Symmonds ran a disappointing race in the semifinal qualifying round and failed to advance to the final. He spent the next four years determined to make amends. In 2012, Symmonds qualified for the Summer Olympics in London. This time, he advanced all the way to the final, where he ran a personal best time of 1 minute, 42.95 seconds, which would have won a medal at any of the previous Games. But four runners were even faster (including Kenyan David Rudisha, who won the gold medal with a world-record time of 1:40.91), leaving Symmonds without a medal.

"That," Symmonds admits, "was a hard pill to swallow." Despite that heartbreak, Symmonds is back at it, currently training to compete at the 2016 Olympics in Rio de Janeiro. "I think that would be a really nice way to round out a perfect decade of running."

His experiences in Beijing and London have given Symmonds a unique perspective on what it means to be an Olympian. "On one hand, we're put on a pedestal, and we're expected to be positive role models and win medals for the country. But," he adds, "that's about all that the public wants from us."

Symmonds rejects the idea that success or failure at the Olympics is all that athletes should be judged by. "Many Olympians have really interesting, diverse backgrounds and are qualified to do many things," he says.

In 2014, Symmonds published his autobiography and is exploring the world of entrepreneurship after inventing Run Gum, a chewing gum infused with caffeine, taurine and B vitamins. The product "may be the closest I've come to actually utilizing my degree in chemistry," says Symmonds.

Such words would make his former adviser smile. "We take great pride in our graduates," says Silverstein. "The fact that a few of them go on to be among the best in the world in their field is extra gravy."

As for his former teammates at Willamette, Symmonds claims that they are equally supportive. "They tell me that they knew I had the talent to be this good all along. That part surprised me!"

Should make for an interesting 10-year college reunion.

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Regeneration of a transgenic mouse model

By Maggie Kuo

Nicole Ward came upon her psoriasis mouse serendipitously. Ward, an associate professor in the department of dermatology at Case Western Reserve University, was working in the department of anatomy there when she discovered the mouse. A neuroscientist by training, she was studying how nerves and blood vessels influence each other's development. Ward was using a transgenic mouse line, the keratinocyte-Tie2 or KC-Tie2 mouse, to manipulate cells in the skin and study how they changed the surrounding blood vessels and nerves. She noticed that the skin of these mice was patchy red and scaly like that of her father, who suffers from psoriasis.

Ward's office happened to be across the hall from faculty members in the dermatology department, and she interacted with them every day. After two years with the anatomy department, she joined the dermatology department, moved across the hall and started characterizing the mouse she was using to study nerve development as a model of psoriasis.

The KC-Tie2 mouse is a remarkably accurate model of psoriasis. Ward and her research team showed that the skin disease developed by the mouse is very similar to human psoriasis physically and biochemically. The mouse also responds to drugs that work in patients and, more impressively, does not respond to drugs that do not work in patients (1).

"Most of the time when people are testing their models against human disease, they just make sure that the drugs that work in patients work in their mouse model. We're really aware that it's equally important to demonstrate that drugs that have failed in clinical trials, that don't improve the patient's disease, also fail in the mouse model," Ward says. "So this mouse has been able to do that."

IMAGE COURTESY OF BILLY DELFS

Results from the KC-Tie2 mouse have been translatable to psoriasis patients. Ward's latest findings were recently published in the journal Molecular & Cellular Proteomics. (See a related story in the Journal News section of this issue.)

Because the KC-Tie2 mouse was developed originally to study nerve development, the fact that it developed psoriasis suggested a connection between the two. This link has been observed anecdotally in psoriasis patients who have undergone knee surgery. After the procedure, "the (psoriasis) plaque on the knee that was operated on goes away so there was speculation among the clinical dermatologists that perhaps the nervous system was contributing to the disease," explains Ward. "There are other similar reports of injury to the nervous system and then remission of the psoriasis in the areas where the nerves had been damaged."

To elucidate the basis for these observations, Ward and her team surgically removed the nerves from the skin of the KC-Tie2 mouse, and the psoriasis improved. After figuring out that certain neural peptides were elevated in the psoriatic skin, they removed the nerves in the skin and put back only the peptides. The psoriasis returned. To verify the causal role of the peptides, they kept the nerves in the skin but blocked the release of the peptides, and again the disease went away (2).

CONTINUED ON PAGE 32

Arrowhead hunting with Jackie Corbin

By Maggie Kuo

Jackie Corbin goes hunting for arrowheads almost every week. Corbin, an emeritus professor of molecular physiology and biophysics at Vanderbilt University, is sitting in his office as we chat on the phone, looking at the arrowheads he has found. He has four frames of them hanging on the wall, each with 25 to 30. "These are all of my best ones," Corbin tells me proudly. "I show off."

Corbin's most recognized scientific contribution is his discovery and characterization of phosphodiesterase 5, PDE5, with his longtime collaborator Sharron Francis. PDE5 degrades the cyclic nucleotide second messenger cyclic guanosine monophosphate and is important in controlling blood flow. Their work became the basis for using inhibitors of PDE5 to treat erectile dysfunction. The erectile dysfunction drugs available now, Viagra, Levitra and Cialis, are all PDE-5 inhibitors.

Corbin is regarded as the leading expert in the cyclic nucleotide field. Scientists come to Tennessee from across the country and around the world to visit him. "Many people would have questions about these," Corbin says about his arrowhead points. "Where did you find them, how old they are, what kind of tribes – so we have many discussions about them."

Corbin likes to give his visitors an arrowhead point in a small frame to take home. "It's a local thing, and they can take away a Tennessee artifact," he says. With each arrowhead frame, he includes a description of the arrowhead, what kind of point it is, and how it was made. "I hope they hang them up, but I don't know what they do with them," he says, with a laugh. We talk more about his arrowhead hunting hobby. Our conversation has been edited for length and clarity.

So where do you go arrowhead hunting?

CORBIN

The best place to go is a plowed field after a rainstorm. I get permission from a farmer to look on his ground, and I sometimes spend a full day with that, walking the fields and looking on the surface. Don't do any digging — that's illegal, in fact. Just look on the surface. Now, in plowed fields, the problem is that many of the arrowheads are broken. They're broken by the farm implements — plows and so forth. So on plowed fields, more than 90 percent of the arrowheads are broken. Sometimes it's just a nick, but still broken.

The other place I hunt, where the arrowheads are not broken, is on river banks. The riverbanks get eroded, so the arrowheads get uncovered; and they've never been plowed, so they're not broken by the implements. I have much better luck on riverbanks, but

CONTINUED ON PAGE 32

CONTINUED FROM PAGE 31

it's much harder to find the arrowheads on riverbanks. There are weeds, poison ivy, chiggers, snakes — everything on the riverbank is rough.

It's a great thrill to find even one in a day; it would be treasure.

How often do you find arrowheads?

I would say maybe, if I go all day, on average, I could find one complete point. There have been many times when I didn't find any, of course, and sometimes I find three, but on average, I can find one complete point. I don't count a broken one. I get a lot of enjoyment, and I sometimes take my students and postdocs with me and they really enjoy it too.

Can you identify the tribe that made an arrowhead?

Well, these are very old, starting about 13,000 years ago going up to 500 years ago or so. The tribes are only very recent. We recognize tribes only 500 years ago, maybe 1,000 years ago; 2,000 to 3,000 years ago on back, we don't know much about tribes, so we refer to these arrowheads as being Paleolithic or Archaic or Mississippian. If I find a point, I would refer to it by saying, "Oh, that's an Archaic point; it's about 8,000 years old." We have a catalog of the shapes and styles, so I can tell almost immediately how old it is and what era when I pick it up out of the field.

It's interesting, because the best points are the oldest ones. You'd think it'd be the other way around — they'd have learned how to make them. But the best ones are the oldest ones, because those are the biggest ones. In the early days, from 13,000 to about 2,000 years ago, there were no bows and arrows. That was a late development. All the early ones are spears or knives, so they're very big and very beautiful. From most of the fields where I look, the points are Paleolithic or Archaic; they're at least 6,000 years old. I find very few real arrow points. They're only 500 to 1,000 years old. You can tell because they are very small, and they are not as well made as the spear points and the knives.

How did you learn all this?

Mostly by reading and experience. I have some buddies that are very good too, and about once a year I go to a show and see what other collectors find. Often, they have a much better set than I do. Most collectors buy and sell them, but I don't do that. I

just find them and keep them. I don't have a single one that I bought.

Early on, I made a rule that I was never going to buy one, because if I buy one, I'll keep on buying more and that's no fun. When I describe a point here on my wall to someone, I want it to be one that I found myself. Some people say, "I want to buy that point," and I say, "Nope. I wouldn't sell that for a million dollars." That's the truth. I wouldn't sell for a million dollars. I worked so hard for these points. I wouldn't sell any of them. I just keep them. I really show off.

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GENERATIONS CONTINUED

CONTINUED FROM PAGE 30

Since Ward moved across the hall in 2005, she has been investigating psoriasis and skin inflammation full-time. Ward has not left behind her neuroscience roots, though.

"I'm lucky I get to play a little bit in the neuroscience sandbox because psoriasis is a very cool disease if you're studying disease pathogenesis. You have so many cell types that are contributing to the inflammation. You have the keratinocytes, the nerves, the blood vessels and all those immune cells," she says. "I always tell patients when I'm talking to them, 'You know, the disease is absolutely fascinating at the scientific level.' It's like a big, ginormous nerd alert, right? But it's like so, so cool."

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

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HOBBIES

Break it down again

"KUCR is a college radio station broadcasting from the University of California, Riverside, and it's my getaway from working long hours in the lab and/or from studying the books. I love hosting my show because it allows me to share amazing sounds from a diverse range of genres to the community, and I'm always discovering new music. The learning never stops!"

– SAM CASTANEDA

Senior undergraduate who is studying and purifying initiation factors by proteolysis methods in the lab of Gregor Blaha

Impact by design

Nonprofit's e-outreach platform matches STEM professionals with students

By Maggie Kuo

Tara Chklovski came to the U.S. from India for graduate school wanting to build airplanes inspired by birds. While she was working on her Ph.D. in aerospace engineering at the University of Southern California, she was surprised not to see the same drive to enter science, technology, engineering, and mathematics – STEM fields – in the U.S. as in her home country. Having realized that she wanted to solve this social problem instead of physics problems of flight, Chklovski founded the science-education nonprofit Iridescent.

Iridescent reaches out to K–12 students in underserved communities. Its flagship program is the Curiosity Machine, an online science-education platform that provides engineering design projects for students to build with the help of mentors who are STEM professionals.

Each project begins with a video in which a STEM professional describes his or her job and career path, explains essential concepts of his or her work, and introduces a design challenge: Build X so that it can accomplish Y. The students plan and execute their designs using common household objects, such as rubber bands and cardboard, and post their prototypes on the Curiosity Machine website. Mentors then correspond with the students online and help them troubleshoot or improve what they have built.

Because mentoring is done online, this outreach avenue is flexible and can be worked into the mentor's schedule. "I can mentor at any time as long as I have a computer and Internet connection," says Christian Marks, a mentor and a Ph.D. student in molecular physiology and biophysics at Vanderbilt University. "I pick one day a week to claim projects and work on those after my work day is done."

While most of the projects focus on engineering and physics concepts, the mentors do not have to be experts in the field. Stephanie Agbu, a mentor and Ph.D. student in developmental genetics at Cornell University, says, "I draw on physics concepts that I learned in high school and college courses to help me mentor."

Students most often need help "solving problems they encounter when building their project designs," Agbu explains. "They may not fully understand the reasoning behind certain aspects of their design, so they do not always yield a functional unit. In this case, I try to help them think of modifications that will enhance their design."

Agbu adds, "The students also need help with thinking of multiple ways to carry out their projects. If a student successfully completes a design, I follow up with questions to help them think of another way they could have successfully done the project or how particular characteristics of their design would change if they were to modify one aspect."

The Curiosity Machine also offers STEM professionals the opportunity to get involved in curriculum development. They can come up with new design challenges based on their research. Although most of the projects on the website are engineering-related, Iridescent is interested in partnering with scientists to broaden its range of topics. Iridescent's staff helps translate complex research into easily understandable ideas and creates a video to capture the concepts of the challenge.

Iridescent also fosters collaboration with underserved communities by training educators, librarians and parents. In fact, the Curiosity Machine is used in a variety of ways in communities. The Chicago and Los Angeles public libraries run it as an afterschool program. In a five-week Curiosity Course, students go to the site, learn about the challenge, build their contraptions and then return home to work on their projects with their online mentors. The Curiosity Machine can be entirely home-based as well: Students start and work on their projects at home with their parents.

Chklovski says the idea for Curiosity Machine came from the model for Teach for America, in which recent college graduates teach in communities with limited access to high-quality education. Teach for America's model, Chklovski says, "was interesting to me because it's life changing" for the teachers. She wanted to provide similar opportunities that were enriching for both the community members and the STEM professionals.

Curiosity Machine mentors say they have found the experience fulfilling. "I encourage children to think critically about the tasks given to them and how they can solve problems they might encounter," Agbu says. "These are two important skills for engineers and scientists, so I am happy that I can help them develop these skills at an early age."

Marks says, "My favorite thing about Curiosity Machine is how excited students are about their projects. I love seeing the students succeed, and I am really impressed by their ideas."

To become a mentor, sign up at www.curiositymachine.org. To get involved with curriculum development, contact Andrew Collins (andrew@iridescentlearning.org) or Tara Chklovski (tara@iridescentlearning.org).

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

Colorful characters

Nobel laureates convey wisdom and whimsy with impromptu sketches of their prize-winning work

By Angela Hopp

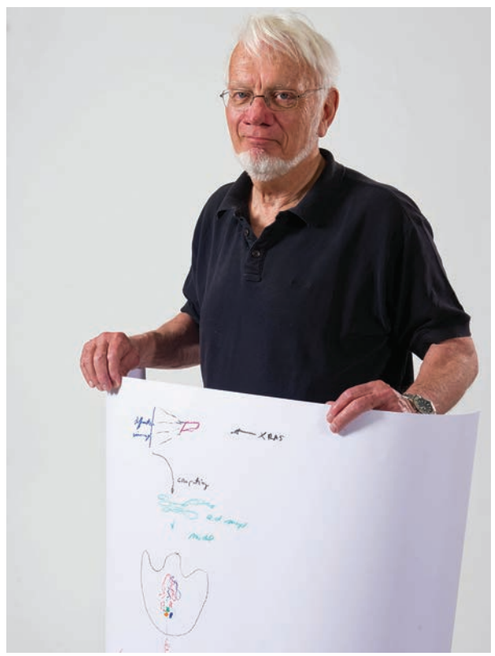
An exhibition last month at the University of California, Davis, featured the Nobel prize-winning work of four members of the American Society for Biochemistry and Molecular Biology.

The "Sketches of Science: Photo Sessions with Nobel Laureates" exhibition at the Mondavi Center for the Performing Arts displayed drawings in crayon by Nobel laureates and photographs of the scientists holding their renderings. German photographer Volker Steger took the photos over several years, often at the annual Lindau Nobel Laureate Meetings in Germany.

"All the laureates I met for a photo shoot were quite surprised by my exceptional request, because I did not inform them beforehand," Steger said in a statement. "The idea was to get something spontaneous. The sketches turned out to be as varied as the Nobel laureates who drew them. But they all equally demonstrate the beauty of intellectual concepts — and of minds at work."

Here we've highlighted the four ASBMB members who participated.

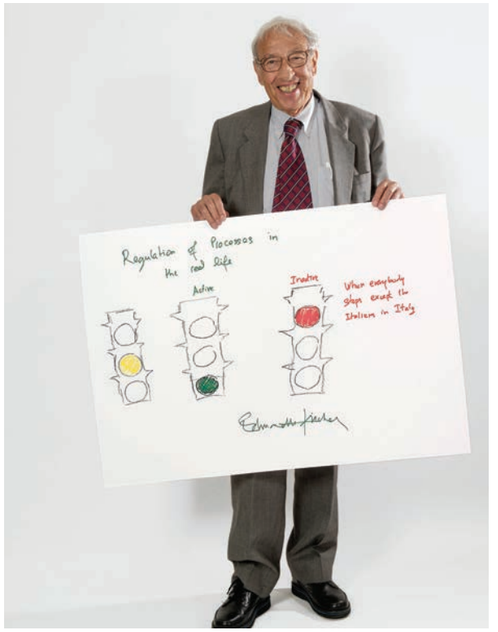
Angela Hopp (ahopp@asbmb.org) is editor of ASBMB Today.



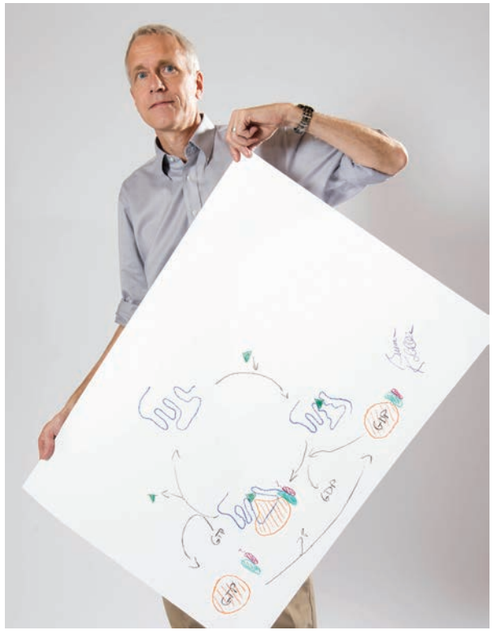
IMAGES COURTESY OF VOLKER STEGER/LINDAU NOBEL LAUREATE MEETINGS

Thomas A. Steitz of Yale University won the Nobel prize in chemistry in 2009 for his studies of the structure and function of the ribosome. He shared the prize with Venkatraman Ramakrishnan and Ada E. Yonath.

Peter Agre of the Johns Hopkins Bloomberg School of Public Health won the Nobel prize in chemistry in 2003 for the discovery of water channels. Agre shared the prize with Roderick MacKinnon, who won for his structural and mechanistic studies of ion channels.



Edmond H. Fischer, professor emeritus at the University of Washington, won the prize in physiology or medicine with Edwin G. Krebs in 1992. The Nobel committee cited "their discoveries concerning reversible protein phosphorylation as a biological regulatory mechanism."



Brian Kobilka of Stanford University, who won the 2012 prize in chemistry with Robert J. Lefkowitz of Duke University, attended the opening ceremony for the exhibition. Kobilka and Lefkowitz won the prize for their studies of G-protein–coupled receptors.

ASBMB 2015 Annual Meeting

BOSTON

March 28 – April 1

ASBMB THEMES AND HASHTAGS

#cancer	Cancer: The War at 44, Warburg at 90
#DNA	DNA Replication and Repair
#ECM	Extracellular Matrices in Health and Disease
#lipids	Lipids- In Vivo Dynamics, Protein Partners and Signaling
#PTMs	Mechanistic Impacts of Post-translational Modifications
#microbiome	Microbiome Dynamics and Health Disparities
#microbiome	The Human Microbiome
#immunology	Molecular Mechanisms of Infection and Immunity
#enzyme	New Directions in Enzymology
#plants	Plant Metabolism
#protein	Protein Nonfolding as a Regulatory Phenomenon
#RNA	RNA Expression and Post-transcriptional Regulatory Events
#protein	What's New in Membrane Transport Proteins
#training	Training the Mind of an Interdisciplinary Scientist
#scicomm	Public Policy and Science Outreach

PLENARY SPEAKERS


C. David Allis,
The Rockefeller University


Bonnie Bassler,
Princeton University


Zhijian James Chen, *University of Texas–Southwestern Medical Center*


Rachel Klevit,
University of Washington


Ian Wilson,
The Scripps Research Institute

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