BREAKING DOGMA?

Researchers are trying to figure out if extracellular vesicles containing RNA represent a new way for cells to communicate.
The Journal of Biological Chemistry’s editors are pleased to announce that 21 papers have won Best of 2014 designations. The Best of 2014 manuscripts were selected from the more than 3,100 papers published last year. One Best of 2014 paper was chosen from each of the journal’s Affinity Groups for its excellence and potential impact on the field.

These 21 papers are free to all. Visit www.jbc.org/site/bestoftheyear.

Breaking dogma?

Regeneration of a transgenic mouse model

Rajendran Mukhopadhyay explores the mysterious world of extracellular RNA.

Matters of the heart

Impact by design

Generations of investigators

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

The premise of unknown unknowns

31 Arrowhead hunting with Jackie Corbin

33 Break it down again

36 Open Channels

Colorful characters

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Colorful characters
Why meet?

By Steven McKnight

ext 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 ASMB 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 told me 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-involved organelles could be born from pre-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 ever 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 high- est of pedestals. Fast-forward almost four decades, and let’s consider how the meeting enterprise has evolved. Instead of being limited to the large ASMB, 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 ASMB annual meeting is open to undergraduates, 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 ASMB annual meeting gives us opportunities to hear about developments at ASMB journals, advocacy efforts for basic research, the diversity of our workforce, educational initiatives and science-outreach activities. As president of the ASMB, 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 Kleve, David Allo, James Chen, Bonnie Basler and Ian Wilson. Together with our ASMB 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 ASMB 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 ASMB is our organization; let’s collectively pitch in at the Boston meeting to make it as healthy as possible!

Steven McKnight (steven.mcknight@asbmb.org) 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.
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 12,000 grants and the CDMRP has more than 6,400 funded awards 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 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.

“(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, pathology 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 had a significant impact on the standards for care provided to patients with breast cancer, neurofibromatosis, ovarian cancer, prostate cancer and spinal cord injuries.

For those interested in the program or funding opportunities, the ASMBM has been told that comprehensive program announcements will be released in March for the FY15 cycle. The program announcements will be included in a database of information on 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.

Two members win awards from ASPET

The American Society for Pharmacology and Experimental Therapeutics will recognize two ASMBM members, Hesh 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 ASMBM 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 1971, 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 and Pharmacology Early Career Achievement Award. Her research focuses on adverse effects associated with non-nucleoside reverse transcriptase inhibitors in HIV.

Rauschel receives ACS Southwest Regional Award

The American Chemical Society recognized Frank Rauschel’s contributions in enzymology and biological chemistry and honored him with the organization’s Southwest Regional Award in November. Rauschel received the award, which included a $2,000 cash prize and a commerorative plaque, at the Dallas–Fort Worth chapter. Rauschel 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. Rauschel 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 carbonyl 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 biocavengers for cholisterase-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

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Donald F. Steiner, 1930 – 2014

By Robert Roskoski Jr.

Steiner’s work centered on the production of proinsulin in 1956. As a school of medicine in 1956. As a degree at the University of Chicago.

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.

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 antiserum 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 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 rat-mating factor. This eventually led to the discovery of the kexin/subtilisin-like prohormone convertases 1/2 and 3 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.

The production of 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 exciting 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 F. Kennedy. Steiner received many offers for positions at other institutions, but he valued his colleagues and chose to remain at Chi-

The starting salary of $9,000 was much more than he could raise his voice under circumstances that would readily elicit expirations from others. He was an efficient and prolific worker who also had time for activities in the arts, especially music.

In 1964, the National Institute 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 scientist who had time for author on several Steiner papers. Then they walked into Steiner’s office, where he was kneeling on the floor fabricating a harbichord. Kozloff won the grant despite this encounter.

Steiner received the University of Chicago 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 difficul-

Robert Roskoski Jr. (robertroskoski@gmail.com) is the scientific director of the Blue Ridge Institute for Medical Research in North Carolina.
A connection between blindness and Parkinson’s disease
By Martina Efeyini

A research team led by Paolo 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 the role of Ran-binding protein 2, or Rabp2, 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 modular 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 Rabp2 develop degeneration of the RPE and secondary breakdown of the blood–retinal barrier. This loss of Rabp2 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 Rabp2 that, when lost, sufficed to recapitulate the degeneration of the RPE. This Rabp2 activity is implicated in controlling nucleocytoplasmic trafficking of selective substrates.

Ferreira’s team also found that the mice that lacked overall Rabp2 activity and other genetic modifiers, because not all mice lacking Rabp2 develop Parkinson’s, but mice with Parkinson’s must have loss of Rabp2 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.”

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 naïve 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.

3-D confocal images of RPE of wild-type mice (top) and knock-out Rabp2 mice with extrusion of degenerating RPE cells (bottom). Ribbon representation of the structure of the binary complex of a Ran-binding domain of Rabp2 with Ran-GDP (middle).
Today f
cGMP to his longtime collabora-
and his later career studying cGMP .

people's health.

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tinationized the field. The discovery of

important for increasing blood flow.

guanosine monophosphate, which is

story for basic research.

A football game does not air with-
avoid with another theme: cam-

or, Sharron Francis. “Sharron was

Glaxo's actions until 2003, Corbin

brought to the Supreme Court, but

The litigation lasted five years and

from that of Viagra or Levitra.

protecting their researchers' interests,

now are much more aggressive in

University technology-transfer offices

is important in regulating blood flow.

ing how cyclic nucleotides control

PKG, and PKG proceeds to turn on

the cellular machinery that results in

that one “was much better than any

that was very different from that of Viag-

to develop tadalafil because of their

Levitra; it's a little bit unique.”

very different from that of Viagra or

Corbin would not advise colleagues

the credit they felt they deserved,

and we did provide a lot of informa-

doing science as a team and helping

papers together — no question that is

that the broader impacts stemming from

university discoveries are fulfilling in

“Discoveries move on and are

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 sci-

enists, Corbin strongly recommends

they consider working with a partner.

“To have around every day someone
to talk about the results and plan

the next experiments, talk about the

students in the lab, write grants and

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 appro-

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To potential scientists, he writes,

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in the study that reported that

an elevated cGMP level medi-

ated penile erection in rabbits.

Corbin and his team believed that

their PDE5 inhibitors 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

and continued working on PDE5 inhibi-

tors, 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 test-

ing 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 commer-

cially as Cialis.

They did not become aware of

Glaxo’s actions until 2003, Corbin

says, after the results of the tadalafil

were published. “We planned to synthe-

size Cialis to do some research with

the compound,” says Corbin. “Raja

looked up the structure and came to

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 Viag-

ra, 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 appro-

ached the technology transfer depart-

ment at Vanderbilt, wondering about

their rights. In 2005, Vanderbilt filed

a civil action lawsuit against the com-

pany; seeking to have Corbin, Francis

and Konjeti added to the tadalafil

patent as joint inventors.

The litigation lasted five years and

and went through two courts. Both
courts ruled against Corbin and his
team. “I guess the major thing the judges
uled was that we did a lot to help

and we did provide a lot of informa-

tion 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 reff

ects, “the legal system rules that who-

ever 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.

 automate penile erection in rabbits,

Corbin and Francis decided to

continue working on PDE5 inhibi-

tors. In the last year of the

grant period, Glaxo recommended

an experimental design. They did so,

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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.

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 com-

pound 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 pharma-

cceutical 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
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.

NPD 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 or NPC2 proteins are expressed or amounts of NPC1 or NPC2 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, 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.

The authors also consider the limitations of using cyclodextrins, such as CYCLO, as a potential NPC therapy. The authors also consider the limitations of using cyclodextrins, such as CYCLO, as a potential NPC therapy. The very exciting finding from John Dietchy’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.

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 that four proteins are promising.

The researchers harvested skin samples from genetically modified mice that deviated from genetically modified mice that deviated from genetically modified mice 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 continued. “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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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 that four proteins are promising. The researchers harvested skin samples from genetically modified mice that deviated from genetically modified mice 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.

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**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 $119 billion in treatments, medications and lost productivity each year (2).

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, plaque, which narrows and hardens

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These studies were presented at the American Heart Association meeting held in November (3, 4).

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

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).

The MIRA program, developed by Lorch and other NIGMS leaders, will fund renewable five-year grants of up to $750,000 for 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 research areas relevant to the institute’s mission. Lorch 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.

“Wall that.”

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

Lorch 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 Lorch. “We are concerned about the possibility that NIH funding will become concentrated in the hands of a small number of (investigators) or institutions,” Haywood wrote.

However, Lorch 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 program,” Lorch said.

References
1. http://1.usa.gov/1v2Zan90
2. http://1.usa.gov/1vSNH
4. http://rct.ly/1v507t1

**NIGMS to pilot grant program**

By Erica Siebrasse

When Jon Lorch 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 Lorch’s idea, Maximizing Investigators’ Research Award, or MIRA, will begin in the summer.

LORCH

An interview about the program, Lorch 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,” Lorch 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. Lorch is also concerned that the time spent writing grants is increasingly burdensome.

The MIRA program, developed by Lorch 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 over- all 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.

Lorch 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, Lorch said, with positive comments from 80 percent of 300 respondents. Lorch 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 Lorch. “We are concerned about the possibility that NIH funding will become concentrated in the hands of a small number of (investigators) or institutions,” Haywood wrote.

However, Lorch 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 program,” Lorch said.

References
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**Continued on Page 16**
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 Sideras is the education and professional development manager for ASBMB. Follow her on Twitter at twitter.com/ericasiebrasse.

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The promise of unknown unknowns

By John Brouse

“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 tends to be the difficult ones.”

— DONALD RUMSFELD

F or 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 phosphatidycholine. How 18:1 is incorporated into phosphatidycholine 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-phosphatidylcholine acyltransferase, known as LPCAT for short (4), or incorporation into diacylglycerol followed by conversion into phosphatidycholine 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 oleic acid), 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, phosphatidycholine 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 1C-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 phosphaticid 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 phosphaticid acid phosphatase activity.

Time for a Hall 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 phosphatidycholine headgroup from phosphatidylcholine...
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 phosphatidylcholine 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.

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.

REFERENCES
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...
CONTINUED FROM PAGE 21
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 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. Eosnox Diagnostics, where Skog works, is gearing up to release a prostate cancer test 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 raffles 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. “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 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 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 tetratspanin 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 Eosnox Sciences. “Almost any vesicle that comes from a tumor cell has a tetratraspan, 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...
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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 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 Danielo 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 the Lundberg, because it had two stream targets to treat cancer and hearing disorders. B

lumberg’s lab was appealing 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 interpreting. 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

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 wasn’t 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-bacca
duror at the National Institutes of Health.

Lundberg’s research is in cancer, more specifically finding biomarkers for bladder cancer. His experiments involve a cell line that secretes exosomes. “You can’t prove the importance of mitochondria by saying, ‘I’m going to knock out mitochondria’ in a cell 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?”

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 interpreting. 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

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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 meetings, 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 educated,” 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 encourage diversity at their institutions, Blumberg’s advice is straightforward: “None of it is tough. Go ahead and do it.”
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, and after 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 rigor 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.”

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.

“Thick,” 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 fulfilling 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 glory.”

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.
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 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.

While on her way to anatomy department, she joined the dermatology department, and she moved across the hall from faculty members in the dermatology department, 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.

“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.”

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 (psoriatic) 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.

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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 arrowheads. “Where did you find them, how old are they, 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?

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 I
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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. Sometimes I find three, but on average, I could 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 about 500 years ago or so. The tribes are only very recent. We recognize tribes about 13,000 years ago; 2,000 to 3,000 years ago; 1,000 years ago; only 500 years ago, maybe 1,000 years ago. There are weeds, poison ivy, chiggers, snakes — everything on the riverbank is rough.

How do you learn all this?
Mostly by reading and experience. I have some buddies that are very good at this. I sometimes I find three, but on average, I could 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.

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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, students can mentor at any time they have built. “I can mentor at any time and day a week to claim their design.”

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 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

A n 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.

Edmund 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.”

Edward I. Alberts 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 Rodrick MacKinnon, who won for his structural and mechanistic studies of ion channels.

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 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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