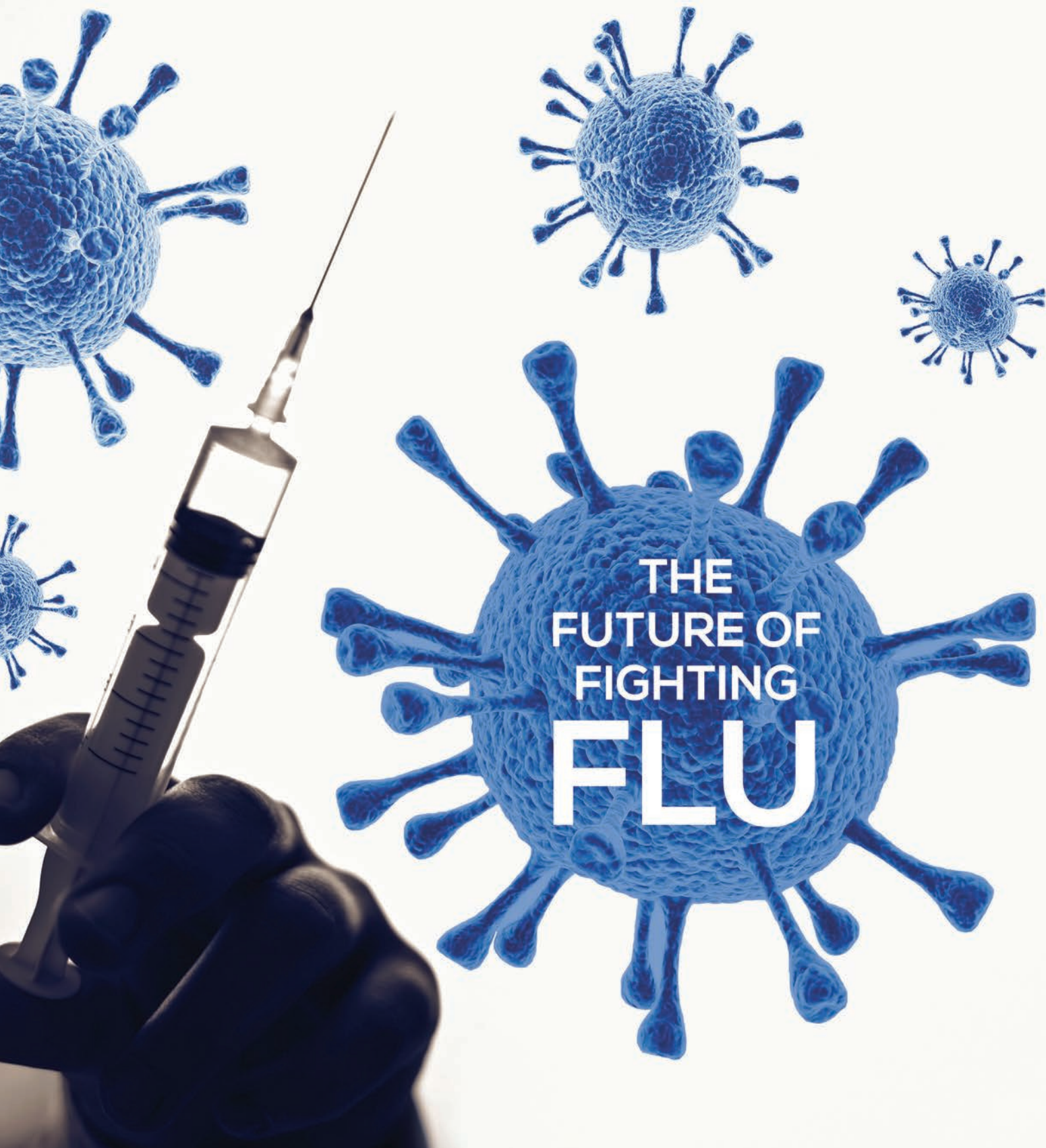


Vol. 17 / No. 10 / November 2018

ASBMB TODAY

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



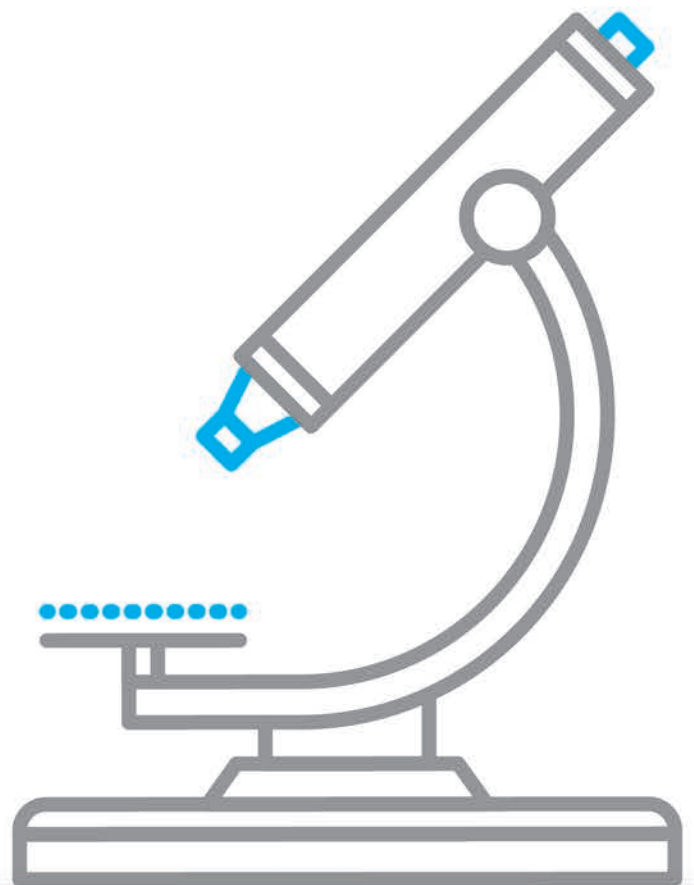
THE
FUTURE OF
FIGHTING
FLU



As an ASBMB member, you can make a difference.

Together, we can continue to advocate for science, connect researchers around the world and build a bright future for biochemists and molecular biologists everywhere.

Now is the time to renew.



WWW.ASBMB.ORG/RENEW

 **ASBMB**
American Society for Biochemistry and Molecular Biology

NEWS

2

EDITOR'S NOTE

What's in a name

3

NEWS FROM THE HILL

Election Day 2018

4

MEMBER UPDATE

6

RETROSPECTIVE

Minor J. Coon (1921 – 2018)

8

NEWS

Her research evolved from chore to passion

9

LIPID NEWS

Unexpected roles of lipid kinase

10

JOURNAL NEWS

10 *Celebrating Herb Tabor's 100 years*

11 *Iron-sulfur cluster research offers new avenues for investigating disease*

12 *What happens to plasmalogens, the phospholipids nobody likes to think about*

13 *Which oil is best for your health?*

14 *Sperm-quality study updates advice for couples trying to conceive*

15 *From the journals*

2



FEATURES

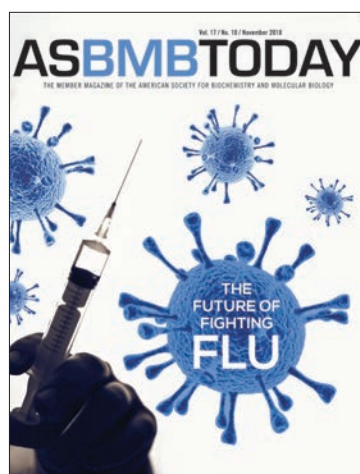
20

THE FUTURE OF FIGHTING FLU

32

MEET KAREN FLEMING

20



Researchers worldwide work to improve existing vaccines, get more people vaccinated and develop universal long-term protection.

32



PERSPECTIVES

36

FUNDING

36 *Chasing unicorns*

37 *Commercial beneficiaries should share costs*

37 *Two funding proposals*

39

PROFESSIONAL DEVELOPMENT

Tweeting for rules

41

AFRICAN-AMERICAN MEN IN THE MOLECULAR BIOSCIENCES

Perspectives for the future and advice for aspiring scientists

39



41



OFFICERS

Gerald Hart
President

Jennifer DuBois
Secretary

Toni M. Antalis
Treasurer

COUNCIL MEMBERS

Squire J. Booker

Victoria J. DeRose

Wayne Fairbrother

Rachel Green

Blake Hill

Susan Marqusee

Celia A. Shiffer

Takita Felder Sumter

JoAnn Trejo

**ASBMB TODAY EDITORIAL
ADVISORY BOARD**

Rajini Rao

Chair

Floyd "Ski" Chilton

Henrik Dohlman

Peter J. Kennelly

Beronda Montgomery

A. Maureen Rouhi

Melissa Vaught

Binks W. Wattenberg

ASBMB TODAY

Angela Hopp

Executive Editor,

ahopp@asbmb.org

Comfort Dorn

Managing Editor,

cdorn@asbmb.org

John Arnst

Science Writer,

jarnst@asbmb.org

Laurel Oldach

Science Writer

loldach@asbmb.org

Valery Masterson

Designer,

vmasterson@asbmb.org

Ed Marklin

Web Editor,

emarklin@asbmb.org

Allison Frick

Media Specialist,

africk@asbmb.org

Barbara Gordon

Executive Director,

bgordon@asbmb.org

EX-OFFICIO MEMBERS

David Bernlohr

Hao Wu

Co-chairs, 2019 Annual

Meeting Program

Committee

Cheryl Bailey

Chair, Education and

Professional Development

Committee

Daniel Raben

Chair, Meetings Committee

Sonia Flores

Chair, Minority Affairs

Committee

Susanna Greer

Chair, Public Outreach

Committee

Matthew S. Gentry

Chair, Public Affairs

Advisory Committee

Amnon Kohen

Chair, Publications

Committee

Lila M. Gierasch

Editor-in-chief, JBC

A. L. Burlingame

Editor, MCP

Edward A. Dennis

Editor-in-chief, JLR

William L. Smith

Editor-in-chief, JLR

For information on advertising, contact Pharmaceutical
Media Inc. at 212-904-0374 or mperlowitz@pmi.com.



www.asbmb.org/asbmbtoday

PRINT ISSN 2372-0409

Articles published in ASBMB Today reflect solely the authors' views and not the official positions of the American Society for Biochemistry and Molecular Biology or the institutions with which the authors are affiliated. Mentions of products or services are not endorsements.

What's in a name

By John Arnst

Instead of telling you some goofy personal anecdote, this month I'm giving this space over to real news. Our science writer John Arnst wrote the following short article for our blog, Wild Types, but it deserves a wider readership. We should all know and ponder the story of Henrietta Lacks — and what Johns Hopkins University has done to ensure her legacy.

— Comfort Dorn, managing editor



COURTESY OF KADIR NELSON/SMITHSONIAN

The world owes much to Henrietta Lacks, pictured here in a posthumous portrait, whose cells were removed during a biopsy in 1951 and used for research without her knowledge or approval.

Johns Hopkins University has announced plans to name a research building on its East Baltimore campus in honor of Henrietta Lacks, whose “immortal cells” have been crucial to biomedical progress over six decades, including the development of anti-tumor and anti-viral treatments and the polio vaccine.

The naming was announced by Johns Hopkins University President Ronald J. Daniels, who was joined by descendants of Lacks, during the ninth annual Henrietta Lacks Memorial Lecture in October. Lacks and the biomedical legacy of her cells, which were taken without her consent in 1951 shortly before her death from cervical cancer, were made famous by the bestselling 2010 book “The Immortal Life of Henrietta Lacks” by Rebecca Skloot.

“This building will be a place that stands as an enduring and powerful testament to a woman who not only was the beloved mother, grandmother and great-grandmother to generations of the Lacks family, but the genesis of generations of miraculous discoveries that have changed the landscape of modern medicine and that have benefited, in truth, the much larger family of humanity,” Daniels said.

The announcement came about five years after Johns Hopkins worked with members of the Lacks family

and the National Institutes of Health to reach an agreement on approval for researchers to gain access to the full genomic sequence of HeLa cells, including traits of the family's genome.

Groundbreaking for the building, which will adjoin the university's Berman Institute of Bioethics and will house programs that enhance participation of members of the community in biomedical research, is scheduled for 2020, and university officials expect construction to be completed in 2022.

“We say very directly to the Lacks family, thank you,” Daniels said. “Thank you for the generosity of spirit, of hopefulness, of honesty, of collaboration that has marked our partnership. Thank you for lending Henrietta Lacks' name to our campus. And thank you for the things that we will do together to honor and celebrate her legacy.”



John Arnst (jarnst@asbmb.org) is ASBMB Today's science writer. Follow him on Twitter @arnstjohn.

Election Day 2018

By Benjamin Corb

In a few days, Americans will exercise the right to vote. This midterm election falls two years into President Donald Trump's first term. Only twice since World War II has the president's party not lost seats in the U.S. House of Representatives or Senate. Polling data and political scientists seem to agree that this year the House is likely to switch to a Democratic majority for the first time since 2010 and the Republican majority in the Senate is likely to remain slim.

What would changes to party control mean, particularly for science funding?

Broadly, Democratic control of the House likely would roll back fiscal policies that have stifled some federal investments in science. Self-imposed caps on domestic spending have forced the U.S. Congress to limit investment in important programs across the government. In recent years, for example, Congress has provided increases for the National Institutes of Health while leaving the Centers for Disease Control and Prevention relatively flat funded. It's possible that a Democratic House will work to raise or remove the spending caps. If the House flips, Democrats likely will work to increase investments in their priorities, such as

environmental sciences.

Democratic control of the House is not likely to have a significant impact on funding for life science research at the National Science Foundation or the NIH. The NIH has been the beneficiary of four straight years of significant budget increases with the Republican majority, and indications are that House Democratic leaders would continue the trend of bipartisan support for biomedical research and innovation.

U.S. Rep. Tom Cole, R-Okla., has been chairman of the Labor, Health and Human Services Subcommittee for the recent budget cycles that have resulted in \$2 billion annual increases at the NIH. A Democratic victory this month likely would elevate Rep. Rosa DeLauro, D-Conn., to chairwoman of the committee. DeLauro is an outspoken champion for the NIH and was a 2015 recipient of the American Society for Biochemistry and Molecular Biology's Howard K. Schachman Public Service Award (with U.S. Sen. Jerry Moran, R-Kan.) for her support of the agency.

A Democratic takeover of the Senate is a slim possibility at best, according to analyses. Assuming that the current Republican majority holds after the election, we might see a renewed interest in bipartisanship

Voting information

Whatever your political bent, the American Society for Biochemistry and Molecular Biology encourages you to take the time to get out and vote. If you don't know where your polling location is or the hours you can vote, visit USA.gov/election-day for all the relevant local information.

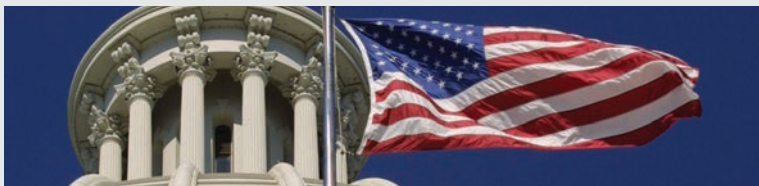
and compromise, as each chamber of Congress will need support from the opposing party for governing to take place.

Whoever wins, the ASBMB Public Affairs Advisory Committee is preparing a welcome package for the newly elected congressional members and their staffs. The package will include state- and district-specific information on federal funding for science, as well as materials explaining the importance of basic science and robust support for the agencies that fund the ASBMB's members.

We look forward to working with members of Congress from both parties to help create the best environment possible for science.



Benjamin Corb (bcorb@asbmb.org) is director of public affairs at the ASBMB. Follow him on Twitter @bwcorb.



Interested in science policy?

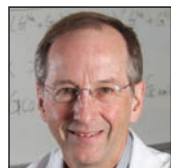
Follow our blog for news, analysis and commentary on policy issues affecting scientists, research funding and society. Visit policy.asbmb.org.

Member update

By Erik Chaulk

Welsh receives Alpert prize

Michael Welsh is one of five scientists to receive the Warren Alpert Foundation Prize for developing



WELSH

disease-modifying treatments for cystic fibrosis.

The prize recognizes outstanding scientists who have made breakthroughs in biomedical research.

Welsh discovered that the cystic fibrosis transmembrane conductance regulator, or CFTR, is an anion channel and revealed how it is regulated.

He and colleagues showed how cystic fibrosis-causing mutations disrupt channel function and discovered that function can be restored to mutated CFTR. That research enabled development of effective medicines.

Welsh is the Roy J. Carver professor of internal medicine and molecular physiology and biophysics at the University of Iowa. He also serves as director of the Pappajohn Biomedical Institute and the Cystic Fibrosis Research Center.

Holz named dean of NYMC grad school

Marina K. Holz has been named dean of New York Medical College's Graduate School of Basic Medical



HOLZ

Sciences.

Holz previously served as the Doris and Dr. Ira Kukin chair in biology and chair of the division of natural sciences and mathematics at the Stern College of Yeshiva University. She also held a

joint appointment in the department of molecular pharmacology at the Albert Einstein College of Medicine.

In her lab, Holz studies the mechanisms of signaling by hormones and growth factors in breast cancer.

She assumed her new role in September.

Duckett named vice dean

Colin S. Duckett has been appointed vice dean for basic science at the Duke University School of



DUCKETT

Medicine.

In this role, Duckett serves as the liaison between the dean's office and the basic science community. He will oversee the biomedical graduate programs and help develop core facilities within the university.

Duckett previously served as chief scientific officer at the Baylor Scott and White Research Institute, Baylor College of Medicine. Prior to working at Baylor, he was a professor for 15 years in the departments of pathology and internal medicine at the University of Michigan Medical School.

Duckett is highly regarded for his work on the inhibitor of apoptosis proteins. He has authored more than 90 papers throughout his career.

Duckett assumed his new role in September.

Schekman to step down from eLife

The founding editor-in-chief of eLife, Randy Schekman, will step down from his role with the journal in early 2019.

Schekman will dedicate more of his time to his responsibilities as chair of the advisory council for Aligning Science



SCHEKMAN

Across Parkinson's, an initiative dedicated to developing strategies to advance knowledge of the underlying mechanisms of the

disease.

Schekman is a cell and molecular biologist at the University of California, Berkeley. Prior to founding eLife, he served as editor-in-chief of the Proceedings of the National Academy of Sciences.

As founding editor-in-chief, Schekman has been instrumental in developing eLife as an innovative publication through its collaborative peer-review process and open-access policy.

In memoriam: Joanne Ravel

University of Texas professor Joanne Ravel passed away June 28 at the age of 93.



RAVEL

The youngest of 10 children, Ravel was born July 27, 1924, at Seton Hospital in Austin, Texas. An Austin resident

her whole life, Ravel attended Austin High School before earning her undergraduate degree and her Ph.D. in biochemistry at the University of Texas, Austin.

After receiving her Ph.D., Ravel remained at UT Austin, where she worked as a research scientist at the Clayton Biochemical Institute. In

1972, she became an associate professor in the department of chemistry at UT. She later held the Ashbel Smith chair, one of UT Austin's highest honors.

Ravel supervised and mentored numerous graduate students and postdoctoral fellows. Several of her students went on to serve as deans and presidents of major universities.

Ravel's husband, Jerome, passed away in 2003. She is survived by her daughter, Margaret, and her son, Stephen.

In memoriam: Peter Reichard

Peter Reichard, professor emeritus at the Karolinska Institute, passed away June 18. He was 93.



REICHARD

Born in Austria in 1925, Reichard moved to Sweden in 1939. He earned his Ph.D. in medicine at the Karolinska Institute

in 1949 before leaving for the United States to complete his postdoctoral studies.

Reichard returned to Sweden and served as a professor of medical chemistry at Uppsala University from 1961 to 1963 before joining the Karolinska Institute in 1964. He became a professor of biochemistry as well as director of the Medical Nobel

Institute for Biochemistry.

Reichard made outstanding contributions in the advancement of nucleic acid biochemistry. He discovered and characterized ribonucleotide reductase, the enzyme that enables DNA synthesis by synthesizing deoxyribonucleotides from ribonucleotides and in the correct proportions for DNA replication.

Reichard valued international collaborations throughout his career, and his laboratory hosted postdoctoral fellows and sabbatical visitors from around the globe. He also was involved deeply in the work of the Nobel Committee and the Nobel Assembly.

Reichard retired in 1991. After the death of his first wife, Dagmar, he married Vera Bianchi, a collaborator and professor at Padua University in Italy, where they lived for several years.

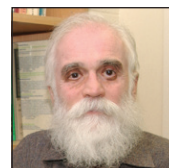
In memoriam: Mahendra Jain

The American Society for Biochemistry and Molecular Biology recently learned of the passing of University of Delaware professor emeritus of chemistry and biochemistry Mahendra K. Jain. He was 78.

Jain was born Oct. 12, 1938, and was raised in India, where he earned a B.S. from Holkar College in Indore and an M.S. from Vikram University

in Ujjain.

He completed his Ph.D. at the Weizmann Institute in Israel and



JAIN

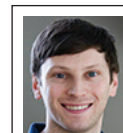
then, in 1967, moved to the United States, where he conducted research at the University of Indiana, Bloomington.

In 1973, Jain joined the department of chemistry and biochemistry at the University of Delaware. He was appointed associate professor in 1975 and full professor in 1981.

Jain made significant contributions to understanding interfacial catalysis associated with the kinetics of enzymes acting on substrates diffusing in two-dimensional membranes. He recognized that enzymes could "scoot" within a membrane or occasionally exit one membrane and "hop" to another.

Jain authored or co-authored more than 200 articles throughout his career as well as several books, including "The Bimolecular Lipid Membrane: A System" and "Introduction to Biological Membranes."

Read a remembrance of Mahendra Jain by his friend and colleague Hal White at asbmb.org/asbmbtoday.



Erik Chaulk (echaulk@asbmb.org) is a peer-review coordinator and digital publications web specialist at the ASBMB.

Send us your news

Have you recently been promoted or honored? Do you have good news to share with your fellow ASBMB members? Email it to us at asbmbtoday@asbmb.org — and don't forget to include a photo!



Minor J. Coon (1921 – 2018)

by F. Peter Guengerich

Minor Jesser “Jud” Coon was born in Englewood, Colorado, on July 29, 1921, and died Sept. 5, 2018. He was introduced to biochemical research by Reuben Gustavson at the University of Colorado. In 1943, he left to study biochemistry at the University of Illinois under William C. Rose, who came from a long line of scientists tracing back to Lafayette Mendel, Russell Chittenden and eventually to J. J. Berzelius.

Rose is known for discovering threonine and for defining the essential amino acids. Jud and his fellow graduate students did two things: They synthesized amino acids and derivatives, and they consumed synthetic diets lacking one amino acid for weeks. Jud remembered these studies with mixed emotions, mostly bad. At one point, he looked so ill that someone, quoting a line from the musical “Oklahoma,” said, “Pore Jud is daid” — the name stuck.

Doing nutritional experiments on your own graduate students with non-GMP diets would not be allowed today, but Jud said none of them suffered any long-term effects other than the disgusting taste. Jud finished his Ph.D. thesis in 1946, remained in the Rose lab briefly and then in 1947 left for a faculty position at the University of Pennsylvania. The graduate studies had given Jud ideas, and he worked on the metabolism of amino acids.

Leucine catabolism leads to beta-hydroxy-beta-methylglutaryl CoA, now best known because of statin drugs that inhibit cholesterol synthesis. Short-chain acids derived from some of the amino acids can have unpleasant olfactory issues. Jud told me one was the pure essence of dirty tennis shoes and that he got a lot of



COURTESY OF LINDA COON AND WILLIAM SMITH/
UNIVERSITY OF MICHIGAN

Jud Coon, pictured around 1970, was chair of the department of biological chemistry at the University of Michigan from 1970 to 1990.

disgusted looks on the train home at night in Philadelphia.

In 1955, Jud accepted an offer in the department of biological chemistry at the University of Michigan, where he remained for the rest of his life. He took two sabbatical leaves with Nobel laureates, first in 1952 with Severo Ochoa at New York University and then from 1961 to 1962 with Vladimir Prelog at the Eidgenössische Technische Hochschule Zürich.

Jud had received the Pfizer Award in Enzyme Chemistry from the American Chemical Society in 1959. After the sabbatical with Prelog, Jud developed an interest in oxidation of hydrocarbons, particularly bacterial omega-hydroxylation. Jud hoped to extend the research to mammalian systems. Omega-oxidation was NADPH-dependent and resided in the microsomal fraction. In the late 1960s, the technology of handling intrinsic membrane proteins was not developed.

In what might be the greatest tour de force from Jud’s lab, Anthony Lu succeeded in separating three components — using glycerol for stabilization and deoxycholate as a detergent — and combining them to reconstitute lauric acid omega-hydroxylation. The three fractions were a cytochrome P450, NADPH-P450 reductase and phospholipid. Anthony told me that they did not even know they were working with a P450 until they took a spectrum one evening in a neighboring lab when that professor was not around. However, none of these components were pure. The reductase was purified to homogeneity by Jud’s student Janice Vermilion. Any of several simple phospholipids could be used for that component. Later efforts led to the purification of multiple rabbit liver P450s to homogeneity. The difficulties in purifying enzymes from tissues are not always appreciated today; not only are these intrinsic membrane proteins, but they had no affinity tags, and many closely related P450s are present in the crude tissues.

The separation and purification of P450s dramatically changed the landscape of drug metabolism and took it from pharmacology into biochemistry. No longer were catalytic activities alone used to describe reactions, but individual enzymes could be characterized in terms of their roles. The pharmaceutical industry is very different and better off today, in part because of Jud’s contributions.

Purification of an enzyme is not a scientific end but only a beginning. In the 1970s to the 1990s, Jud continued to do research in multiple aspects of P450-related science. He characterized an ethanol-inducible P450 in rabbits, resolving some of the



COURTESY OF WILLIAM SMITH/UNIVERSITY OF MICHIGAN

Jud Coon is pictured around 2010 with Anthony Yu (left), a former postdoc in the Coon lab, and Paul Hollenberg (right), a former student and later chair of pharmacology at the University of Michigan.



ASBMB

Jud Coon (left) presents the ASBMB William C. Rose Award to F. Peter Guengerich in 2005. Coon studied biochemistry with Rose at the University of Illinois and was the first recipient of the Rose award in 1979.

controversies about ethanol oxidation systems. He also contributed much to our understanding of the catalytic mechanisms of both P450 and NADPH-P450 reductase, involving his colleagues John Groves and Vincent Massey. Jud published 91 papers in the *Journal of Biological Chemistry* alone.

From 1970 to 1990, he was chair of the department of biological chemistry at Michigan. He served as secretary (1981-1984) and president (1991-1992) of the American Society for Biochemistry and Molecular Biology. He also headed the advisory committees for the biennial international meetings Microsomes and Drug Oxidations and also Cytochrome P450 for nearly 20 years. Jud was elected to the National Academy of Sciences in 1983. In 1979, he received the ASBMB William Rose Award and in 1980 the Brodie Award in Drug Metabolism from the American Society for Pharmacology and Experimental Therapeutics. He received an honorary Doctor of Medicine degree from the Karolinska Institute, and in 1988 he was named Michigan's scientist of the year.

He was a mentor in the true sense of the word. Many of the leaders in the P450 field, both in academia and the pharmaceutical industry, trained in his group. I was fortunate to be a postdoc in his group (1973-1975). I am not sure I appreciated it all then, but I learned many lessons from Jud:

- Hard work pays off eventually.
- Appreciate science.
- Treat your students and postdocs fairly and with respect.
- Focus on things that your lab does well.
- Do not neglect your family.
- Respect individuals you do not agree with; be courteous.
- Contribute to your scientific community — your department or a society, for example.
- Be philosophical; you cannot digest everything at every meeting.
- Don't worry about lack of lab space; there is always room for another body or piece of equipment.
- Write well!

He was a real stickler on writing. I thought he hated everything I ever wrote. Years after I left, he told me he thought my papers were well-written. I even became an editor, and

now I am as hard on my students' writing as Jud was.

Jud also had another side. He was humorous, witty and enjoyed art and music as well as his family. Jud was married for 52 years to Mary Louise Newbern, whom he met at Illinois. She passed away in 2000, and his son, Larry, also died in the same year.

Jud is survived by his daughter, Susan Coon, and her family and daughter-in-law, Linda Coon, and her family. They both deserve thanks for all their help and care of Jud in recent years, and a number of former students and colleagues maintained close contact with him.

Jud Coon had a long and successful career, and we will miss him. Those of us who trained with him feel a common bond, and I have tried to develop my own laboratory like his. I can pay him no higher compliment as a mentor than this: It was from him that I learned how to be a professor.

F. Peter Guengerich (f.guengerich@vanderbilt.edu) is a professor of biochemistry and holds the Tadashi Inagami chair in biochemistry at Vanderbilt University.

Her research evolved from chore to passion

By *Nathalie Gerassimov*

A high school chemistry class first got Grace Ferri interested in science.

“I learned why salt affects the boiling temperature of water,” she said. “I learned to appreciate the atoms, the molecules, the ions. I could finally understand how the world around me worked on a deeper level.”

That chemistry class was the first in a series of experiences — including founding an American Society for Biochemistry and Molecular Biology Student Chapter — that helped the Massachusetts native identify her passions and shape her goals.

Ferri entered Boston University as a chemistry major but switched to biochemistry and molecular biology, which she thought would better prepare her to pursue a career as a physician.

As a pre-med student, Ferri was urged by her advisors to do undergraduate research, which she first perceived as a chore but later learned to love. She won a research fellowship sponsored by the Arnold and Mabel Beckman Foundation and joined an X-ray crystallography lab for her two final years as an undergraduate. Ferri was attracted to her lab by the enthusiasm and passion of Karen Allen, her



COURTESY OF GRACE FERRI

Grace Ferri, former president of the ASBMB Student Chapter at Boston University, is a singer as well as a scientist. Now in med school, she'd like to specialize in otolaryngology — care of the ear, nose and throat.

research mentor.

Ferri said she eventually “fell in love with the process of crystallography, even though it can be tedious and discouraging at times.”

As with high school chemistry, she enjoyed the way the scientific process built knowledge from the base up — data from those protein crystals was teased into atoms making up a newly solved 3D protein structure.

Ferri learned about ASBMB Student Chapters at a Beckman conference where she made a presentation as part of her fellowship. She wanted to bring the chapters' opportunities for

networking and research development to BU. She sought advice from local ASBMB chapter presidents, especially from Northeastern University. This inter-chapter connection led to collaborative efforts such as a symposium where students from all the ASBMB chapters in the Boston area presented their research.

Ferri enjoyed being the BU chapter president in part, she said, because she led a great executive team. Each member would decide on a contribution they wanted to make and would lead that effort while simultaneously involving the team. One manifestation of this arrangement was a career panel featuring representatives from AstraZeneca and Constellation Pharmaceuticals.

A multitude of clubs and events competed for students' attention at BU. Ferri's advice to others facing similar challenges is to advertise events months in advance. She recommends relaying the value of involvement in the ASBMB to other students through personal stories and encouraging them to get involved.

Grace started medical school at BU in August with the goal of becoming a physician-scientist. As a singer herself (she occasionally performed the national anthem at BU hockey games), she is interested in specializing in otolaryngology.

Attracted to her lab by the enthusiasm and passion of Karen Allen, her research mentor, Ferri said she eventually “fell in love with the process of crystallography, even though it can be tedious and discouraging at times.”



Nathalie Gerassimov (nathalie.gerassimov@gmail.com) is a Ph.D. student at the Johns Hopkins University School of Medicine.

Unexpected roles of lipid kinases

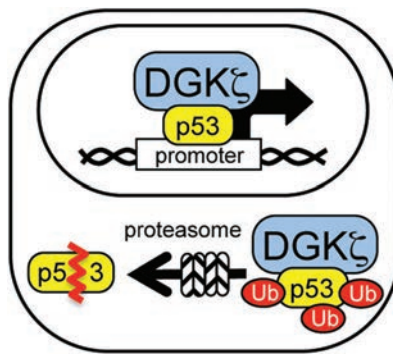
By Toshiaki Tanaka & Kaoru Goto

Phospholipids are not mere structural components of animal cell membranes. Many of their metabolites are physiologically functional and are pivotal in intracellular signaling. Of those, diacylglycerol, or DAG, is a second messenger activating proteins containing a C1 domain, such as protein kinase C.

Evidence shows that phorbol esters, synthetic functional analogues of DAG, constitutively activate signal transduction pathways that lead to tumor formation. Thus, normal cells must regulate DAG levels within the physiological range. DAG kinases, or DGKs, are the key enzymes that regulate DAG levels. DGK phosphorylates DAG to phosphatidic acid, another lipid messenger molecule. DGKs are thought to be involved in the balanced control of these two lipid messenger signaling systems.

DGKs differ in their molecular structure, enzymatic activity, subcellular localization and binding partners. One DGK, DGK-zeta, contains both a nuclear localization signal and nuclear export signal (1), suggesting a shuttling between the nucleus and the cytoplasm. Morphological studies on animal tissues report that DGK-zeta predominantly localizes to the nucleus in some cell types, while it exhibits both nuclear and cytoplasmic localization in others. DGK-zeta translocates from the nucleus to the cytoplasm in hippocampal neurons under stress conditions such as transient ischemia and seizures, and appears to be involved in stress responses.

What roles are assigned to DGK-zeta in the nucleus and the cytoplasm?



COURTESY OF KAORU GOTO

Functional implications of DGK-zeta in p53 regulation: Nuclear DGK-zeta modulates p53 transcriptional activity; cytoplasmic DGK-zeta facilitates p53 protein degradation.

Current data suggest that nucleocytoplasmic shuttling of DGK-zeta in neurons has a dual effect: While decreased levels of nuclear DGK-zeta lead to suppression of p53 transcriptional activity, increased levels of cytoplasmic DGK-zeta facilitate p53 protein degradation. Recent studies reveal that DGK-zeta associates with p53, and DGK-zeta deletion suppresses p53 transcriptional activity under basal and DNA-damage conditions (2). DGK-zeta association with p53 facilitates cytoplasmic degradation of p53 through the ubiquitin proteasome system, or UPS. DGK-zeta deficiency, therefore, results in increased p53 levels. Another study showed that DGK-zeta is degraded after cytoplasmic translocation in neurons, leading to increased levels of p53 protein and aberrant cell cycle reentry. In all, the levels of cytoplasmic DGK-zeta may serve as a suppressor for p53 by facilitating its degradation, thus suppressing its

cytotoxic effects.

What are the potential effects of DGK-zeta on other transcription factors? Nuclear factor kappa-light-chain-enhancer of activated B cells, or NF-kappaB, for example, is important in numerous biological processes, particularly immune response. A recent study showed that DGK-zeta knockdown enhances the NF-kappaB pathway in response to inflammatory cytokines. DGK-zeta downregulation accelerates phosphorylation of the p65 subunit and its nuclear translocation, increasing NF-kappaB transactivation activity. These reports suggest that DGK-zeta exerts a regulatory effect on p53 and NF-kappaB (3).

A key question is determining the molecular mechanisms exerted by DGK-zeta on p53 and NF-kappaB. We want to know whether DGK-zeta catalytic activity, which alters the balance of DAG and phosphatidic acid in the nucleus and cytoplasm, is essential. How DGK activity modulates transcriptional activities is not known, but it turns out that p53 degradation mediated through cytoplasmic DGK-zeta and UPS is not kinase activity-dependent. We have found unexpected roles of DGK-zeta on transcription factors; there is much to learn about how lipid-metabolizing enzymes impact cellular signaling involved in transcriptional regulation.



Toshiaki Tanaka (ttanaka@med.id.yamagata-u.ac.jp) is an assistant professor in the department of anatomy and cell biology, Yamagata University School of Medicine.



Kaoru Goto (kgoto@med.id.yamagata-u.ac.jp) is a professor in the department of anatomy and cell biology, Yamagata University School of Medicine.

REFERENCES

- Goto, K. & Kondo, H. *Proc. Natl. Acad. Sci. USA*. **93**, 11196-11201 (1996).
- Tanaka, T. *et al. J. Cell Sci.* **126**, 2785-2797 (2013).
- Tanaka, T. *et al. Adv. Biol. Regul.* **60**, 15-21 (2016).

Celebrating Herb Tabor's 100 years

By *Sasha Mushegian*

Montgomery County, Maryland, home of the National Institutes of Health, is celebrating a local hero — one who also happens to be a hero of the global scientific community. Herbert Tabor, longtime editor of the **Journal of Biological Chemistry** and a senior investigator at the NIH, is turning 100 years old on Nov. 28, and the county has declared that date to be Herbert Tabor Day in his honor.

Through the end of 2018 and into 2019, the scientific community also will celebrate his accomplishments in the pages of JBC (though “pages” is perhaps the wrong word, given that Tabor exhibited his characteristic pioneering vision as editor in 1995 when he made JBC the first scientific journal to go fully online).

Tabor served as editor-in-chief of JBC from 1971 to 2010 and continues to do editorial work for the journal, assigning manuscripts to academic editors. The American Society for Biochemistry and Molecular Biology's Herbert Tabor Research Award and JBC's Herbert Tabor Young Investigator Awards for early-career authors of outstanding JBC papers are given in his honor.

In late November, JBC will publish a series of review articles on the topic of polyamine biology. Tabor and his wife and scientific collaborator, the late Celia White Tabor, began studying the biosynthesis of the polyamines spermidine and spermine at the NIH in 1952. Their work highlighted the range of biological processes that involve polyamines, from viral sporulation to mitochondrial maintenance. From the foundation laid by the Tabors, research on polyamines has continued to expand. The reviews in the new series — from authors in the U.S., Canada, Japan and Israel — will



ASBMB

Herb Tabor, who celebrates his 100th birthday this month, served at the Journal of Biological Chemistry's editor-in-chief for almost 40 years.

examine the roles of polyamines in protein translation and ion channel regulation; polyamine diversity in bacteria, archaea and trypanosomes; polyamine catabolism in the context of oxidative damage; and much more.

In addition to the polyamine series, another collection of reviews and reflections, JBC Milestones: Herbert Tabor's 100th Birthday Collection, slated for January 2019, will celebrate Tabor's legacy more broadly by surveying the advances in various fields of research that were made over the course of his tenure at JBC. Discoveries in areas like chromatin and transcription, protease structure and function, and cytochrome P450 enzymology appeared in the journal during this time; experts in these fields dedicate their reviews of these topics to Tabor.

An underlying theme in these scientific syntheses is that Tabor's rejection of arbitrary disciplinary boundaries, and his favoring of rigorous and careful work over what was trendy, enabled these foundational discoveries to find a home in JBC.

Finally, JBC is soliciting memories, photos and well wishes from those who have known Tabor and will post them at jbc.org. His decades of mentorship and training have rippled throughout the scientific community; we hope those whose lives he's touched will join us in celebrating his milestone birthday.

Happy Herbert Tabor Day!



Sasha Mushegian (amushegian@gmail.com) is a postdoctoral fellow at Georgetown University. Follow her on Twitter @sash_mu.

Iron–sulfur cluster research offers new avenues for investigating disease

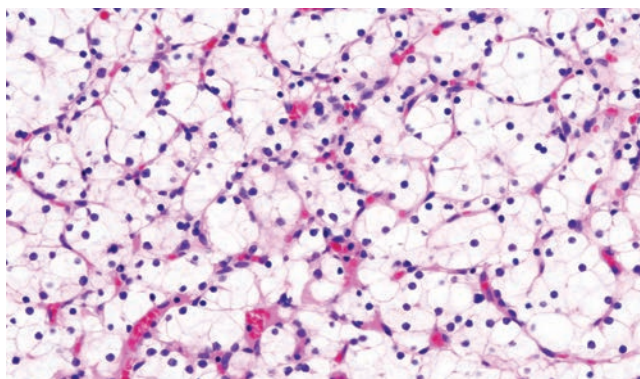
By Sasha Mushegian

Many important proteins in the human body need iron-sulfur clusters, tiny structures made of iron and sulfur atoms, to function correctly. Researchers at the National Cancer Institute, the National Institutes of Health and the University of Kentucky have discovered that disruptions in the construction of iron-sulfur clusters can lead to the buildup of fat droplets in certain cells. These findings, published in the **Journal of Biological Chemistry**, provide clues about the biochemical causes of such conditions as nonalcoholic fatty liver disease and clear-cell renal carcinoma.

“Iron-sulfur clusters are delicate and susceptible to damage within the cell,” said Daniel Crooks, the postdoctoral fellow who led the new study. “For this reason, the cells in our body are constantly building new iron-sulfur clusters.”

Crooks began studying the enzymes that build iron-sulfur clusters during his graduate studies in Tracey Rouault’s lab at the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the NIH. Mutations in one of these enzymes can cause ISCU myopathy, a hereditary condition in which patients, despite seeming strong and healthy, cannot exercise for more than a short time without feeling pain and weakness.

It was clear to Crooks that lifelong deficiency of iron-sulfur clusters



This stained histopathologic image shows clear-cell carcinoma of the kidney from a nephrectomy specimen. The cancer is named for its accumulation of lipid droplets.

COURTESY OF KGH/WIKIMEDIA COMMONS

caused profound changes in how cells processed energy. But he wondered exactly what happened in a cell in the first moments after something went wrong with iron-sulfur cluster production. Which of the many proteins that need iron-sulfur clusters were affected first, and what effect did this have on cell metabolism?

Crooks developed experimental methods to abruptly stop iron-sulfur clusters from being manufactured in cells and to monitor what happens to how these cells process glucose. Ordinarily, over a series of metabolic steps, cells would convert glucose into energy. But without iron-sulfur clusters, an enzyme called aconitase that carries out one of the steps in this process doesn’t work. As a result, the cells quickly accumulated an intermediate metabolic product called citrate, which eventually was converted into droplets of fat.

Over-accumulation of fats in tissues where they’re not normally found is a hallmark of numerous diseases, including nonalcoholic fatty liver disease, a risk factor for cirrhosis and

liver cancer. These findings suggest that this state could be caused by failures of iron-sulfur cluster production — for example due to cellular stressors or toxin exposure.

“We’re hoping that the people who are working so hard on nonalcoholic fatty liver disease will find our paper helpful to their research,” Rouault said.

Crooks, working in the laboratory of surgeon and scientist W. Marston Linehan at the NCI, is now examining the role of iron-sulfur

cluster formation and aconitase function in cancers such as clear-cell carcinomas. Various cancers often are characterized by excessive fat accumulation in cells. In fact, this accumulation of lipid droplets is where clear-cell carcinomas get their name: when a slice of such a tumor is fixed on a slide and its proteins are stained, the large areas of lipid accumulation in the cells look transparent.

“We really want to look at the beginnings of cancer,” Crooks said, “... to understand whether the lipids were formed from glucose or other fuels and whether the lipids are important for pathogenesis, or whether they’re just bystanders that form in response to metabolic reprogramming, which is likely to include disruption of iron sulfur protein activities.”

DOI: 10.1074/jbc.RA118.001885



Sasha Mushegian (amushegian@gmail.com) is a postdoctoral fellow at Georgetown University. Follow her on Twitter @sash_mu.

What happens to plasmalogens, the phospholipids nobody likes to think about

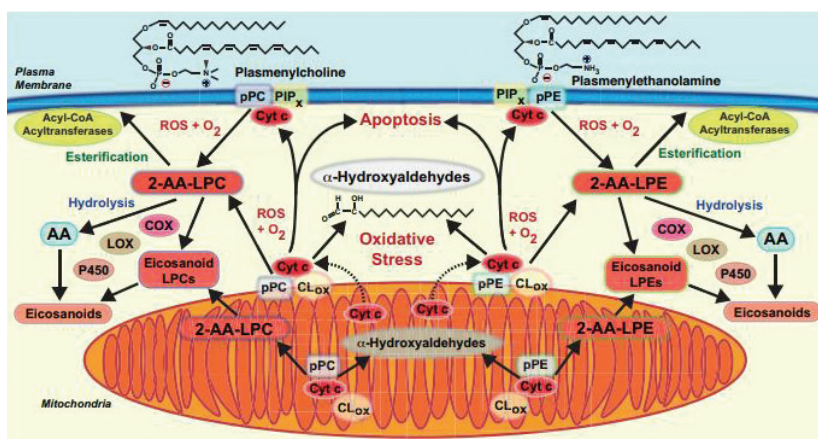
By Sasha Mushegian

Alzheimer's disease patients lose up to 60 percent of a component called plasmalogen from the membranes of the cells in their brains, but we don't know how or why. In a paper in the *Journal of Biological Chemistry*, researchers at Washington University in St. Louis provide the first report of an enzyme that breaks down plasmalogens, a breakthrough in understanding the molecular processes that occur during Alzheimer's and other diseases.

Plasmalogens are particularly abundant in the heart and brain, where they are involved in structuring cell membranes and mediating signals. Plasmalogens are phospholipids defined by a particular chemical bond called a vinyl-ether linkage. Due to the technical difficulties of studying plasmalogens, however, many aspects of their biology are unknown, including how the vinyl-ether bond is broken to break down plasmalogens in cells.

Richard Gross is the researcher at Washington University who oversaw the new study. "These molecules, plasmalogens, have been swept under the rug because nobody likes to think about them," Gross said. "(They're) hard to work with. They're susceptible to light, they're stable in only certain solvents, they have a limited lifespan after they're synthesized unless extreme precautions are taken, and they're expensive to make and synthesize."

In the new study, Gross' team performed painstaking experiments to find the elusive mechanism by which plasmalogens are enzymatically



COURTESY OF RICHARD GROSS

This diagram shows signaling pathways affected by cytochrome c's degradation of plasmalogen.

degraded. Cytochrome c is a protein typically found in mitochondria, where it facilitates electron transport. It can be released into the cell under stressful conditions.

Gross' team showed that cytochrome c released from the mitochondria can acquire a new function: acting as a peroxidase to catalyze the breakdown of plasmalogens in the cell. Further, the products of this reaction are two different lipid signaling molecules that previously were not known to originate from plasmalogen breakdown.

"That was one thing that surprised us," Gross said of the signaling products. He said he also was surprised by the ease with which the bond is broken. "The implication is that there is probably a lot of plasmalogen (breakdown) that's going on in conditions of oxidative stress."

The results tie in with another observation about the brain cells of Alzheimer's disease patients, which is that they often have dysfunctional

mitochondria and a resultant release of cytochrome c.

Gross is interested in delving deeper into how and why plasmalogen loss occurs in Alzheimer's patients, particularly those who develop the disease in old age, not due to familial mutations. Gross speculates that as people age, the accumulation of reactive oxygen species leads to cytochrome c release, activation of its peroxidase activity and plasmalogen breakdown in many membranes.

The results also have implications for understanding disorders in the heart and other plasmalogen-rich tissues, integrating studies of mitochondria, cell membranes and cell signaling under stressful conditions.

"This is like a quantum jump into the future," Gross said.

DOI: 10.1074/jbc.RA117.001629



Sasha Mushegian (amushegian@gmail.com) is a postdoctoral fellow at Georgetown University. Follow her on Twitter @sash_mu.

Which oil is best for your health?

A network meta-analysis extracts insight from disparate studies

By *Laurel Oldach*

If you've ever gotten confused trying to keep up with nutrition research, you're not alone. The field is big, and news reports often consider each study in isolation. Even if you're familiar with the literature, studies can be hard to compare because of differences in design, duration, sample size and effect size.

Lukas Schwingshackl, a researcher at the German Institute of Human Nutrition, is among a wave of scientists using sophisticated statistical tools to reduce uncertainty about what the mountain of data in the nutrition literature can tell us. In a paper published in the **Journal of Lipid Research**, Schwingshackl and colleagues used an emerging technique called network meta-analysis to extract insight from published studies on the effect of various dietary oils on blood lipids.

If you want to lower your low-density lipoprotein cholesterol, or LDL, the research is clear about one thing: You should replace saturated fats with unsaturated fats. If you want to know exactly which fat is best, that's a harder question. Many of the studies establishing that mono- and polyunsaturated fats are better for blood lipids than saturated fats swapped out one food source at a time, making it hard to tell which of a plethora of vegetable oils might be most beneficial.

To get around the fact that there has been no giant study comparing all available oils, Schwingshackl's team constructed a network meta-analysis showing how different oils and solid fats have been matched up. The researchers rounded up 55 random-



ized intervention trials dating to the 1980s that assessed the effects on participants' blood lipids of consuming the same number of calories from different oils or fats. To be included in the analysis, a study had to compare the effect of two or more oils or fats (from a list of 13) on patients' LDL or other blood lipids, such as total cholesterol, HDL-cholesterol or triglycerides, over at least three weeks.

Suppose both butter and sunflower oil had been tested against olive oil. The statistical approaches of network meta-analysis would allow the team to infer a quantitative comparison between butter and sunflower oil even if they had never faced off in the clinic. Schwingshackl explained, "The beauty of this method is that you can compare a lot of different interventions simultaneously ... and, in the end, you get a ranking. You can say, 'this is the best oil for this specific outcome.'"

In this study, the final ranking indicated that, as your doctor has told you for years, solid fats like butter and lard are the worst choice for keeping LDL low. The best alternatives are oils from seeds.

"Sunflower oil, rapeseed oil, safflower oil and flaxseed oil performed

best," Schwingshackl said. "Some people from Mediterranean countries probably are not so happy with this result, because they would prefer to see olive oil at the top. But this is not the case."

The research comes with a few important caveats. For starters, it measured only blood lipids. "This is not a hard clinical outcome," said Schwingshackl. "LDL is a

causal risk factor for coronary heart disease, but it's not coronary heart disease."

However, he said, it might be difficult to conduct a study comparing those clinical outcomes — for starters, someone would need to find study participants willing to eat just one type of fat for years at a time.

Meta-analyses run the risk of misleading by combining several pieces of low-confidence data into a falsely confident-sounding ranking. In this case, for example, there was not enough evidence to choose a "winner" among the seed oils with confidence. What's more, the oils best at lowering LDL were not the most beneficial for triglycerides and HDL cholesterol. However, with the appropriate caveats in mind, Schwingshackl is optimistic about the potential for network meta-analysis to help researchers synthesize disparate clinical studies.

DOI: 10.1194/jlr.P085522



Laurel Oldach (loldach@asmb.org) is a science communicator for the *Journal of Lipid Research and Molecular & Cellular Proteomics* and a staff writer for *ASBMB Today*. Follow her on Twitter at @LaurelOld.

Sperm-quality study updates advice for couples trying to conceive

Clinical trial suggests doctors also should change IVF protocol

By Laurel Oldach

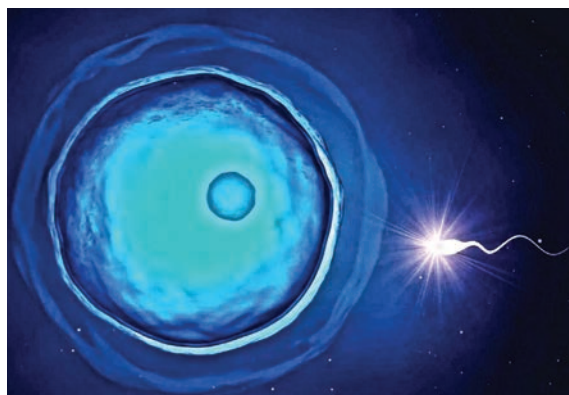
Could doctors at fertility clinics be giving men bad advice? Two clinician-researchers at the Center for Reproductive Medicine of Shengjing Hospital in Shenyang, China, think so.

Research from Da Li and XiuXia Wang's labs, published in the journal **Molecular & Cellular Proteomics**, upends conventional wisdom that abstaining between efforts to conceive can improve a couple's chances of success. The research team worked with almost 500 couples to test whether how long a couple waits between efforts to conceive could change their success rate.

"For years, men have usually been advised to limit sexual activity to increase the chances of pregnancy," said Li. "However, it's time to change our minds."

Some earlier studies had shown that semen produced shortly after a man's most recent ejaculation — within three hours or so — had faster and more motile sperm than if the man abstained for several days before ejaculating again. But it wasn't clear why the sperm changed or whether the changes affected fertility. So researchers set up a few side-by-side experiments.

They looked at individual subjects' semen after they had abstained for either several days or just an hour or two, comparing the volume of semen and the mobility of sperm. As had been observed earlier, the sperm from shorter abstinence periods



COURTESY OF KARL-LUDWIG POGGEMANN/FLICKR

An artist's representation of fertilization of an oocyte by a sperm cell.

moved faster.

Using mass spectrometry to look at the protein makeup of the samples, the team found major molecular differences. The majority of the affected proteins were involved in cell adhesion, a function that sperm need in order to fuse with egg cells.

The team also observed changes to proteins involved in sperm motility and metabolism, especially proteins that handle reactive oxygen species, a byproduct of cellular energy production. Although reactive oxygen species are needed for some normal sperm functions, an excess can damage sperm's genetic material.

According to Li and Wang's results, the longer sperm exist, the more vulnerable they are to DNA damage by reactive oxygen, which could harm their ability to form a viable embryo.

To see whether the changes to sperm were affecting fertility, the research team also ran a study of about 500 couples preparing for in vitro fertilization at the fertility clinic. They asked men in the control group

for semen samples after several days of abstinence, whereas men in the experimental group abstained for less than three hours before providing their samples. The IVF team proceeded as usual with the two types of sample, using them to generate and then implant embryos.

"A typical live birth rate in a cohort of this size is about 30 percent," Li said. In the experimental cohort, live births were higher by one-third.

"Our data indicate that couples with relatively normal semen parameters should have frequent sex around the ovulation period," Li said. "This could make all the difference to their efforts to start a family."

Meanwhile, IVF treatments at the Center for Reproductive Medicine, which treats about 5,000 infertile couples per year, also are being updated to use semen from more closely spaced ejaculations.

The team plans to continue working with patients, Li said, and will investigate differences in post-translational modifications that his lab saw between the types of samples. "This is a very new field," he said, noting that there are many unanswered questions about the changes the team observed. DOI: 10.1074/mcp.RA117.000541



Laurel Oldach (loldach@asbmb.org) is a science communicator for the Journal of Lipid Research and Molecular & Cellular Proteomics and a staff writer for ASBMB Today. Follow her on Twitter at @LaurelOld.

From the journals

By *Gelareh Abulwerdi, Sasha Mushegian, Laurel Oldach & Kerri Beth Slaughter*

We offer a selection of recent papers on a variety of topics from the **Journal of Biological Chemistry**, the **Journal of Lipid Research**, and **Molecular & Cellular Proteomics**.

The complex life cycle of bones

Lateral meningocele syndrome, also known as Lehman syndrome, is a rare genetic disorder affecting the musculoskeletal system. The disorder is associated with gain-of-function mutations in the gene for the transmembrane receptor Notch3. Ernesto Canalis and colleagues at UConn Health examined the effects of these mutations on the mouse skeleton

to understand the role of Notch3 in bone formation. They found that the mutant Notch3 triggered increased osteoblast proliferation, which counterintuitively resulted in reduced bone volume because of increased bone resorption. The findings were published in the **Journal of Biological Chemistry**.

DOI: [10.1074/jbc.RA118.004242](https://doi.org/10.1074/jbc.RA118.004242)

Structure determines bacterial virulence

Campylobacter concisus and *Campylobacter jejuni* are both gram-negative bacteria that occupy the same ecological niche. While *C. jejuni* has been studied extensively in

the pathogenesis of gastrointestinal diseases, there is very little information regarding the pathogenicity of *C. concisus* in such disorders. In a recent study published in the **Journal of Lipid Research**, Katja Brunner and colleagues at University College London investigated the structural differences of lipooligosaccharide, a common virulence factor known as LOS, between the two bacterial species. Through extensive mass spectrometry studies, the authors showed that the backbone of LOS in *C. concisus* is less phosphorylated and lacks sialylation, which hampers the interaction of the bacteria with a transmembrane protein that causes

Proteomics of fish evolution

Ten thousand years ago, the ancestor of the three-spined stickleback lived only in the ocean. Today, its descendants have adapted to colonize many fresh, brackish and saltwater habitats, an evolutionary phenomenon known as adaptive radiation. Because of its recent, rapid diversification, the stickleback is used widely as a model organism in evolution and ecology research.

Researchers at the University of California, Davis, and Mexico's Centro de Investigación en Alimentación y Desarrollo are reporting a new approach to understanding stickleback evolution. The researchers developed an assay using data-independent acquisition mass spectrometry to quantitate the most abundant proteins in gill tissue. They used the approach to compare four stickleback populations from environments ranging from Baja California to Anchorage, Alaska, that vary in water salinity, temperature and parasite exposure. Their research was published in **Molecular & Cellular Proteomics**.

Even in a small number of fish from each location, Johnathon Li and colleagues were able to identify proteomic signatures that appear to reflect adaptations to living in each location. The researchers anticipate that



COURTESY OF ASTRID ANDREASEN/WIKIMEDIA COMMONS

This 1994 postage stamp from the Faroe Islands in the northern Atlantic Ocean shows an illustration of three-spined sticklebacks.

the proteomic assay will be useful for complex ecological modeling in future studies.

DOI: [10.1074/mcp.RA118.000973](https://doi.org/10.1074/mcp.RA118.000973)

— *Laurel Oldach*

Steps forward for an anti-addictive plant compound

The opioid addiction crisis has revealed the need for safe treatments for withdrawal symptoms. The plant world is a promising source of psychoactive molecules that could be investigated for this purpose, but research into these drug candidates often is hampered by regulatory and technical roadblocks.

One plant with potential as an opioid addiction treatment is iboga (*Tabernaemontana iboga*), a shrub from west central Africa. In its native range, its root bark is used in traditional medicine and in rituals by practitioners of the Bwiti religion. In Western countries, iboga (and in particular its bioactive compound ibogaine) has been discussed as a potential anti-addictive substance since the 1960s, when the researcher and advocate Howard Lotsof used it to treat his own heroin addiction. Although clinical data are lacking and ibogaine remains unapproved for medical use, demand for the substance is sufficient that the iboga plant reportedly has become overharvested.

Hoping to help stabilize the ibogaine supply chain and facilitate research into ibogaine and related compounds, researchers at the John Innes Centre led by Scott C. Farrow are studying ibogaine biosynthesis.

The researchers produced the first transcriptome of the iboga plant. They then identified candidate genes that could be involved in ibogaine production by inferring comparisons to synthesis pathways of similar compounds in other plants. Ibogaine is a monoterpene indole alkaloid; alkaloids with similar structures (called iboga-type alkaloids) have been studied for their anti-cancer properties. By heterologously expressing candidate enzymes in yeast and *E. coli* with putative ibogaine precursors as substrates, the researchers showed that the



COURTESY OF MARCO SCHMIDT/WIKIMEDIA COMMONS

Branches and fruit of an iboga shrub in the Limbe Botanical Garden, Cameroon. The plant's bioactive compound, ibogaine, long has been discussed as a potential anti-addictive substance.

two final enzymes in the pathway were a cytochrome P450 and an O-methyltransferase. They published their study in the **Journal of Biological Chemistry**.

The cytochrome P450, which the researchers named ibogamine-10-hydroxylase, is the first enzyme known to hydroxylate the iboga-type alkaloid scaffold, making it potentially a useful tool for developing new ibogaine derivatives. These findings, along with the publicly available ibogaine transcriptome, should enable further discovery of biosynthetic enzymes, leading to synthetic production of ibogaine and other bioactive molecules.
DOI: 10.1074/jbc.RA118.004060

— Sasha Mushegian

adherence, invasion and production of pro-inflammatory mediators. This study provides insight to differences in the LOS structure of these two organisms and how that correlates with their virulence.

DOI: 10.1194/jlr.M085860

Arctic insights into rubisco

The CO₂-fixing enzyme rubisco is the most abundant enzyme on earth, but its catalytic properties vary among species. Marine phytoplankton generally have some of the most efficient

rubisco enzymes known. Among the phytoplankton, diatoms are major players in the marine carbon cycle, but their rubisco enzymes have not been characterized. Karin Valegård and colleagues at Uppsala University showed that rubisco enzymes from five arctic diatom species were heavily post-translationally modified, suggesting that the role of these modifications in rubisco function should be investigated further. The findings were published in the **Journal of Biological Chemistry**.

DOI: 10.1074/jbc.RA118.003518

How a common drug causes liver failure

Acetaminophen is a common pain reliever found in every pharmacy. However, it is also the No. 1 cause of acute liver failure in the United States. In the liver, acetaminophen is converted into a new compound that covalently binds to proteins with thiol groups. These covalent binding events contribute to the toxicity of acetaminophen, but they do not account fully for its role in liver failure.

James Chun Yip Chan and colleagues at the National University of

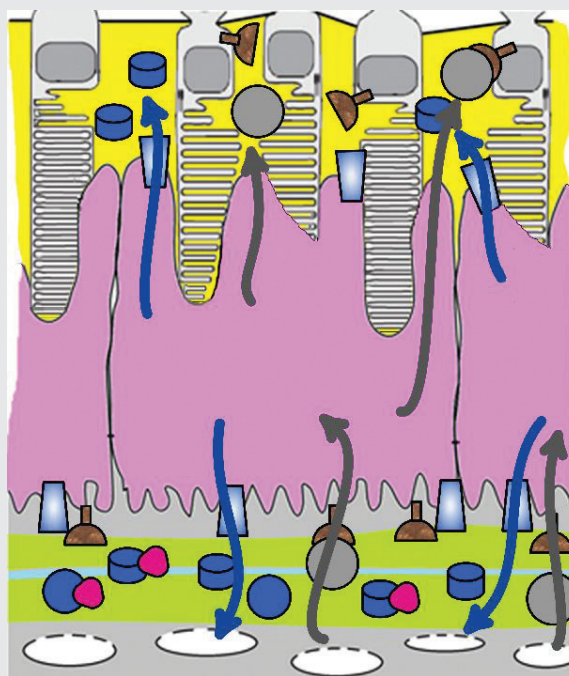
Solving the mystery of cholesterol deposits in the retina

Cholesterol deposits in the retina are linked to the onset of age-related macular degeneration, but it isn't yet clear where the deposited cholesterol comes from. Some pathology studies suggest that it is secreted by the retinal pigment epithelium, or RPE, in particles similar to low-density lipoprotein, or LDL. But human genetic studies show a link between macular degeneration and genes involved in making high-density lipoprotein, or HDL. In a recent paper in the **Journal of Lipid Research**, Nicholas Lyssenko and colleagues at the University of Pennsylvania investigated HDL and LDL-like particle synthesis in the RPE.

The RPE forms a barrier between rod and cone photoreceptors and the capillaries that supply them with nutrients. Many epithelia actively control the nutrients that cross from the bloodstream into nearby tissues; the RPE does the same for the retina.

Researchers used a polarized tissue culture model of the RPE to trace isotope-labeled cholesterol. They observed that RPE cells were able to generate nascent HDL particles, but when ambient cholesterol was low, HDL synthesis was minimal, and cholesterol release occurred mainly through diffusion. When more cholesterol was available in the media, mimicking a person with elevated cholesterol levels, HDL synthesis was more robust, and RPE cells made more HDL at the photoreceptor side than at the capillary side. The authors also found that RPE cells secreted LDL-like particles weakly and mostly toward the photoreceptor side.

The research suggests that cholesterol deposited in



COURTESY OF NICHOLAS LYSENKO ET AL./UNIVERSITY OF PENNSYLVANIA

Cells in the retinal pigment epithelium (purple), which forms a barrier between photoreceptor cells (top/yellow) and capillaries (yellow-green), take up cholesterol from the bloodstream and export it in high-density lipoproteins (blue arrows) or in low-density lipoproteins (gray arrows). Raising the cholesterol available in the bloodstream increases the export of both types of lipoprotein toward the photoreceptors.

the retina in age-related macular degeneration comes primarily from HDL secreted by the RPE.

DOI: 10.1194/jlr.M087361

— Laurel Oldach

Singapore examined a post-translational modification known as glutathionylation to understand its role in acetaminophen toxicity. In a study published in the journal **Molecular & Cellular Proteomics**, they showed that acetaminophen induces protein glutathionylation, which leads to mitochondrial dysfunction, deficits in energy metabolism and other effects linked to acetaminophen toxicity. This research helps explain a potential marker of drug toxicity and may be used in the future to reduce cases of liver failure worldwide.

DOI: 10.1074/mcp.RA118.000875

Understanding an anti-malarial target

Efforts to control malaria are thwarted by drug resistance, motivating the search for new anti-malarial drugs. Several anti-malarial clinical candidates act on the ATPase PfATP4 in malaria parasites. PfATP4 is difficult to express heterologously, so its function has been poorly understood, and efforts to design better molecules that target it have been limited. James E.O. Rosling and colleagues at Australian National University developed

a membrane ATPase assay to examine PfATP4's biochemical properties. In the **Journal of Biological Chemistry**, they reported that PfATP4 is a pH-sensitive sodium transporter and identified the range of its sensitivity to an anti-malarial molecule under physiologically relevant conditions.

DOI: 10.1074/jbc.RA118.003640

Vitamin E formulations in low blood cholesterol

Chylomicron retention disease, known as CMRD, and abetalipopro-

teinemia, or ABL, are rare genetic disorders that cause impairment in absorption of fats and certain vitamins, resulting in hypocholesterolemia. One of the hallmarks of this group of diseases is severe vitamin E deficiency. Charlotte Cuerq and colleagues at Lyon Sud Hospital investigated the effect of two formulations of vitamin E (Tocofersolan and alpha-tocopherol acetate) on patients with CMRD and ABL in comparison to healthy volunteers.

In a paper published in the **Journal of Lipid Research**, they showed that in CMRD patients, Tocofersolan is better absorbed than the alternative formulation, as measured by a higher bioavailability after a single dose administration. To study how these two formulations change the absorption and storage of vitamin E, the authors administered the molecules for four months and found that vitamin E levels are higher in red blood cells, adipose tissue and plasma of patients with CMRD irrespective of the formulation. These observations are consistent with the less severe clinical phenotype in patients with CMRD than in patients with ABL. DOI: 10.1194/jlr.M085043

Transcription factor allows parasite hijacking

Leishmania are intracellular parasites that deactivate host macrophages to evade the immune system. Previous evidence suggested that the parasite manipulated host miRNA as part of this process. In a paper in the **Journal of Biological Chemistry**, Lucie Colineau and colleagues at the University of British Columbia confirmed that Leishmania infection uniformly downregulated host cell miRNA expression. They also showed that this effect depended on expression of the host transcription factor c-Myc. Silencing c-Myc restored miRNA expression and reduced Leishmania's intracellular survival. DOI: 10.1074/jbc.RA118.002462

Identifying bias in gene expression profiles

The compact nucleus of a cell houses all the information needed to make thousands of proteins. This information is found within genes that are organized carefully into clusters. Clustered genes often are transcribed into mRNA at the same time even though they may not be functionally related. However, research in cell lines has shown that cells can regulate expression of these unrelated genes at the protein level.

Piotr Grabowski and colleagues at the Institute of Biotechnology in Berlin examined factors that may contribute to the coexpression of functionally unrelated genes. In a study published in the journal **Molecular & Cellular Proteomics**, they describe how they used mouse tissues to show that epigenetics play an important role in regulating the coexpression of certain genes, but coexpression was buffered at the protein level. This research suggests that monitoring protein coexpression may be more useful than studying mRNA coexpression data for understanding functional genomics. DOI: 10.1074/mcp.RA118.000935

A key enzyme in pseudoephedrine synthesis

Ephedrine and pseudoephedrine are pharmacologically important molecules produced by plants. The biosynthetic pathways in plants that produce these molecules are incompletely characterized, and commercial production of these molecules uses chemical rather than biological synthesis. In a study published in the **Journal of Biological Chemistry**, Jeremy S. Morris and colleagues at the University of Calgary identified the N-methyltransferase responsible for the final step in the synthesis of these molecules in Ephedra sinica. They then showed that this enzyme, when heterologously expressed in E. coli, was able to produce (pseudo)ephed-

rine, potentially paving the way for commercial production by engineered micro-organisms.

DOI: 10.1074/jbc.RA118.004067

New opportunities to treat cholera

Cholera infection causes deadly dehydrating diarrhea, but the molecular details of how it does so are incompletely known. Diarrhea occurs when the chloride transporter cystic fibrosis transmembrane conductance regulator, or CFTR, is activated by cyclic adenosine monophosphate, or cAMP, in intestinal cells, but which biochemical pathway cAMP comes from in this context was unclear. Andrew Thomas and colleagues at Cincinnati Children's Hospital Medical Center showed that the cAMP-generating adenylate cyclase AC6 is associated with CFTR in epithelial cells. When challenged with cholera toxin, cells in which AC6 was knocked out did not secrete fluid, suggesting that the AC6-CFTR complex could be a target for anti-diarrheal drugs. The findings were published in the **Journal of Biological Chemistry**.

DOI: 10.1074/jbc.RA118.003378



Gelareh Abulwerdi (gelareab@umaryland.edu) is a Ph.D. candidate at the University of Maryland, Baltimore. Follow her on Twitter @gelareh_science



Sasha Mushegian (amushegian@gmail.com) is a postdoctoral fellow at Georgetown University. Follow her on Twitter @sash_mu.



Laurel Oldach (loldach@asmb.org) is a science communicator for the Journal of Lipid Research and Molecular & Cellular Proteomics and a staff writer for ASBMB Today. Follow her on Twitter at @LaurelOld.



Kerri Beth Slaughter (kerri.slaughter@uky.edu) is a graduate student in the biochemistry department at the University of Kentucky. Follow her on Twitter @KB_Slaughter.

Upcoming ASBMB events and deadlines

NOV

American Diabetes Month

14: Annual meeting abstract deadline

14–17: Annual Biomedical Research Conference for Minority Students (ABRCMS)

27: Annual meeting travel award application deadline

27: Student chapters renewal deadline

DEC

1: World AIDS Day

4: ASBMB-Deuel Conference on Lipids early registration deadline

9–12: Special Symposium The Many Faces of Kinases and Pseudokinases

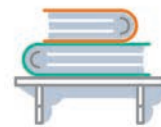
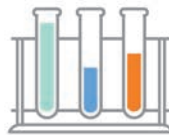
10: Advocacy Training Program application deadline

JAN

Cervical Health Awareness Month

22: ASBMB-Deuel Conference on Lipids abstract deadline

31: ASBMB Honor Society application Deadline



ASBMB-DEUEL CONFERENCE ON LIPIDS



March 5–8, 2019

Laguna Cliffs Marriott

Dana Point, Calif.

ASBMB.ORG/DEUELCONFERENCE



THE FUTURE OF FIGHTING FLU

Researchers worldwide work to improve existing vaccines and develop universal, long-term protection

By John Arnst

In what an epidemiologist would consider a perfect flu season, the strains that the current influenza vaccine protects against would match perfectly those strains in circulation. If a person got a flu shot and had the misfortune to walk into someone else's virus-laden sneeze cloud, they'd only be sick a few days rather than a week and would experience milder muscle aches and fever than without it. But when a pandemic strain emerges or one of the circulating strains mutates, the vaccine does little to protect the infected.

This happened last flu season, when the targeted H3N2 strain mutated beyond the protective abilities of the vaccine. Recent estimates confirmed that the 2017-2018 season was exceptionally dire — according to the Centers for Disease Control and Prevention, around 80,000 people died in the U.S., compared with 12,000 to 56,000 per year in other recent years.

Anthony Fauci, director of the National Institute of Allergies and

Infectious Diseases, said the H3N2's mutation was only part of the problem.



FAUCI

“We had a vaccine that, against H3N2, was only 25 percent effective, and we had a virus that was particularly virulent,”

Fauci said. “You put those two things together, and you wind up getting a season in which you have a lot of hospitalizations and more deaths than we've seen in a very long time in a seasonal flu context.”

Additionally, every few decades a new strain of influenza emerges against which the human population has no pre-existing resistance, causing a flu pandemic. In 1918, crowded wartime environments set the stage for a worldwide, multiwave flu pandemic that infected an estimated 500 million people and left 50 million dead, with 675,000 deaths in the United States. At the time, the influenza virus had yet to be isolated, let

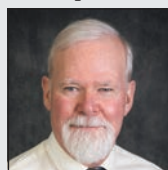
Antivirals

While flu vaccines were developed as early as 1938 and first distributed to U.S. soldiers in World War II, drugs that can reduce the duration of flu symptoms were not available until Tamiflu hit the market in 1999. The anti-viral, whose efficacy has been questioned in recent years, is recommended to be taken within 48 hours of the onset of flu symptoms and works by preventing neuraminidase proteins from cleaving sialic acids on the inside of a host cell. This leaves a virus functionally unable to exit the cells.

In the nearly two decades that it's been available, Tamiflu has been the only available anti-viral on the market. A competing product produced by the Japanese pharmaceutical company Shionogi, which uses a different mechanism to interfere with the protein's activity, may upend that dominance if it is approved for sale in Europe and the U.S.

When faced with neuraminidase inhibitors, however, flu viruses sometimes can mutate to subvert the mecha-

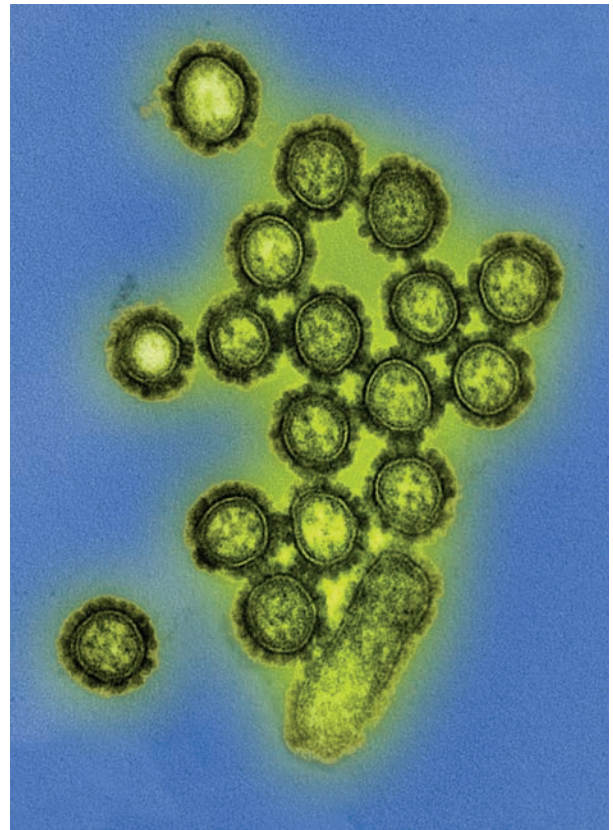
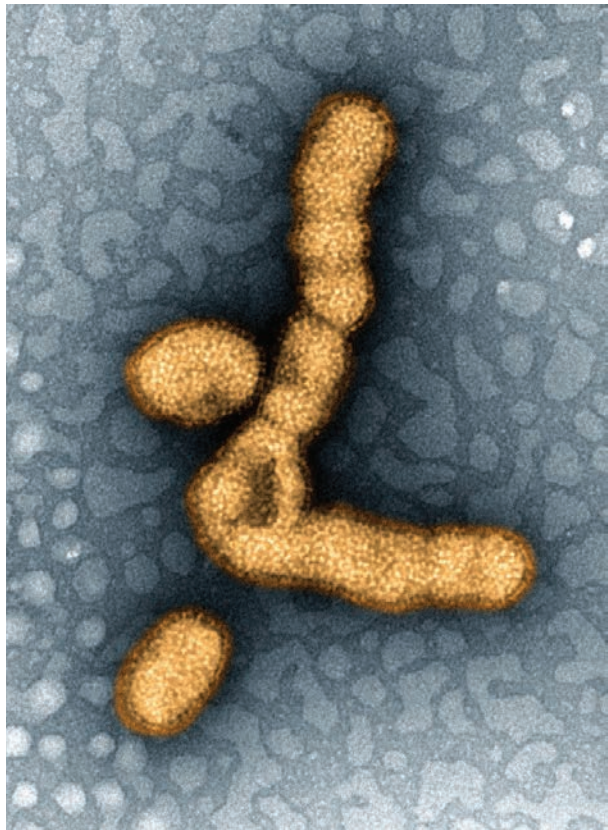
nism. At National Jewish Health, an academic medical research facility in Denver, Dennis Voelker is working with lipids to develop chemical inhibitors of viral replication that would preclude this by targeting an essential mechanism that the virus can't mutate its way around.



VOELKER

“Our approach has been to look for inhibitors of viral attachment to cells,” Voelker said. He and his colleagues began working on viral inhibitors after finding that a phospholipid they'd been working with was able to bind to sialic acid receptors on the outside of flu particles essential to the virus' ability to adhere to cells.

“If you mutate the ability to bind to phospholipids, you're probably also going to mutate the ability of the virus to bind to the cell surface,” Voelker said. “What we really need is crystal structures showing just how the lipids interact with the virus, and we're in the process of doing that.”



COURTESY OF NIAID

While influenza virions are typically spheroid in appearance, they can also be filamentous.

alone incorporated into a vaccine, and antivirals were several decades away (see box: Antivirals). With medical science in its infancy, public health measures were the strongest tools governments could bring to bear.

The most recent pandemic occurred in 2009, when a strain of H1N1 that became called “swine flu” spilled over from pig populations, hosts for several flu strains, to humans in North America. It infected 60.8 million people in the U.S., hospitalized more than 270,000 and killed more than 12,000. While millions of doses of vaccine for H1N1 were manufactured by industry, purchased by the federal government and distributed free of cost, the vaccine doses took months to produce, ultimately arriving late in the pandemic.

If a flu vaccine worked against every potential strain of the virus, however, the 2009 pandemic and last

season might have played out differently. The idea of such a universal vaccine has been gaining traction among researchers who study infectious disease; in February, the NIAID published a blueprint for the development of a universal flu vaccine in the *Journal of Infectious Diseases*.

As flu season gears up again, a handful of labs, including several at the NIAID and Mount Sinai Hospital, have candidates for a universal flu vaccine in various stages of development, and a number of private industry and public university researchers are attempting to improve on existing vaccine formulations.

Drift and shift

Influenza’s structure and status as an RNA-negative virus make it friendly to the mutations that let it evade vaccines. If you slid samples of



H1N1 and H3N2 swine flu viruses are endemic among pig populations in the U.S. and are believed to be spread through close contact among pigs. While they cost pork producers an average of \$3.23 per pig, the viruses, for which the animals can be immunized, only spill over into human populations during rare antigenic shifts.

the virus into an electron microscope, you'd likely see spheres bristling with lollipoplike extensions, the tops of which are made out of either hemagglutinin or neuraminidase. These spherical proteins are the keys the virus uses to get in and out of cells in its host organism respectively and to which the Hs and Ns in flu virus names correspond, as in H1N1.

The viruses come in four major categories — A, B, C and D — but influenza B viruses do not circulate in animals, C viruses are believed to cause only mild respiratory illnesses in humans and D viruses affect only cattle. The flu vaccines produced every year and approved for distribution by the Food and Drug Administration are designed to protect against two A strains (an H1N1 and an H3N2) and one B strain, with some quadrivalent formulations protecting against an additional B strain.

The strains change every year because influenza is highly prone to mutations caused by errors during viral replications. While these mutations happen frequently within a flu season, the changes are usually minor enough that the existing flu vaccine protects against the new viruses in the short term. Over the course of a flu season like last year's, however, this process, known as antigenic drift, can change a virus beyond the protective capabilities of the vaccine.

On rare occasions, influenza A viruses mutate in a more nefarious manner. Antigenic shift occurs when two viral strains with starkly different hemagglutinin sequences coinfect a host and swap genetic material, which is what happened in pigs in 2009. According to Barney Graham, deputy director of the NIAID's Vaccine Research Center, this process is made possible by the influenza virus' seg-

mented genome and amplified by the flight patterns of migratory birds, a major reservoir of many flu subtypes.



GRAHAM

Influenza “has eight gene segments that encode influenza virus protein, and because there are so many types of influenza virus and so many influenza viruses carried by migratory birds, these influenza viruses can drop into places where more than one virus can infect the same cell,” Graham said. “There is such a large zoonotic pool in pigs and birds that influenza viruses will never be eradicated, so we have to cope with that diversity.”

Stalking heads

One of the universal vaccine candidates designed to tackle that viral diversity was developed at the Vaccine Research Center in Graham’s lab on the National Institutes of Health campus in Bethesda, Maryland. The vaccine uses self-assembling nanoparticles made of the iron-containing protein ferritin to display a conserved portion of the stalks that connect to all influenza head proteins. This elicits antibodies that can interact with a plethora of influenza strains.

As effective as these antibodies may prove to be, however, they still run up against immunodominance, a problem caused by the body’s repeated exposures to influenza antigens.

After the body is first exposed to influenza, it tends to mount future immune responses that are biased against antigens from the initial infection, NIAID director Fauci said. “It’s called imprinting, or original antigenic sin, and it tends to complicate the nature of the immune response that you have against an influenza vaccine or an influenza virus.”

This immune response means that subsequent infections and vaccinations against flu antigens cause the body to build up immunity against

the parts of the flu virus that are no longer relevant to the strains it may encounter, such as older hemagglutinin proteins.

So to improve their vaccines, the researchers decapitated them.

“We can design headless, trimeric stem antigens, put them on nanoparticles and get very good antibodies against the stem region,” Graham said.

In a 2015 paper in the journal *Nature Medicine*, Graham and colleagues reported that this type of nanoparticle vaccine made with the stem of an H1 influenza virus could partially protect ferrets, the preferred model organism for human respiration, and completely protect mice against a lethal strain of H5N1.

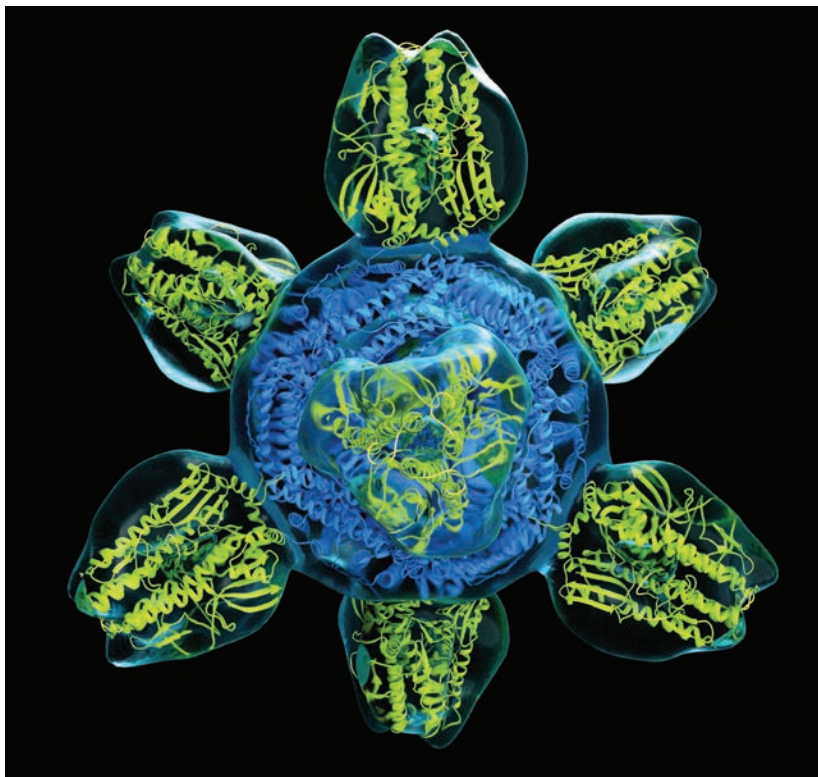
The researchers also tackle immunodominance by attaching a variety of hemagglutinin molecules onto the same nanoparticle, which increases the chance for a cross-reactive antibody response; or by accumulating breadth against the various hemagglutinin subtypes by administering individual hemagglutinin-bearing nanoparticles serially.

“These new ways of displaying and designing proteins have really opened up a lot of new options for making these vaccines,” Graham said. He and colleagues have a nanoparticle vaccine using a full-length hemagglutinin that has just completed enrollment in a clinical trial and intend to bring a headless stem hemagglutinin vaccine to early clinical trials next spring, he said.

Trials of the chimera

Another promising universal flu vaccine candidate that targets the conserved stalk regions is being developed at the Icahn School of Medicine at Mount Sinai in New York by the labs led by Pater Palese, Florian Krammer and Adolpho García-Sastre.

“We already have very good vaccines against flu,” said Palese, a veteran of influenza research and vac-



COURTESY OF JOHN GALLAGHER & AUDRAY HARRIS/LABORATORY OF INFECTIOUS DISEASES

One of several universal flu vaccine candidates being developed at the NIAID's Vaccine Research Center is a nanoparticle hybrid consisting of a protein scaffold (blue) and eight influenza hemagglutinin proteins (yellow).

cine development. "They are underappreciated, underutilized, but they are certainly much better than their reputation."



PALESE

To quiet the body's immune response against the hemagglutinin heads in their vaccine, the Mount

Sinai researchers developed chimeric flu proteins that consist of the conserved stalk region and artificial protein heads only found in birds, which the immune system ignores.

"What we are doing is redirecting the immune system toward these conserved regions," Palese said.

Their universal flu vaccine is being evaluated in two clinical trials using a live attenuated inhalable platform and a traditional injectable platform, respectively backed by the Bill & Melinda Gates Foundation and GlaxoSmithKline.

In the universal flu vaccine trials,

recipients are inoculated with an initial chimeric vaccine followed by a secondary chimeric vaccine with a slightly different head group; both heads will be overlooked by the body's immune response.

In the trial of 100 volunteers funded by the Gates Foundation, the nasal spray vaccine is being evaluated for safety. In the 400-patient trial backed by GSK, the injectable vaccine is being evaluated for safety and its ability to induce an immune response. In more extensive future trials, the efficacy and potential adverse reactions of the vaccines would be monitored in as many as 3,000 volunteers for one to four years.

"I can tell you that we have not heard, either for the Gates Foundation trial or for the GSK trial, whether there are any safety issues," Palese said. "We would have heard that, so I think that looks very good."

Both trials are also taking samples to evaluate the optimal schedule for

immunization, including the number of doses a patient might need over several months. This information ultimately may help researchers determine the duration of the vaccine's cross-protection, or how long a patient would be protected against circulating flu strains.

"I'd like to see a lifetime kind of approach," Palese said. "For example, if one gets infected with an influenza virus in 2018, there is very good evidence that that protection lasts for the entire life against that particular strain."

Against the strain

In August, a paper published in *Nature Communications* by researchers at the University of Pennsylvania's Perelman School of Medicine led by Scott Hensley and Drew Weissman found that it was possible to elicit an immune response against a number of hemagglutinin stems in mice and ferrets by using a vaccine made of messenger RNA encoded in lipid nanoparticles.

Another vaccine candidate, developed by Jeffrey K. Taubenberger at the NIAID's Viral Pathogenesis and Evolution Section, uses a cocktail of viruslike particles, or VLPs, of hemagglutinin proteins from four strains of H1, H3, H5 and H7 that have caused significant outbreaks in humans and animals. The VLP-based vaccine is administered in a two-step process where an initial vaccination primes the immune system and a second vaccine that boosts the immune response. It is being tested in ferrets after having success in mouse models.

This two-step approach is similar to that taken by the Israel-based company BiondVax Pharmaceuticals, which has a vaccine candidate in second-stage human trials in the U.S. and more advanced trials in Europe. The vaccine, called M-001 for now, works by first priming the immune system with peptides that span the length of hemagglutinin's stems, followed up by a vaccine that uses a whole, heat-killed influenza virus to

boost the response.

However, even if a vaccine candidate like M-001 were to become available in the next few years, it likely would be only the first major step in developing universal protection.

"Achieving an effective universal influenza vaccine will have to happen in an iterative way," Graham said. "To start, we will try to make a vaccine that doesn't have to be remade every year. And then a vaccine that hopefully wouldn't have to be given every year."

Old formulas, new tools

While the various universal vaccine candidates are put through their paces, researchers are working on novel ways to enhance vaccine efficacy by tweaking existing methods.

During a flu infection, the lungs mount their own immune response, which includes tissue-resident memory T and B cells as well as antibodies. In a paper in the journal *Frontiers in Immunology*, researchers at the University of Iowa led by Kevin Legge found that a nasally administered influenza A



LEGGÉ

vaccine containing nanoparticles made up of biodegradable polyanhydride polymers could provide a robust

immune response against both homologous and heterologous flu strains in the lungs of mice.

Legge and his colleagues wanted to generate the immunity that normally would be prompted by an infection without the symptoms and risk such an infection would carry. While standard vaccines already prompt an antibody and B-cell response, Legge said, years of work in animal models has suggested that the T cells play a significant role in controlling infection and also might give protection against heterologous challenges or flu strains with entirely different hemagglutinin proteins.

This further was corroborated



COURTESY OF GREG KNOBLOCH/CDC

A microbiologist at the Centers for Disease Control and Prevention “candles” a chicken egg to find the injection site for the influenza virus; the virus’ proteins will be harvested to make a vaccine.

when the pandemic H1N1 hit in 2009.

“Where researchers were looking at T-cell responses in humans ... those patients that had T-cell responses did much better than those that did not,” Legge said.

When Legge’s group added the hydrophobic polyanhydride nanoparticles to the nasal spray vaccines, they found that the particles caused a stronger tissue-resident memory response. They were surprised when subsequent infection with proteins from an H3N2 virus was able to

protect the mice from proteins from an H1N1 virus.

In addition to the nanoparticles and standard vaccine components, Legge and his colleagues had considered adding an anti-neuraminidase element to increase the vaccine’s efficacy. If the flu vaccines were able to confer protection against completely different flu strains, this would be another, albeit unanticipated, pathway to universal protection against flu viruses.

After working in the mouse model, which isn’t an ideal proxy for the

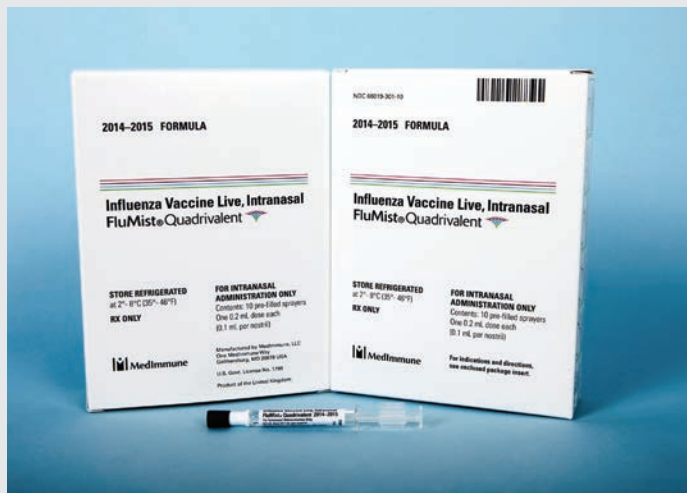
Strains, shots and sprays

Each season's flu vaccine protects against three or four strains of the virus, which are selected by experts convened by the World Health Organization every February for the Northern Hemisphere's flu season and in September for the Southern Hemisphere's flu season. These experts base their decisions on which flu strains have been found most prevalent by hundreds of surveillance laboratories around the world. While a number of factors are in play when the flu peaks in each hemisphere, including increased travel and children returning to school, one of the strongest drivers is the drop in humidity with colder temperatures, which is favorable to flu particle transmission, although the crowding in cities recently was found to make it easier for viruses to find new hosts in any weather.

For more than 70 years, viruses for these vaccines have been grown in hens' eggs over several weeks, inactivated with heat and mixed with an adjuvant to stimulate the body's immune response and a handful of preservatives at biologically safe levels, including formaldehyde and thimerosal. The vaccines then are administered with a microneedle, and over the next two weeks, recipients' bodies begin producing antibodies against the three or four strains of virus of which the vaccine contains components. Both the universal vaccines developed at Mount Sinai that are now in clinical trials are prepared using this egg-based method.

In 2012, the FDA approved a faster, cell-based process that uses mammalian cells rather than hens' eggs, to incubate flu viruses. The process is initiated with viruses that were grown in eggs. It takes days rather than weeks to generate enough flu antigens in the cells to produce vaccines. Additionally, the cells can be frozen, or "banked," allowing for rapid vaccine production in the event of a pandemic event, without the need for using eggs. As of 2016, the vaccine, sold as Flucelvax, has been approved by the FDA to include four strains of flu virus.

In 2013, the FDA approved an entirely egg-free vaccine production method in which flu antigens are grown recombinantly in insect cells. In this process, manufacturers isolate hemagglutinin proteins from the targeted influenza viruses, combine them with a secondary virus that can grow in the insect cells and incubate the recombinant virus in the cells. After several days, the hemagglutinin proteins can be purified from the insect cells and incorporated into a vaccine. Additionally, older



COURTESY OF HEATHER RICHMOND/CDC

The nasal spray vaccine FluMist, which will be available for the upcoming flu season, is approved for use in persons 2 through 49 years of age.

adults can get higher-dose flu shots or shots with an additional adjuvant, both of which induce a stronger immune response.

In 2018, the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices reinstated its recommendation for a quadrivalent nasal spray vaccine, FluMist, which uses a live-attenuated virus grown with an egg-based process. The nasal spray, made by the pharmaceutical company MedImmune, first received FDA approval in 2003 but was not available for the past two flu seasons after the advisory committee recommended against using it due to lower than expected effectiveness. This season, MedImmune has been slower to roll out the vaccine than its competitors, possibly due to a delayed start in production.

When a nasal spray vaccine is administered, the upper nasal passages are exposed to a live but weakened virus that can't replicate lower in the respiratory tract, which induces a more robust immune response in children than the standard inactivated flu vaccine administered intramuscularly via microneedle. The discrepancy in immune response is a consequence of viral exposure; when you breathe in a sneezy stranger's airborne flu particles, they're going to hit your nasal passages first and begin replicating there. If left unchecked, the viruses can work their way down into the lungs, where they can devastate bronchial tissue, create an opportunity for secondary bacterial infections or spur a cytokine storm, an all-out immune attack by the body that can wreak havoc on the lungs.

human respiratory system, Legge and his colleagues tested the vaccine in ferrets, where it worked

“It’s worked in two animal models, so we’re continuing to move forward to get this closer to being used in clinical trials,” Legge said.

Another method for tweaking existing vaccine production methods involves using a novel adjuvant that boosts vaccine strength such that the volume administered is small enough to be delivered by an intradermal, microneedle-dotted bandage. The system was described in September in the journal *Science Advances* by researchers at the University of Washington and the nonprofit Infectious Disease Research Institute in Seattle.

“Seventy to 80 percent of your immune system actually resides on the surface of your skin,” said Darrick Carter, the first author on the paper.



CARTER

“So when we give an intramuscular injection, we actually bypass a lot of these protective cells and inject right into the

muscle where there are not that many immune cells.”

The researchers loaded up an available FDA-approved microneedle, the NanoPass Microneedle, with flu proteins grown recombinantly in and harvested from tobacco plants (see box: Strains, shots and sprays) and a novel adjuvant called GLA-AF, or aqueous formulation of glucopyranosyl lipid adjuvant. A different form of GLA previously had been demonstrated in intramuscular injections in humans to be able to reduce the standard dose of flu vaccine needed from 100 micrograms to 3.8 micrograms.

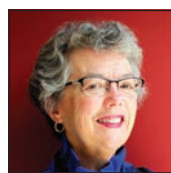
“Down the road,” Carter said, “what we want to do is to make this a self-administratable bandage where you would take it, remove a liner, put it on your skin, and then you’d be protected.”

If such a vaccine could be mailed to households, this could increase overall vaccine coverage by removing the need to visit a physician or phar-

macist to become immunized, Carter said. As with all existing and developing flu vaccines, though, the greatest obstacle to a self-administered vaccine might be convincing people that they need to be protected from influenza in the first place.

Changing norms

Myths and misconceptions about the flu vaccine are pernicious and among the most significant reasons people decide against getting an annual flu shot.



QUINN

According to Sandra C. Quinn, senior associate director of the University of Maryland’s Maryland Center for Health

Equity and author of several papers about racial disparities in influenza vaccination rates in the U.S., interaction between patient and doctor is one of the most effective ways to build people’s trust in flu vaccines.

When Quinn and colleagues conducted interviews, focus groups and a national survey with black adults, they found that a physician’s recommendation had a significant effect on the likelihood that a black adult would get vaccinated.

“In our research, we see some things are on the side of the patient or people in the community and some things are on the healthcare system side,” Quinn said. “In (a recent) survey of 819 African-American adults, 25 percent said that the provider’s recommendation was fairly important, and 30 percent, extremely important.”

While black and white Americans both fall short of the goal of having 70 percent of the population immunized against flu, Quinn said, the disparity in protection is real. In the 2016-2017 flu season, the CDC estimates around 45 percent of white adults received a flu shot, while only 37 percent of black adults did. This carries ramifications beyond just exposure to flu, as the infection



has additional risks for individuals with asthma, diabetes, heart disease, hypertension and obesity, all of which disproportionately affect black Americans.

“It’s really critical when people are in the doctor’s office, seeing the nurse practitioner, seeing the physician, that they get a strong recommendation, and particularly those people at high risk,” Quinn said.

While a universal flu vaccine is an undoubted boon, work will need to be done on an individual and community level to ensure that everyone who should get a vaccine does.

“This is not a case where ‘if you build it, they will come,’” Quinn said. “I think we’re going to have to do a lot of public education and provider education around vaccines and build trust in those vaccines as they come out.”

And over the past three decades, a wealth of epidemiologic studies have found that vaccinating schoolchildren against influenza can help protect

high-risk members of society, including those who are immunocompromised or for whom the vaccine is less effective, such as the elderly. Mathematical modeling indicated that the same protective effect as immunizing 90 percent of adults above retirement age could be achieved by protecting 20 percent of children in primary and secondary school — a population that also hasn’t been overexposed to a lifetime of flu antigens.

“If we’re really going to be successful with a universal flu vaccine, we’re going to have to do it in children,” Fauci said. “We’re going to have to imprint the children with the universal flu vaccine, so that in any subsequent exposure they have to influenza, they’ll revert back to a response against the universal components.”



John Arnst (jarnst@asbmb.org) is ASBMB Today’s science writer. Follow him on Twitter @arnstjohn.

JBC

JOURNAL OF
BIOLOGICAL
CHEMISTRY



Help JBC celebrate Dr. Herbert Tabor!

Dr. Tabor will turn 100 on Nov. 28, 2018.

The Journal of Biological Chemistry plans to celebrate his birthday by recognizing his scientific contributions and generous leadership (over four decades as editor-in-chief and continuing service as co-editor) in several ways.

We invite you to submit your best wishes, reflections on Tabor's scientific and/or personal contributions, fondest memories and snapshots. The submissions will be collected and published online during Dr. Tabor's birthday month as part of our celebration.

jbc.org/site/home/tabor_birthday/

Meet Karen Fleming

The JBC associate editor elucidates the energetics of transmembrane proteins in her lab and works to empower young women for success

By John Arnst

If a cell's membrane is its first line of defense, the transmembrane proteins dotted throughout are its exploitable weaknesses. Alpha helical transmembrane proteins, oriented as right-handed spirals, are the more common type and are implicated in most biological processes. The second form of transmembrane proteins, beta barrels (so called because they look like barrels with beta strand staves), are less common and only are known to appear in mitochondria, chloroplasts and the outer membranes of gram-negative bacteria.

At Johns Hopkins University, Karen Fleming's lab examines the energetics of how both types of transmembrane proteins interact with their membranes and environment.

Now a professor in the Thomas C. Jenkins Department of Biophysics at Hopkins, Fleming received her undergraduate degree in French and premedical studies from the University of Notre Dame and her Ph.D. in biochemistry and molecular biology from Georgetown University. After conducting her postdoctoral work at Yale University, where she subsequently worked as a research scientist, she started her lab at Hopkins in 2000. In addition to running her lab, Fleming hosts workshops at Hopkins that cover gender biases in science, technology, engineering and math professions, and sessions promoting confidence in women.

Fleming joined the ranks of associate editors at the Journal of Biological Chemistry in July 2017. As a



COURTESY OF JOHNS HOPKINS UNIVERSITY

Karen Fleming, a professor of biophysics at Johns Hopkins University, started as a Journal of Biological Chemistry associate editor on July 1, 2017.

with John Arnst, ASBMB Today's science writer, about her work. The interview has been edited for clarity and length.

What is your group focused on?

We study membrane protein folding using biophysical approaches. The proteins we're currently working on are targets for potential future antibiotics, and one of them is an essential protein in *E. coli* and other gram-negative bacteria.

What was your academic background and training?

I was always interested in science. There are a number of doctors and nurses in my family, and I thought that I would pursue medicine, but I don't like blood, and that pushed me in this direction of research. As a

graduate student, I fell in love with proteins, and I've been working on proteins and membrane proteins ever since.

One of my first projects was trying to develop a fluorescence assay. It didn't really work, but I just really liked the approach. I also like the ability to use the language of math to describe biological processes. I think that a mathematical understanding brings a lot of clarity to the systems, and it can predict future behavior if the system is well described. One of the really exciting areas where biophysics and math meet biochemistry is systems biology, because you need to know the fundamental biology that's going on in order to apply the tools of mathematics to be able to describe the system as a whole.

After graduate school, I did a post-doc with Don Engelman at Yale in the department of molecular biophysics and biochemistry working on how transmembrane alpha helices interact: What forces are involved? What stabilizes them? What destabilizes them? These are fundamental questions, because all helical membrane proteins have these interactions and need them in order to be able to function.

I continued studying transmembrane helix-helix interactions when I started my own lab, and about 10 years ago, I pivoted to working on the other major class of membrane proteins. Those are called transmembrane beta barrels, and they're found in the outer membranes of bacteria and also in mitochondria. They're building blocks of the outer membrane, and we're studying how their polypeptide chains undergo conformational changes to reach their native state and what forces are involved with that transformation.

This pivot to a new area is one of the things I love about discovery science — you can't always predict where your science is going to be five years from now, right? You work to understand fundamental processes, and you follow the findings wherever they lead you.

When we worked on helix-helix



ASBMB

Karen Fleming was on a panel at the 2014 ASBMB annual meeting that discussed career paths and how women can better promote themselves and support one another in reaching their goals.

interactions, we worked on a number of systems. One of these was relevant to mechanisms of breast cancer. And even though we didn't work on the translational side of breast cancer, I think that translational research at the National Institutes of Health shows, over and over again, that you have to be able to understand basic biology to be able to develop effective therapeutics.

Can you tell us about your workshops on gender and bias?

I started running workshops and speaking out on this topic about four or five years ago. It basically started out as journal clubs of papers in the social psychology literature that investigated various aspects of perceptions of gender differences for STEM fields and how this relates to unconscious bias and discrimination in a male-dominated workplace.

One of the earliest papers I covered was the Jo Handelsman paper from 2012 that showed that both men and women faculty discriminate against young women to the same extent. I think this paper is particularly

important because it shows that bias in science is a community problem, not a problem with men per se, and this acknowledgment makes the discussion more welcoming to men. The journal clubs grew into positive workshops on topics like confidence and bystander intervention, things we can all do to be better and to nurture a more inclusive community.

I am also part of a team that built an art exhibit here called Women of Hopkins, which has a physical exhibit and a website to show images of women with an association with Hopkins who have accomplished great things. Images can be so influential on who we are and who we can become, so it's important for young women to have role models of successful women. The response has really been overwhelming.

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

No, I was always going to do something science-y. It wasn't like a choice. It's more like a calling.

When did you first become involved with JBC?

My very first paper was published in JBC many years ago, and I also published a really nice paper in JBC as a postdoc together with another associate editor, Phyllis Hanson.

It's an honor to be able to shepherd papers through the publishing process at JBC, especially as a biophysicist. This is an important time, because JBC has a really long history of publishing seminal biophysics papers, and I think the reason I came on the editorial board was to reinvigorate that in a more modern way.

What do you do outside of the lab? Do you have advice for balancing life in the lab with life outside?

I think if I was going to give any advice at all, it would be to schedule

exercise. It always seems like an add-on, but it's really essential to prioritize your health, which helps to deal with the stresses of the demanding job that we have. I am actually a terrible athlete, but I started running when I was an assistant professor. I have completed maybe a dozen half-marathons over the years. I also find myself thinking more creatively during this time.

I also have a lot of hobbies: I like to take pictures and play with photos, and I am a pretty active genealogist. I grew up sewing, and lately I've been sewing new canvas for our boat. I learned how to knit in the past couple of years and am now striving to knit something I'm willing to wear.

I read when I have time and enjoyed the Alexander Hamilton book by Ron Chernow, and I'm a really big fan of the musical. I think it's a good thing to be knowledgeable about the history of our country. Too often it's romanticized, and really, the founders were all trying to work it out the best way that they knew how, but they weren't exactly all friends and there were lots of compromises.

Do you have any words of wisdom or a favorite motto for young scientists?

Do what you love and love what you do. There should be more days than not when you wake up and you look forward to doing science and you're excited about the questions you're asking, and that can sometimes be hard. Getting experiments to work can be challenging, but at the end of the day, you have to love what you do, because life is short and you only get one chance to live it.



John Arnst (jarnst@asbmb.org) is ASBMB Today's science writer. Follow him on Twitter @arnstjohn.

asbmb.org/careers

ASBMB



ASBMB professional-development resources

Job board

asbmb.org/jobboard

The ASBMB job board has listings from academia, government and industry. Looking for your next hire? Members can post jobs for free.

Grant-writing training

asbmb.org/grantwriting

This Washington, D.C.-based summer workshop yields impressive results; 75% of participants end up with successful grants within two years.

Communications training

asbmb.org/commcourse

Can't travel for training? Take the ASBMB's "The Art of Science Communication" online course to gain the skills, knowledge and mindset necessary to become a great presenter.

Small meetings

asbmb.org/specialsymposia

Small meetings are offered throughout the year on a wide range of scientific topics. Interested in organizing a meeting? Members can work with the ASBMB to plan and organize a special symposium.

Careers blog

asbmb.org/careersblog

Every week, our jobs blog presents insights into the current job market.

Webinars

asbmb.org/webinars

We offer live webinars and recordings of past webinars on topics including getting funding, salary negotiation, research careers in industry and more.

Video tutorials

asbmb.org/careers/tutorials

Our video series has tips on networking, dressing professionally, building a personal brand and more.

Advocacy Training Program

asbmb.org/advocacy/atp/

The ASBMB ATP is a six-month externship that provides hands-on science policy and advocacy training and experience.

Chasing unicorns

How do we define productivity?

By Peter Kennelly

In May 2017, the National Institutes of Health announced plans to cap the number of awards that an individual investigator could receive in order to free up funds to invest in young investigators. The science-funding agency justified this decision in part by citing published analyses indicating that productivity per dollar awarded began to decline as investigators accumulated multiple concurrent R01 grants.

The plans were quickly retracted (although the NIH's neuroscience institute announced plans this spring to limit grants to well-funded labs), but the proposal highlighted the continuing desire of many institutional administrators to devise metrics for quantifying the productivity of academic scientists.

When looking at the analyses cited by the NIH, a universal theme becomes evident — the measures of productivity focus exclusively on either the number of publications generated or some derivative thereof, such as impact factor or citation index. No effort is made to assess, nor is any explicit value attached to an investigator's contributions to the training of the next generation of scientists.

Counting only co-authored papers is like rewarding someone who produces a given quantity of lumber by clear-cutting a patch of forest to the same degree as someone who produces the identical quantity by carefully selecting the trees to be removed and replanting afterward. If we as a community are to inform our decision-making processes with data



COURTESY OF LYDIA POLIMENI/NIH

The James H. Shannon Building, also known as Building One, on the National Institutes of Health campus in Bethesda, Md.

pertaining not just to the immediate quality but also the long-term sustainability of the biomedical and molecular life science research enterprise, then education and training must be incorporated into any discussion concerning metrics of productivity.

One may counter by saying that a causal, linear relationship exists between the amount of publishable research generated by a student or other trainee and the quality of the training received while resident in the laboratory where the research was performed. However, while output of publishable data from individual students and postdoctoral trainees may vary greatly, in general, the capacity to generate publishable data increases with the amount of experience and training received over time,

reflecting all the students' educational and training experiences. The value we implicitly place on prior training becomes evident whenever a principal investigator makes decisions about how to staff a laboratory or what expectations to place on new and current group members. In both hiring and admissions, experience as an undergraduate research student, summer intern, graduate student and so forth carries weight across academia, government and industry. Yet no accepted mechanism exists for recognizing and crediting undergraduate and graduate research mentors for their contributions to their students' long-term success.

How can we remedy this? One way would be to give prior research

CONTINUED ON PAGE 38



Commercial beneficiaries should share costs

By Michael Malamy

It has long been established that the benefits of research funded by the National Institutes of Health flow freely to academic and commercial enterprises and ultimately to the general public whose taxes have funded the research. It is now evident that because of limitations of the NIH budget, many meritorious grant applications are not being funded. The negative results of this funding crunch have been widespread; not only has important research into vital issues of disease causality and treatment been delayed, but the research infrastructure in manpower has been seriously compromised. Long-productive labs have been closed, established scientists no longer participate in research, and most importantly, graduate students and young professors are being persuaded that academic research is not a viable career choice.

Congress and the American public have been generous in supporting research in basic and applied medical sciences, but this support has not kept up with the explosion in knowledge that now presents the opportunity to approach and solve some of the fundamental problems in medicine. A new model is needed for supplementing the NIH budget with additional funding not derived from the federal budget. I am suggesting that some of the costs be shared by those commercial interests that benefit from NIH-funded research.

The “wool tax” in Australia is one model for this type of research funding support. A certain percentage of revenue from the wool industry is set aside to support research that could impact the wool industry; this could be basic research in animal husbandry or diseases of sheep, but the tax also

has funded basic research in protein chemistry of wool proteins.

Another possible model would be to impose a license fee and royalty structure on companies that use NIH-funded basic or applied research findings in their product development. Commercial support of NIH funding could be offset by tax credits for the participating companies, thus reducing the direct costs to these companies.

Many other equitable models could be proposed, but the governing principle should be that companies that benefit from NIH-supported applied or basic research compensate the sources of these discoveries.

Michael Malamy (michael.malamy@tufts.edu) is a senior tenured faculty member at Tufts University School of Medicine.



Two funding proposals

By Michael R. Stallcup

One of the main problems facing all biomedical researchers these days (new and old ones alike) is that there are simply too many scientists applying for too few dollars. Changing the number of scientists who apply for funding is difficult to address, and a huge increase in the budgets of federal funding agencies does not look likely in the near term. But there are some things that could be done to make more funding available to researchers within the current budgets of federal funding agencies.

Currently, federal agencies will allow principal investigators to pay for

up to 95 percent of their salaries from grants. If the percentage of salary that could be obtained from federal grants and contracts were to be limited to, say, 50 percent, this would make more funds available for the actual research and would, in effect, make universities and other research institutions take more responsibility for the salaries of their employees. A gradual implementation of such a policy over several years would allow the research institutions to make adjustments and avoid the adverse impact of a fast transition.

Another problem more specific

to researchers in biochemistry and molecular biology is the difficulty in getting funding for basic research that has no obvious translational potential in the near term. I think this problem can be solved only by creation of new National Institutes of Health study sections with a mandate to review basic research. Currently, much of the basic research is crowded into a few study sections or sent to study sections that place a premium on translation.

Michael R. Stallcup (Michael.stallcup@med.usc.edu) is a professor of biochemistry and molecular medicine at the University of Southern California.

CONTINUED FROM PAGE 36

mentors a share of the credit for their trainees' subsequent publications. While an admittedly imperfect measure of a mentor's education and training contributions, allowing former mentors to list themselves as "shadow" co-authors in progress reports and biographical sketches would allow a single metric to express both their immediate and long-term contributions to the research enterprise. It also acknowledges that our focus on publications as the ultimate currency for determining value likely will persist for many years to come. Under this model, progress reports and biographical sketches would include lists of papers on which a scientist-educator participated directly as well as those that benefited from their training activities.

Should papers by former trainees be counted the same as papers where the investigator is an explicit co-author? Should a paper published two years after moving on from a mentor's tutelage count the same as one published a decade later? Current models focused on research productivity already struggle with weighing how much a given publication reflects the contributions of each of its authors: Should a three-author paper on which a researcher is listed as second author be weighted equally with a second authorship on a six-author paper? This has not, however, kept the scientific community from using paper counts in some form or another as the default metric for assessing productivity, progress or impact.

Given that current systems are both imperfect and persistent, how could (or should) we weigh papers

If we as a community are to inform our decision-making processes with data pertaining not just to the immediate quality but also the long-term sustainability of the biomedical and molecular life science research enterprise, then education and training must be incorporated into any discussion concerning metrics of productivity.

by trainees? First, I would propose a time limit. Only papers authored by a former trainee during the next stage in their training would be eligible. So if one mentored an undergraduate research student for at least one academic year, as documented by transcripts, only papers containing work performed as a graduate student would be eligible. Similarly, a graduate student's former major professor would be able to cite work done during the student's (first) postdoctoral training position.

How do we translate this into a number that can be added to traditional research publications to give a total paper count? An undergraduate research mentor could be credited for, say, a tenth of a publication for every first-author paper their trainee produces in graduate school and perhaps 5 percent of second-author publications. Given the more intensive nature of graduate training, perhaps these figures could be raised to 20 percent and 10 percent, respectively, for a major professor. In this scenario, when a principal investigator fills out their progress report for a three-year grant award, they would be able to cite not just the three papers on which they were a co-author but also the two first- and three second-author

papers published by their former graduate students as postdoctoral trainees during that same period and the three second-author papers published by their former undergraduate research students. So instead of a paper count of 3, their count would be $3.0 + (2 \times 0.2) + (3 \times 0.1) + (3 \times 0.05) = 3.85$, nearly 30 percent higher than someone who had no former students publish.

Does this formula give too much or too little credit for training contributions? Readers can and undoubtedly will raise numerous objections to my approach. However, what should not be in dispute is that in these times of tight funding, regulatory micromanagement and administrative obsessiveness with accountability, it is more important than ever to focus on the sustainability of the research enterprise when making strategic decisions such as where to allocate resources. To do so, we must more explicitly and generously reward the educational and training activities that develop the intellectual infrastructure upon which "productivity" relies.

Whatever the merits of the "credit for future publications" model described above, I hope it will provoke reflection and discussion of how we assess the success of scientist-educators.

Share your funding ideas

The American Society for Biochemistry and Molecular Biology Public Affairs Advisory Committee welcomes your thoughts on the future of science funding. They can be broad or detailed. Check out "The future of funding" call for submissions at asbmb.org/asbmbtoday.



Peter Kennelly (pjkennel@vt.edu) is a professor of biochemistry at the Virginia Polytechnic Institute and State University.

Tweeting for rules

How a PI crowdsourced his lab manual

By Jeffrey Pines

As a principal investigator, Roy Salomon mulls the many facets of lab life. Salomon, a neuroscientist at Israel's Bar Ilan University, has chewed over everything from how to title emails to what a lab's goal should be.

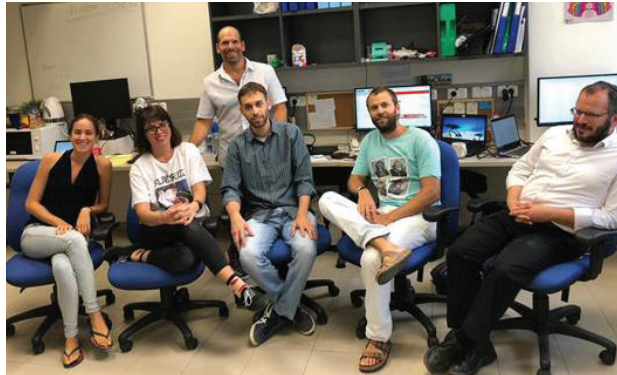
His lab at Bar Ilan's Gonda Multidisciplinary Brain Research Center, his first as a PI, concentrates on the cognitive and neural processes underlying perceptual consciousness and bodily self-consciousness, using electroencephalography, magnetoencephalography and fMRI.

Salomon realized that he needed a manual explaining lab rules and expectations while he was waiting in an airport lounge on the way to a conference.

"I was speaking to a colleague, who is also an early-stage PI, about students and conduct with them," he said "Specifically, we were debating how formal or open to be with our students. Israel is a very informal place with (few) barriers of formality. On one hand, this allows you to benefit from the great ideas of young students; on the other hand, students can also be too casual in their conduct and striking the right balance is difficult. This is when we understood we need a guide to make conduct rules clear."

None of the labs he'd previously worked in had manuals.

"There were many issues to touch upon and make decisions about," he said. "Then I realized there must be



COURTESY OF ROY SALOMON

Neuroscientist Roy Salomon, pictured here standing behind members of his laboratory at Bar Ilan University in Israel, reached out to the science community on Twitter for help in developing a code of conduct and manual for his lab.

others who have faced this dilemma before, and I reached out to the community."

Salomon turned to Twitter, tweeting in late July, "PIs, do you have a document with lab rules outlining expectations and conduct in the lab? Trying to draft something, and would love to be guided by others' experience. Feel free to RT. THX."

Some fellow-scientists tweeted responses; others emailed him.

U.S.-based researchers shared some well-thought-out documents, Salomon said. The one from Mariam Aly at Columbia University was closest to his needs, and his document is largely based on her suggestions.

"First, I felt that having a clear statement about the PI's commitment and responsibility to students is a great idea," he said. "This should be expressed explicitly, as students often don't really know what to expect, and demand, from us. Second, I found that writing out the lab's scientific goals was helpful in forming a long-term vision for our work."

Paying it forward

When Aly, also a cognitive neuroscientist, was starting her own lab less than two years ago, she wanted to help her trainees strike a balance between their professional growth and private lives, she said. People often share career advice and tips for young researchers on Twitter, and before she wrote her manual, Aly saw some of this guidance while browsing the social media site.

Though they're both neuroscientists, Aly wasn't following Salomon on Twitter when he posted his lab manual question. She thinks it might have been retweeted by someone she follows.

"At the time I saw Roy's tweet, there weren't very many responses to it, so I figured I'd respond with my own manual," she said.



ALY

Aly also wrote an article for *Nature* in September about the benefits of having a lab manual.

Jonathan Peelle, a cognitive psychologist at Washington University in St. Louis, and Maureen Ritchey, a cognitive neuroscientist at Boston College, both shared their lab manuals with Salomon on Twitter.

Peelle wrote the first draft of his manual in 2012, and he eventually posted it to GitHub.

"I am a big supporter of openly

From the Salomon lab manual

Roy Salomon wrote his lab manual to help himself and his researchers. Here are some excerpts:

You aren't expected to come into lab on weekends and holidays, and you aren't expected to stay late at night. You are expected to get your work done (whatever time of day you like to do it).

My commitments to my students:

- Maintain a vision of where the lab is going.
- Provide the funding necessary to keep the lab going.
- Meet with you regularly to discuss your research projects. The definition of "regularly" may change over time or over the course of a project, but for now, I mean once a week or more often as needed.
- Give you my perspective on academia and issues related to professional development.
- Support your career development by introducing you to other researchers in the field, writing recommendation letters for you, providing you with opportunities to attend conferences when possible, and promoting your work in talks.
- Care about you as a person and not just a scientist.

Communication

Email:

You can email me anytime.

Whatsapp:

Slab articles is only for articles and resources.

Slab is for fun, lunch and gossip.

We can create ad hoc groups for tight and quick communication.

You can Whatsapp me personally for urgent stuff; otherwise mail me.

Phone:

During business hours, call me if needed urgently; otherwise email.

If very urgent/emergency, call me any time.

sharing data, analysis code and anything else that we scientists produce that might possibly be of use to



PEELLE

others," he said.

"My hope was that someone would find it useful."

For example, Peelle writes in his manual that he

expects postdocs "to move towards being more PI-like, including giving talks, writing grants, and cultivating an independent research program (while still supporting the lab's research)." He expects doctoral students to "seek out and apply for fellowships and awards. Realize there are times to pull all-nighters and times for leaving early to go to the park to enjoy the sunshine."

Ritchey said her manual largely

was modeled on (and sometimes quotes from) Peelle's.

"I've benefitted so much from other people sharing their resources,



RITCHEY

so it's important to me to pay it forward," she said. "If it can help someone else out, why not share? I also thought it would be useful

for showing prospective trainees what our lab culture is like."

Writing a manual takes time, effort and a commitment to updating it, which may be why many labs don't have them. Aly suggests other members of the lab can pitch in and ease the burden on the PI.

She invites others to use her manual and wiki to suit their needs, including copying parts of them, as

long as they credit her.

When Salomon wrote his manual, he had his students help him, and they're already finding it helpful in their lab life, he said. He's overheard them telling one another to look in the manual when questions come up.

"I had one of my students call me out for not turning the lights off when I was the last to leave," he said. "I laughed and told him he was right to do so, as the manual is the law of the lab."



Jeffrey Pines (jpines5720@gmail.com) has worked as a journalist since 1994, covering corporations and investors for Bloomberg News, Bridge News and Dow Jones, and writing about a variety of topics for service and housing providers for the elderly. He served in the U.S. Air Force as a public affairs specialist.

Perspectives for the future and advice for aspiring scientists

By Suzanne E. Barbour

For the final article in this series, we asked our cohort of African-American male molecular bioscientists (see box) to answer the following questions:

- Based upon your experiences, what advice would you give yourself if you had your career to do over?
- What advice do you have for African-American male students who aspire to careers in science?

Their responses provide insight into a continuing struggle but also convey a sense of optimism.

The struggle continues

In the first two parts of this series, our participants described the challenges of being “the only one.” As they reflected on the future, some of the same concerns came to mind.

Nisan Hubbard, the youngest in the group, said he believes society has a long way to go when it comes to supporting the experience of African-American men in science, technology, engineering and mathematics. “It is hard to market yourself when you are being evaluated on a different spectrum than everyone else,” he said. “There are still obstacles that even the most prepared struggle through. It seems like we have to work harder just to get an inkling of respect.”

Joseph Chaney mentioned the importance of having a critical mass of African-American men in science.

“I understood the frustrations that could come with doing something like this, so it is all about realizing my strength and worth, and buckling down and getting it done. I wouldn’t change it for the world.”

— CRAIG CAMERON

“I am hopeful that as we expose more African Americans to the sciences at early ages, we’ll see more positive change,” he said.

The future is bright

Though they are aware of the struggle, our participants generally expressed optimism for the future of African-American men in science.

Christopher Barnes sees efforts being made to ensure more inclusiveness in the scientific community. “It seems that institutions are making a push to increase diversity among their faculty,” he said, “and I think that is an important step to ensure that anyone who strives to be a scientist can and will have the opportunity to do so and be successful at it.”

Craig Cameron sees the issue of critical mass in the context of his institution. “Each year, the number of African-American men who aspire to do science increases,” he said. “I see it here at Penn State. I have gone from having few, if any, African-American men in advanced science courses that I teach to having many. I now have more African-American men seeking

out research opportunities in my lab than ever before.”

Even Hubbard, with his concerns about an uneven playing field, expressed optimism. “We are starting to take the STEM world by storm,” he said. “It is not just one-off experiences, but a continuing flow of talent into the world of science that needs to be maintained and supported. It may not happen in the next quarter-century, but I think we are taking the proper steps to get to that point. And it is African-American men who are taking those steps to be able to achieve.”

How to prepare

The participants offered advice to young African-American men considering careers in science, much of it couched as what they would have told themselves early in their careers.

As the only member of the cohort who did not pursue an academic career, Carleton Barbour had advice that would be valuable for any path. “If I started my career over, I would not be as obsessed with mastering my current job and I would spend more time mastering the skills needed

AFRICAN-AMERICAN MEN IN THE MOLECULAR BIOSCIENCES — A THREE-PART SERIES

This is the third of three articles exploring the experiences of African-American men in the molecular biosciences through interviews with five African-American men at various stages in their careers, including two students, two faculty members and a researcher in the biotechnology industry.

The careers of these five men span nearly four decades when taken together and include experiences in academia, industry and consulting. Although each has had unique experiences, the commonalities in their stories provide insight into the challenges and opportunities facing African-American men in the molecular biosciences. This series is an exploration of their lived experiences, hopes for the future and advice to the next generation of African-American men who aspire to careers in the molecular biosciences.



HUBBARD

NISAN HUBBARD, a doctoral candidate at Northwestern University, is completing a Ph.D. in reproductive biology.



CAMERON

CRAIG CAMERON holds the Eberly family endowed chair in biochemistry and molecular biology at the Pennsylvania State University, and his laboratory focuses on genetic replication in positive-strand RNA viruses and transcription in mitochondria.



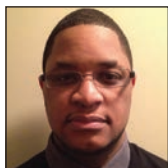
BARNES

CHRISTOPHER BARNES is a Howard Hughes Medical Institute Hannah Gray postdoctoral fellow in Pamela Bjorkman's laboratory at the California Institute of Technology.



BARBOUR

CARLETON BARBOUR is lead scientist in process and analytical development at Emergent BioSolutions, a biotechnology company focused on developing medical countermeasures for biological and chemical threats. He is also the author's brother.



CHANEY

JOSEPH CHANEY is an assistant professor of biochemistry at Xavier University of Louisiana, where he studies molecular nanomotors.

for my next job," he said. "I advise students to consider their career goals and to master skills that progress them toward those goals, regardless of whether the new skills apply to their current positions. In my experience, those that prepare themselves for their next positions, even before they are comfortable with their current role, are the employees who are the most successful.

"I also advise students to take calculated leaps of faith during their careers and move toward their next desired position as quickly as pos-

sible," he said. "I moved from an industrial research job to an industrial analytical support job to pharmaceutical product development. Each move was a leap of faith that my schooling and experience would ensure my success in the next role."

Cameron's career has included academics and consulting. "What matters most is a welcoming environment and nurturing scientific role models and mentors," he said. "Seek these, and success will likely be a part of the future."

As the only graduate student in

the group, Hubbard expanded on the themes of a welcoming environment and nurturing role models. "I would say to seek support, find your trust circle, self-care when you need to, and also to adapt very quickly to your surroundings and your new life or opportunity," he said. "New prospects always have aspects that can be hard to get through, can make you question yourself and your abilities; realize that there is light on the other side, but you can't always do it alone. Find your center, adapt, and do not only survive, but excel. You are there for

a reason, and no, it is not the color of your skin but the intellect of your thought and the body of work you bring to the table.”

Barbour offered advice targeted at students considering careers in industry. “I advise students to carefully consider their expectations of their employers and their employers’ expectations of them,” he said. “Since companies exist to sell products and earn money for their owners, students should recognize that continuous employment is not a given and jobs filled with only enjoyable tasks do not exist.

“At the same time, students should be mindful of whether their job expectations are reasonable given their job descriptions,” he said. “There is a fine balance between employees doing too little to justify their jobs and employers asking too much for what they pay.”

Barbour emphasized the importance of being proactive and a self-advocate when building a career in industry. “I should have been much more outspoken early in my career, when my career path at a company was defined,” he said.

Remember that you love science

A strong underlying theme throughout the interviews was these men’s love for science. Though they have experienced challenges and loneliness, each participant emphasized the joy that discovery brought into their lives.

“My career has been challenging and rewarding and provided an ongoing opportunity to be paid to play every day,” Barbour said.

Cameron echoed this sentiment, saying that “the ability to make impactful discoveries and share that experience with a team of extraordinary of human beings” was one of his favorite parts of his career.

Perhaps the most exuberant enthusiasm came from Hubbard. “This is something that I love and something I want to do,” he said. “I understood the frustrations that could come with doing something like this, so it is all about realizing my strength and worth, and buckling down and getting it done. I wouldn’t change it for the world.”

About parts one & two

The first article in this three-part series focused on the importance of mentoring, particularly for African-American men in the biosciences. The second article discussed managing underrepresentation in science. Read them at asbmb.org/asbmbtoday.

It was an honor to interview these five inspiring men. Their enthusiasm for preparing the next generation of diverse molecular bioscientists is both admirable and infectious. Every one of us, whatever our race, ethnicity or gender, can learn from their lives. In the face of challenges, frustrations, and sometimes downright hostility, they remain positive, optimistic and thoroughly in love with their science.

In Cameron’s words, “The future is bright.”



Suzanne E. Barbour (sbarbour@uga.edu) is the dean of the University of Georgia Graduate School.

BOOKS BY ASBMB MEMBERS

A Practical Guide to Writing a Ruth L. Kirschstein NRSA Grant

By Andrew D. Hollenbach, co-director of basic science curriculum, school of medicine, and professor, department of genetics, Louisiana State University Health Sciences Center New Orleans



This second edition includes changes to the application since the first edition and continues to provide F-series grant applicants and mentors insider knowledge on the process by which these grants are reviewed, biases that contribute to reviews, the extent of information required in the application, a deeper understanding of the exact purpose of each section of the application, and key suggestions and recommendations on how to best construct every section of the application. This book is a solid resource for trainees and their mentors to use as a guide when constructing F30, F31, and F32 grant applications.

Are you an ASBMB member who has published a book in 2018?

If so, we’d like to feature your work in an upcoming issue of ASBMB Today. Please email a synopsis (<100 words), an image of the book’s cover and your headshot to asbmbtoday@asbmb.org.

CALL FOR SUBMISSIONS

ASBMB Today will launch two essay series in 2019:

What I wish people understood about _____

Is there an aspect of your life, personal or professional, that others just don't get? Fill in the blank in this sentence, and then set the record straight.

Night shift

Life does not end when the sun goes down, and our experiences are often heightened at night. Tell us a story about what you do while others sleep.

We are also looking for submissions for:

Black History Month 2019

We seek prose and art about contributions by black scientists to the biosciences, including essays, nonfiction, photographs and illustrations. Deadline: Dec. 1

For information, email asmbmtoday@asbmb.org
or go to asbmb.org/asmbmtoday and click **SUBMIT**.

ASBMBTODAY

ASBMB Special Symposia Series

The Many Faces of Kinases and Pseudokinases

Dec. 9-12, San Diego

Evolution and Core Processes in Gene Expression

May 9-12, 2019, East Lansing, Mich.

Transforming Undergraduate education in the Molecular Life Sciences

July 25-28, 2019, San Antonio, Texas

Membrane-Anchored Serine Proteases

Sept. 12-15, 2019, Potomac, Md.

Reminder: ASBMB members save on meeting registration.

www.asbmb.org/specialsymposia

 **ASBMB**

CLASSIFIEDS

University of California, San Diego: Associate Teaching Professor (LSOE) - Biochemistry and Biophysics

UC San Diego

Candidates must have a Ph.D. in Biochemistry, Chemistry, Chemical Education or a closely related field and demonstrate potential for a recognized program of excellence in teaching. Candidates must also demonstrate that they are strong chemistry educators. A successful candidate should have a well-articulated plan of contributing to programs that increase the access and success of underrepresented students and faculty in the sciences. We especially welcome candidates who have already participated in, contributed to or created such programs, who can articulate how this experience helped shape their plan, and who have a commitment to helping shape and expand the University's diversity initiatives. Applications should include a statement describing past and/or potential contributions to equity, diversity and inclusion. To apply, visit: apptrkr.com/1309904

University of Michigan-Dearborn: Chair, Department of Natural Sciences

 UNIVERSITY OF MICHIGAN-DEARBORN

The University of Michigan-Dearborn (UM-Dearborn), a regional campus of the University of Michigan located in the city of Dearborn, Michigan, seeks an experienced leader to serve as the next Chair of the Department of Natural Sciences within the College of Arts, Sciences, and Letters. The Department offers programs in biology, chemistry and physics, and the interdisciplinary areas of biochemistry, earth science, environmental science and microbiology. The Chair will work in close partnership with the Dean and the other department chairs during a time of unprecedented growth within the University. To apply, visit: imsearch.com/6772

Johns Hopkins University: Assistant or Associate Professor



The Department of Biology, Johns Hopkins University, Baltimore, Maryland (www.biology.jhu.edu) invites applications for a tenure-track or tenured position, as Assistant or Associate Professor, in the broad areas of cell biology and RNA biology. The anticipated starting date of the appointment is July 1, 2019. To apply, visit: apply.interfolio.com/53380

Macmillan Learning: Biochemistry Contract Author



The Biochemistry Contractor is responsible for writing clear assessment questions and answers of varying difficulties, which test students' understanding and application of concepts in biochemistry. S/he will author hints, answers and feedback that provide insightful diagnosis of student mistakes and misconceptions and coach students toward comprehension. To apply, visit: **To apply, contact angela.piotrowski@macmillan.com**

To see a full list of jobs, please visit asbmb.org/careers.

Interested in posting a job in ASBMB Today and on our online job board?
Visit asbmb.org/advertise to learn more.





**BOLD
DISCOVERY**

**HAPPENS
BEYOND**

**JOIN US AT THE 2019
ASBMB ANNUAL MEETING**

ABSTRACT DEADLINE: NOV. 14

Learn more about submitting your abstract
and how to apply for travel awards:

asbmb.org/meeting2019

 **ASBMB '19**
ANNUAL MEETING
ORLANDO | APRIL 6-9

Held in conjunction with

