

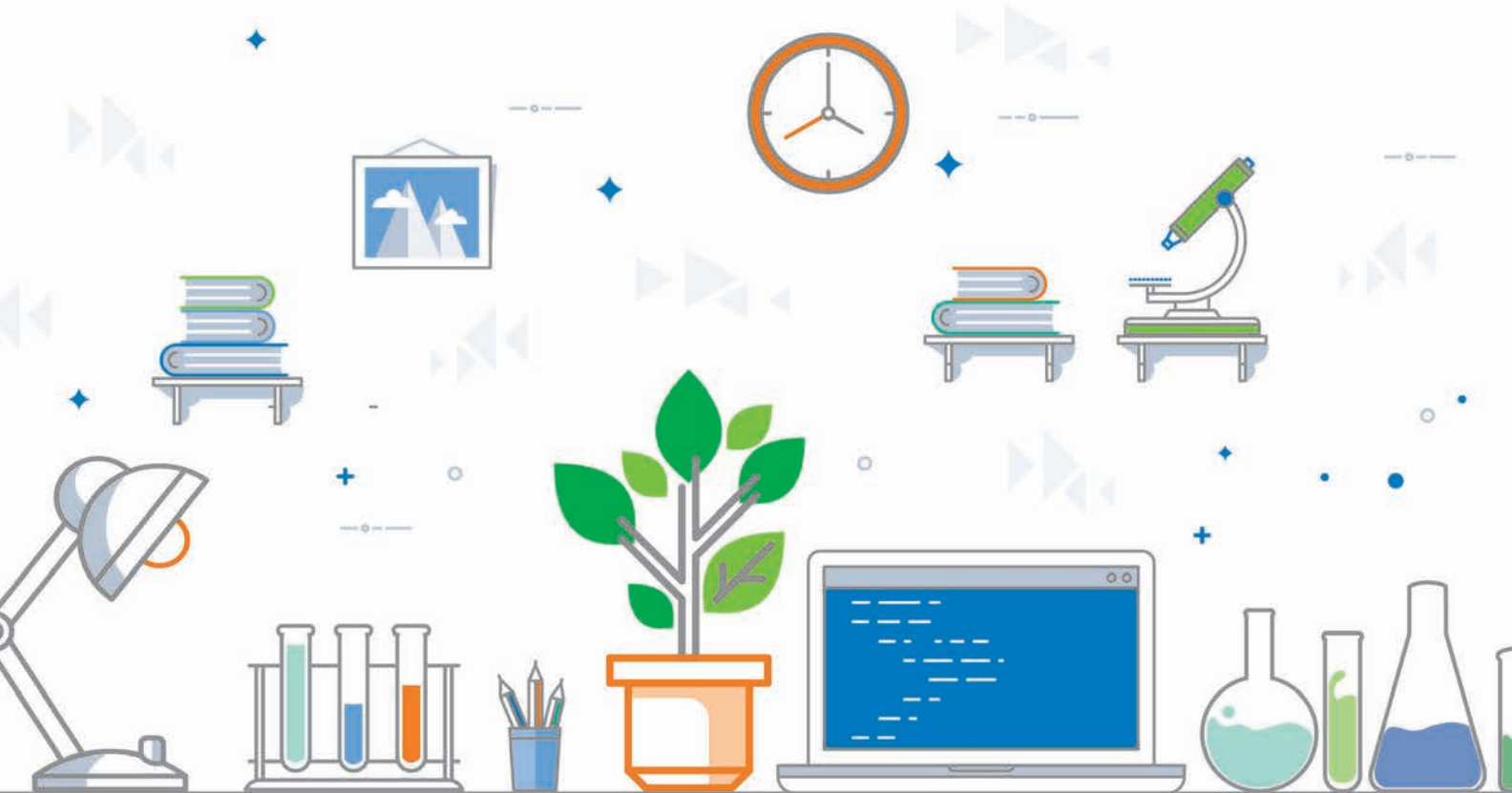
Vol. 17 / No. 5 / May 2018

ASBMB TODAY

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

THE GUT-BRAIN CONNECTION

Puzzling out Parkinson's disease



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asbmb.org/jobboard

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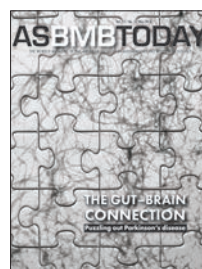


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PRESIDENT'S MESSAGE

Our day on the Hill

By Natalie Ahn

Thanks to the Bipartisan Budget Act of 2018 and the accompanying omnibus appropriations bill, fiscal 2018 will see a significant boost in federal funding for science research. This includes increases of \$295 million for the National Science Foundation and \$3 billion for the National Institutes of Health. At the NIH, nearly every institute will receive a hike of 5 percent or more. Already, there are signs that this will result in more funding for the investigator-initiated research project grants on which many of our members depend.

This welcome trend did not occur without sustained activity by scientists advocating for the support of research and infrastructure. The American Society for Biochemistry and Molecular Biology Public Affairs Advisory Committee is one of the most active groups in this effort.

When scientists make personal visits to their congressional leaders, their voices are heard. Thus, each April, the PAAC organizes Capitol Hill Day, putting scientists face to face with elected representatives. This year, 16 faculty members and industry scientists and 20 students and postdocs spent a full day on the Hill, making a total of 85 visits to the offices of legislators from 25 states.

I teamed up with Mallory Smith, a graduate student at the University of Kansas, and Matt Gentry, a professor at the University of Kentucky and chair of the PAAC. Together, we visited our respective House members and all six senators from Colorado, Kansas and Kentucky.



ALL PHOTOS COURTESY OF HILL DAY PARTICIPANTS AND ASBMB STAFF

Natalie Ahn, Mallory Smith and Matt Gentry pause outside the meeting room of the House Committee on Science, Space and Technology during their ASBMB Capitol Hill Day visits to legislators.

Our message to each senator and representative emphasized three points.

First, on behalf of all of us in the research enterprise, we thanked our legislators for their support of science. We explained how federal research dollars support industry, jobs, education and health for their states. And we reminded them that even with recent budget increases, funding for research still has not kept pace with inflation. Spending caps and sequestration have weakened research and development, and these trends must be reversed. We need sustainable, predictable investments in science to ameliorate the damage from boom and bust cycles.

Second, we conveyed the ASBMB's opposition to directing research funding toward specific diseases or conditions. While we appreciate this support, we believe that discov-

CONTINUED ON PAGE 4

Be a hometown science advocate

By Daniel Pham

This is an exciting time for science. Scientists are running for office in record numbers and are making their voices heard through emails, petitions and phone calls to Washington, D.C. Our members lobbied Congress during last month's Capitol Hill Day, and thousands participated in the second annual March for Science.

While many efforts focus on federal advocacy, local activism is also crucial. Policies enacted in statehouses and city halls can have major impacts on research institutes within their jurisdictions. To focus on garnering support for life science research at the local and state level, the American Society for Biochemistry and Molecular Biology is launching its Advocacy Training Program. And we are searching for 10 scientists to be the first ASBMB ATP delegates to cultivate the energy of local grassroots science advocacy.

This nationwide six-month externship will provide hands-on science policy and advocacy training and experience, beginning in June. Delegates will first complete a digital advocacy training course to equip them to build and support local sustainable science advocacy activities. In this informal training phase, the program will provide a substantial overview of the advocacy landscape and how to navigate it.

Through the summer, delegates

will join bimonthly hour-long conference calls on specific policy topics. Before each call, they will receive curated materials to read and watch, such as those produced by the American Association for the Advancement of Science. ASBMB public affairs staff, sometimes with a guest expert, will underscore specific points before facilitating an open discussion of these topics, similar to discussions that take place in scientific journal clubs. Potential topics include how science agencies such as the National Institutes of Health make policies, how Congress passes laws and budgets, and what effective advocacy looks like. Delegates also will complete homework assignments to prepare them to meet with their state and local representatives in August.

And they will not stop there. From September until December, delegates will develop and carry out an advocacy calendar tailored to their specific regions. They will learn how to recruit like-minded scientists and identify allies who will assist in and amplify their advocacy efforts. Through this program, scientists will become trained science advocates, will develop and contribute to local science advocacy efforts, and will build a regional network of grassroots and professional science advocates.

We are looking for passionate scientists who seek new opportunities in advocacy. We recognize that

the course is intensive, and we expect delegates to commit about two hours a week to this endeavor. Whether you are an undergraduate passionate about science education, a member of your institution's science policy group or a scientist looking to increase diversity in your lab, this program may be the right fit for you. The ATP does not require you to leave your lab for a prolonged period, and it will provide you with the training and support required to become the tip of the spear in our advocacy efforts.

Our goal is to have one ASBMB delegate from every state able to provide up-to-date local intel on relevant policy issues and plug into their local network to amplify the ASBMB's national advocacy campaigns. We hope our inaugural class of ATP delegates will not only participate in our programs but also help us to develop and strengthen the ATP for the next class.

Please go to asbmb.org/advocacy/ATP to learn more about the program and to apply to become a 2018 ATP delegate. If you have any questions about the application or the program, email us at publicaffairs@asbmb.org.



Daniel Pham (dpham@asbmb.org) is the public affairs manager at the ASBMB.



Check in every other week for a new **Pipettes & Politics** podcast episode to hear candid conversations about topics like new legislation in Congress, policies at federal agencies and policy issues within the research community.



CONTINUED FROM PAGE 2

ery and innovation are best served when scientists determine the course of their research. And the greatest outcomes are achieved when scientists win grants based on exemplary, peer-reviewed applications.

Third, we underscored the need for policies that strengthen the nation's scientific workforce. This

requires support for bills that enhance education in science, technology, engineering and mathematics. The ASBMB also supports passage of a comprehensive immigration reform bill and expansion of the pool of visas available for foreign scientists to study and work in the U.S.

The responses we received were heartening. All of us heard support and agreement on the need for further

increases in research funding. We found uniform support for STEM education. And we saw recognition of the contributions from foreign-born scientists and of the need to retain them to keep research strong in America.

Our day on the Hill showed that bipartisan support for science research and education is strong in both legislative chambers. You can



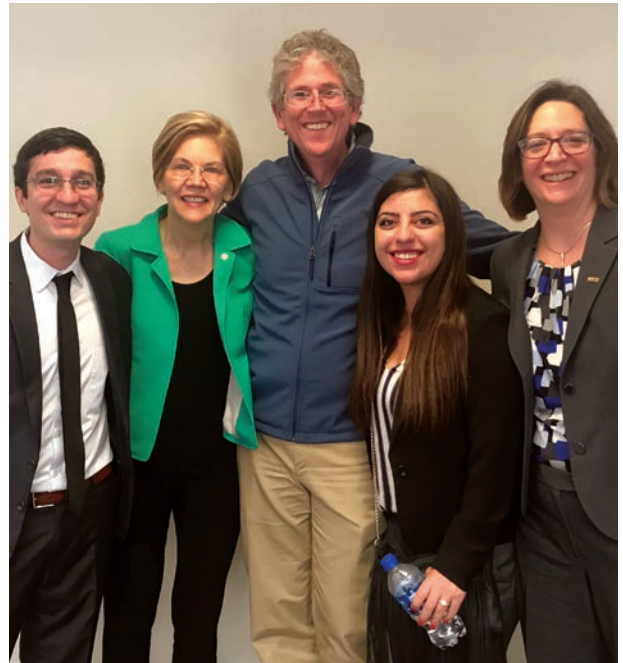
Khaliyl Lane (left), legislative assistant for Sen. Richard Blumenthal, D-Conn., poses with the Connecticut Hill Day delegation of Susan Baserga (PAAC member), Sarah Smaga and Alex Freedenberg.



Hill Day participant Emily Myers (right) poses for a photo with U.S. Rep. Pramila Jayapal, D-Calif.



Hill Day participants Adrienne Lee (left) and Leah Cairns stop for a photo in front of the office of Sen. Tim Kaine, D-Va.



The Hill Day Massachusetts delegation poses with Sen. Elizabeth Warren, D-Mass. (second from left). Members include (from left to right) Damien Cabral, Nick Rhind, Andrea Hadjikyriacou and Tricia Serio.



Hill Day participants Dorothy Shippen (PAAC member), Daniel Hass, Spencer Shelton and Williamson Turner enjoy the blossoming trees in Washington, D.C.



Susan Forsburg (PAAC member), Levi Evans and Tino Sanchez pose in front of the U.S. Capitol.

See more photos of Hill Day in our slide show at asbmb.org/asbmbtoday.



ASBMB Hill Day participants Andrew Garfoot (left) and Jonathan Sachs (PAAC member, right) meet with Sen. Ron Johnson, R-Wisc.



Pictured with Rep. Hank Johnson, D-Ga., are Hill Day participants (from left) Samantha Acacio, Kimberly Jackson (PAAC member) and Anita Corbett (PAAC member).

read about Hill Day in the recap at policy.asbmb.org and learn about the activities of the PAAC at asbmb.org/Advocacy and policy.asbmb.org. The ASBMB will continue to advocate for you at the highest levels of Congress. Want to get involved in advocacy? It's an experience that will expand you. Join the Grassroots Advocacy

Network (asbmb.org/Advocacy/GrassrootsNetwork/), or, to learn more, email Public Affairs Director Ben Corb at bcorb@asbmb.org.

Finally, to continue this fight for your teaching and research, we need your support and participation. If you're not a member of the ASBMB, now's the time to join. If you're a member, invite a colleague to join.

Help us amplify our message about the value of your work and strengthen our collective voice in U.S. science policy.



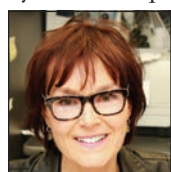
Natalie Ahn (natalie.ahn@colorado.edu), a professor of chemistry and biochemistry at the University of Colorado, Boulder, is president of the ASBMB.

Member update

By Erik Chaulk

Rochester's Maquat wins Wiley Prize

University of Rochester School of Medicine and Dentistry professor Lynne E. Maquat has won the Wiley Prize in Biomedical Sciences.



MAQUAT

Awarded since 2002, the Wiley Prize recognizes novel and innovative research in the biomedical sciences. Maquat is being honored for elucidating the mechanism of nonsense-mediated messenger RNA decay, a fundamental process through which cells remove defective transcripts that can encode toxic proteins.

Maquat holds the J. Lowell Orbison endowed chair and serves as professor in the department of biochemistry and biophysics. She is the founding director of the university's Center for RNA Biology, where she has established herself as a leading figure in RNA research.

The award carries a \$50,000 prize, which was presented to Maquat in April at Rockefeller University in New York City.

Trinity names Bowie an associate dean

Andrew Bowie, a professor at Trinity College Dublin's School of Biochemistry and Immunology, has been named an associate dean of research. In his new role, Bowie will develop Trinity's research strategy with the university's



BOWIE

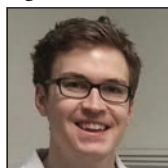
dean of research.

Bowie, who studies innate immunology, has served as director of research in the school of biochemistry and immunology (2005 to 2009) and head of immunology (2011 to 2017).

He is a member of the Royal Irish Academy.

McCarty wins Fulbright scholarship

Nicholas McCarty won a Fulbright scholarship to study at Imperial College London.



MCCARTY

McCarty completed his undergraduate studies in bioengineering at the University of Iowa. In Dale Abel's lab, McCarty studied diabetes, insulin signaling and heart failure.

At Imperial, he'll focus on developing CRISPR, the groundbreaking genetic engineering tool, while he pursues a one-year master's degree in systems and synthetic biology.

Caruthers, Pennington recognized for inventions

Marvin Caruthers and the late Mary Engle Pennington were named this year to the National Inventors Hall of Fame. Founded in 1973, the hall of fame honors individuals, both living and deceased, who conceived and patented groundbreaking technological innovations.

Caruthers is being honored for developing methods for the chemical synthesis of DNA. His work significantly advanced biological research

and the biotechnology industry. A distinguished professor of chemistry and biochemistry, Caruthers



CARUTHERS

has served on the faculty at the University of Colorado-Boulder since 1973. He also co-founded several biotech companies, including Amgen, Applied Biosystems, Array BioPharma and miRagen Therapeutics.

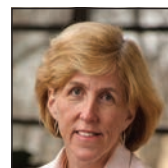


PENNINGTON

Pennington, who lived from 1872 to 1952, was a bacteriological chemist, food scientist and refrigeration engineer who worked in the U.S. Department of Agriculture's Bureau of Chemistry, which later became the Food and Drug Administration. Pennington is being honored posthumously for her innovations in food preservation and storage, which greatly improved the lives of many Americans. Among her inventions were a poultry-cooling rack, a bacteria-resistant method of treating eggs, and a sterile food products container.

Helen Hobbs wins Harrington Prize

Helen Hobbs, professor at the University of Texas Southwestern Medical Center at Dallas and a



HOBBS

Howard Hughes Medical Institute investigator, won the Harrington Prize for Innovation in Medicine. Established in 2014, the

Harrington Prize recognizes scientists who have conducted groundbreaking and creative research with potential for clinical impact.

Hobbs was honored for her discovery, together with her lab partner Jonathan Cohen, of the link between PCSK9, a gene mutation, and lower levels of low-density lipoprotein, commonly known as bad cholesterol. Her research has led to improved treatment of high cholesterol.

The prize carries a \$20,000 honorarium, a lectureship at the American Society for Clinical Investigation's annual meeting and publication of a personal essay in the *Journal of Clinical Investigation*.

Hobbs has served on the faculty at UT Southwestern since 1987. There, she founded the Dallas Heart Study, a multiethnic, population-based study seeking to improve diagnosis, prevention and treatment of heart disease.

In memoriam: Roswell Boutwell

Roswell Boutwell, professor emeritus of oncology at the University of Wisconsin–Madison, passed away at the age of 99 in August in Middleton, Wisconsin.



BOUTWELL

Boutwell was born in Madison, Wisconsin, in 1917. He completed undergraduate studies at Beloit College before earning both his M.S. and Ph.D. in biochemistry at the University of Wisconsin–Madison.

Boutwell was a founding member of the department of oncology at the McArdle Laboratory for Cancer Research at Madison, where he contributed significant research toward understanding cancerous tumor growth. Among his many research accomplishments, he demonstrated the correlations between caloric intake and cancer.

In addition to serving on the faculty at Madison, Boutwell was appointed to the National Cancer Advisory Board from 1984 to 1990 and acted as a consultant to both the Food and Drug Administration and the Environmental Protection Agency.

His wife of 72 years, Luella Mae “Lou” Fairchild, passed away in 2015. He is survived by his three sons, Paul, Philip and David.

In memoriam: Kevin Catt

Kevin Catt passed away after a long illness in Bethesda, Maryland, in October. He was 85.



CATT

Born in Richmond, Victoria, Australia, Catt attended the University of Melbourne, where he earned his medical degree in 1960. He later earned his Ph.D. in biochemistry at Monash University in 1967.

Catt moved to the United States in 1969 and a year later began work at the National Institutes of Health's National Institute of Child Health and Human Development. He went on to serve as chief of the section on hormonal regulation and chief of the endocrinology and reproduction research branch at the NICHD. He invented the solid-phase radioimmunoassay in addition to developing other novel methods for research studies and clinical investigations.

A prolific author, Catt published more than 700 scientific papers and book chapters throughout his career. He retired from the NIH in 2012.

He is survived by his wife, Maria Dufau, and sons, Nicholas and Matthew.

In memoriam: Charles Dreiling

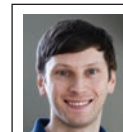
Charles Ernest Dreiling passed

away at his home in Foresthill, California, in January of brain cancer. He was 76.

Dreiling was raised in Seattle, Washington, and attended the University of Washington for his undergraduate studies. He later earned his M.S. in biological chemistry from New Mexico State University and his Ph.D. in biochemistry and biophysics from Oregon State University.

He spent his career at the University of Nevada, beginning as an assistant professor in the biology department and rising to associate professor in the biochemistry department. Dreiling received the Faculty Development Program Award and the Outstanding Teacher Award, among other honors.

He met his wife of 46 years, Penny Marie Kee, while in Seattle. After Kee's death, Dreiling met and married his wife of five years, Nancy Lea McEnroe-O'Brien. Dreiling is survived by his wife; his children, Derek and Amy; and his brother, Tom.



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!



IN REMEMBRANCE

The following ASBMB members died in 2017 and early 2018

Bruce Anderson 1929–2017	Daniel W. Foster 1930–2018	Lea Reshef 1930–2017
William K. Bates 1936–2017	Richard A. Harvey 1936–2017	Angelo M. Scanu 1924–2018
Norman I. Bishop 1928–2017	Claude Klee 1931–2017	Milton Schlesinger 1927–2017
H. Alex Brown 1960–2017	Neil B. Madsen 1928–2017	Eric Shooter 1924–2018
Gene Brown 1926–2017	David Millhorn 1945–2017	Carolyn Slayman 1937–2017
Roswell Boutwell 1917–2017	Leonard E. Mortenson 1928–2017	David Burrad Smith 1916–2017
Kevin J. Catt 1932–2017	William R. Moyle 1944–2017	Aloys L. Tappel 1926–2017
Eric E. Conn 1923–2017	Kenneth E. Neet 1936–2017	Ching C. Wang 1936–2017
Harold Deutsch 1918–2017	Eldon C. Nelson 1935–2017	Milton Weiser 1930–2017
Charles E. Dreiling 1941–2018	Harvey S. Penefsky 1926–2017	Charles Yanofsky 1925–2018

We also recently learned of the passing of these members

Douglas L. Coleman 1931–2014	John J. “Jack” Marchalonis 1940–2007	Maria Tomasz 1932–2016
Darrel E. Goll 1936–2008	Andrew D. Robertson 1959–2014	Ignacio Tinoco 1930–2016
Priscilla Hele 1920–2013	John Shainoff 1930–2015	William J. Williams 1926–2016
François Jacob 1920–2013	George Taborsky 1928–2016	Donald Wetlaufer 1913–2004
Leon Lack 1922–2014	John F. Thompson 1919–2013	

An unusual form of antibiotic resistance in pandemic cholera

By Sasha Mushegian

Cholera is a devastating disease for millions worldwide, primarily in developing countries, and the dominant type of cholera today is naturally resistant to one type of antibiotic usually used as a treatment of last resort.

Researchers at the University of Georgia now have shown that the enzyme that makes the El Tor family of *Vibrio cholerae* resistant to those antibiotics has a different mechanism of action from any comparable proteins observed in bacteria so far. Understanding that mechanism better equips researchers to overcome the challenge it presents in a world with increasing antibiotic resistance. The research was published in the **Journal of Biological Chemistry**.

Cationic antimicrobial peptides, or CAMPs, are produced naturally by bacteria and by animals' innate immune systems and also are synthesized for use as last-line drugs. Cholera strains achieve resistance to CAMPs by chemically disguising the bacterium's cell wall, which prevents CAMPs from binding, disrupting the wall and killing the bacterium. M. Stephen Trent's research team in Georgia previously had shown that a group of three proteins carried out this modification and had elucidated the functions of two of the proteins. The team reported the role of the third protein — the missing piece in understanding CAMP resistance — in the new paper.

Jeremy Henderson, then a graduate student, led a research project that showed that this enzyme, AlmG, attaches glycine, the smallest of the amino acids, to lipid A, one of the components of the outer membrane of the bacterial cell. This modifica-



COURTESY OF M. STEPHEN TRENT/UNIVERSITY OF GEORGIA

This image shows an electron micrograph of the bacterium *Vibrio cholerae*, the causative agent of cholera.

tion changes the charge of the lipid A molecules, preventing CAMPs from binding.

Lipid A modification is a defense mechanism observed in other bacteria, but detailed biochemical characterization of AlmG showed that the way this process occurred in cholera was unique.

"It became apparent over the course of our work that how (this enzyme) improves shield functionality is quite different than would be expected based on what we know about groups of enzymes that look similar," Henderson said.

AlmG is structured differently from other lipid A-modifying enzymes, with a different active site responsible for carrying out the modification. In addition, AlmG can add either one or two glycines to the same lipid A molecule, which

also has not been observed in other bacteria. "It just opens up the door for this operating with a completely different mechanism than what's been described in the literature for related proteins," Henderson said.

Genes encoding determinants of antibiotic resistance can spread between different species of bacteria, so the unique mechanism of CAMP drug resistance in *V. cholerae* is of potential concern if it jumps to bacteria already resistant to first-line drugs. "The level of protection conferred by this particular modification in *Vibrio cholerae* puts it in a league of its own," Henderson said.

DOI:10.1074/jbc.RA117.000131



Sasha Mushegian (amushegian@asbmb.org) is scientific communicator for the Journal of Biological Chemistry.

Simulations might speed drug target discovery

By *Sasha Mushegian*

Researchers at the California Institute of Technology have developed an approach to overcome a major stumbling block in testing new drug targets. The work was reported in in the **Journal of Biological Chemistry**.

Proteins embedded in cell membranes are potential targets for drugs to treat a number of diseases, from infectious diseases to cancers. Membrane proteins (which include transporters, channels and receptors) are the targets of almost 70 percent of FDA-approved drugs.

However, it is notoriously difficult for researchers to produce membrane proteins in the lab in sufficient quantities to be able to purify them and conduct experiments with potential drugs. Thomas F. Miller III and William M. Clemons Jr. of the department of chemistry and chemical engineering at Caltech wondered whether there was a way to help researchers experiencing this problem.

“Our motivation for this project was really born out of frustration with this general problem, which is that membrane proteins are very hard to produce at scale for experimental purposes,” Clemons said.

To produce proteins of interest, researchers typically insert the gene encoding the protein into a laboratory workhorse cell line, such as *Escherichia coli*; this process is called heterologous overexpression of a protein. But membrane proteins typically are overexpressed in only very small amounts for reasons that have been poorly understood until now. Individual researchers sometimes spend years trying to modify their proteins of interest in ways that will make them more efficiently expressed in the lab.

“People just hunt around in the dark to hopefully find something that

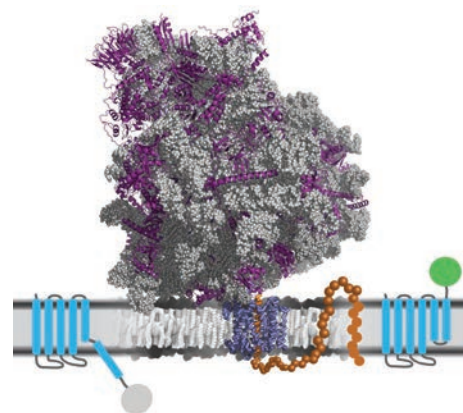
works better so that they can get enough protein to perform their studies,” Miller said. “New tools are needed to rationally enhance that, to do it in a more purposeful way.”

To see whether there were any general principles that could guide attempts to improve membrane protein expression, Clemons and Miller and their graduate students Michiel J.M. Niesen and Stephen S. Marshall focused on a specific step in the process: the point when a cell actually inserts a newly synthesized protein into the membrane.

The efficiency of insertion — that is, the fraction of the time that a protein is inserted into the membrane correctly — depends on the protein’s amino acid sequence. The team developed a computational simulation method to predict how a change in the sequence would affect insertion efficiency.

In the new study, the team tested how this predicted efficiency related to protein expression in the lab. The team systematically produced many variants of a particular protein and used the algorithm to predict each variant’s membrane insertion efficiency. Then the researchers quantified how much protein was produced. As they had hypothesized, improved insertion efficiency correlated with improved protein yield.

Now researchers interested in studying a particular membrane protein can use these simulation tools to predict what changes they should make to their protein sequence in order to produce the membrane protein in the lab. There are caveats: If a particular protein in a particular cell type is subject to inefficiencies at steps



COURTESY OF THOMAS MILLER III AND WILLIAM CLEMONS JR./CALTECH
A new method improves protein yield by predicting membrane insertion efficiency, a key step in the expression of membrane protein.

in its synthesis other than membrane insertion, then the new method may not help. But the researchers are confident that the method offers a way forward for many membrane protein researchers struggling to express their proteins.

“We believe that the tools we’ve developed here have the potential to really revolutionize membrane protein expression,” Clemons said. “There are still things we have to do to fully realize that, but this paper demonstrates that the potential is there.”

The researchers are teaming up with others to put these tools to work.

“There are many membrane protein targets that are of real importance and real value for pharmaceutical and drug design purposes,” Miller said. “If we can help people by bringing an elusive target within grasp, it would be a big victory.”

DOI: [10.1074/jbc.M117.813469](https://doi.org/10.1074/jbc.M117.813469)



Sasha Mushegian (amushegian@asmb.org) is scientific communicator for the Journal of Biological Chemistry.

Gene therapy shows promise for deadly childhood disorder

By Laurel Oldach

Babies with the rare, deadly genetic disorder Sandhoff disease begin to miss developmental milestones just months after birth. Lacking muscle tone, they never learn to sit up; they develop heads too large to lift and eventually suffer uncontrollable seizures. There is no cure.

Cynthia Tift of the National Human Genome Research Institute, part of the National Institutes of Health, studies the disease. “With excellent supportive care, children can survive until age 5 or so,” she said.

A paper in the **Journal of Lipid Research** by senior investigators Tift and Richard Proia and lead author Laura Allende of the NIH’s National Institute of Diabetes and Digestive and Kidney Diseases and their colleagues describes an important step toward gene therapy for children with Sandhoff disease.

The disease is a lysosomal storage disorder. Enzymes in the lysosome normally break down unneeded molecules. When an enzyme doesn’t work, the molecule it should degrade begins to accumulate.

Sandhoff disease disrupts the function of an enzyme that breaks down complex lipids called gangliosides. Ganglioside accumulation eventually causes cell death in the brain and spinal cord.

The first human model

The researchers wanted to know whether the problems that appear soon after birth in Sandhoff patients actually develop during pregnancy. The disease is so rare that Tift estimates five children are born with it in the U.S. each year. Therefore, most of what is known about the disease



COURTESY OF THE NATIONAL TAY-SACHS & ALLIED DISEASES ASSOCIATION

Parents hold the hand of their daughter, who was born with Sandhoff disease.



COURTESY OF THE NATIONAL TAY-SACHS & ALLIED DISEASES ASSOCIATION

Cash, a little girl who died of Sandhoff disease, snuggles with her family in their Team Cash T-shirts.

comes from studying genetically engineered mice, which are not a perfect comparison.

This study began when a baby with Sandhoff disease came to Tift’s clinic, where the medical geneticist treats patients with infantile and milder

adult-onset forms of the disease.

Researchers took skin cells from the baby and reprogrammed them into induced pluripotent stem cells. Those cells, like the ones in an embryo, can mature into any cell type in the body.

The team created healthy control

cells by using CRISPR/Cas9 genome editing to correct one copy of the affected gene in the patient's stem cells. The researchers then induced the two sets of stem cells to grow into simple groups of brain cells, organoids about the size of a pencil eraser. The researchers compared the healthy and Sandhoff-affected organoids to find out how the disturbed enzyme might affect early development.

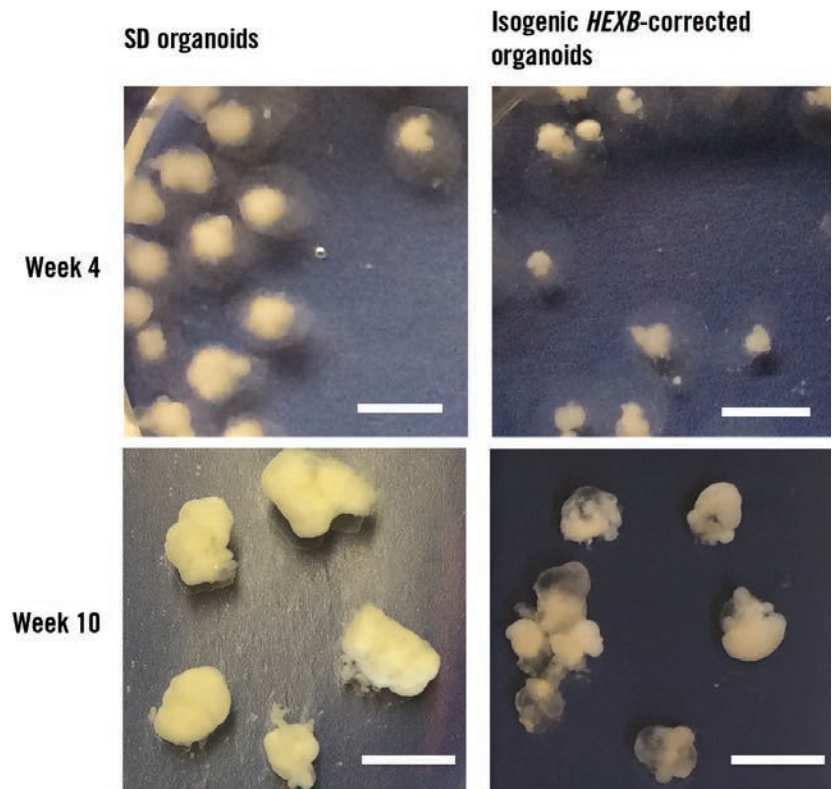
Unexpected problems

As expected, researchers saw accumulation of ganglioside molecules in the Sandhoff organoids. The healthy organoids did not show this accumulation, confirming that the genetic intervention had worked. But the researchers also found something surprising.

"The major feature of this disease, in humans and in mouse models, is the neurodegeneration," Proia said. Instead of cell death in the Sandhoff disease organoids, the researchers saw cell overgrowth. Although there was no difference between the stem cells, the Sandhoff organoids were much larger than the healthy ones, mimicking the large brains of patients.

The profile of genes expressed in the healthy organoids looks a lot like the first trimester of pregnancy. However, the researchers found that the organoids with Sandhoff disease had changes in genes that govern cell maturation. Instead of settling into a role as differentiated adult cells, the Sandhoff cells just kept growing. It remains to be determined how the disrupted ganglioside enzyme leads to changes in gene expression.

Ron Schnaar, a professor at Johns Hopkins University, researches gangliosides in the brain but was not involved in this study. "Most of us have been thinking of lysosomal storage diseases as if everything is just fine until these molecules begin to build up," he said. "But there has always been a bubbling issue of whether the molecules themselves have an effect,



COURTESY OF LAURA ALLENDE/NIH

Laura Allende and colleagues found that "minibrains" grown from the tissue of a patient with Sandhoff disease (left column) grow much larger than otherwise identical cells with the mutation in the HEXB enzyme gene corrected by genome editing (right column).

other than building up to tremendous amounts."

Schnaar said this paper is the first to address that question, showing that disruption of gangliosides does affect brain development in humans.

A path to gene therapy

CRISPR, the researchers' original approach to correct the gene, is still far from the clinic. Therefore, the researchers also tested a more practical gene-therapy approach that had been successful in animal models of Sandhoff disease.

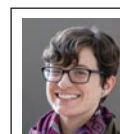
They used a virus to introduce a healthy version of the gene for the gangliosidase enzyme to 4-week-old Sandhoff organoids. About two weeks after receiving the gene therapy, the organoids that had been treated were closer in size to the healthy organoids and no longer had large clumps of

ganglioside.

"That's the first proof of principle in a human model system that gene therapy may actually be beneficial for these kids," Tiffit said. The viral gene-therapy approach is in clinical studies for other lysosomal storage disorders, and the first FDA-approved gene therapy for any genetic disorder uses a similar virus.

The child whose skin cells were used for this study died at age 4. While it comes too late for her, the research strikes a hopeful note for future generations of children with Sandhoff disease.

DOI: 10.1194/jlr.M081323



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Keeping tabs on thousands of protein variants

By Laurel Oldach

Perhaps you have seen a time-lapse video of a busy city sidewalk. As people come and go, they blur together into a crowd with no distinguishing features. You could count the number of people pushing strollers in each frame, but it might be hard to tell how long one parent has been circling the same block with a colicky baby.

As proteins are made and destroyed in a cell, they tend to blur together too. Many proteomics studies measure with precision the number of copies of each protein species but not how long each one lasts. In a new paper in the journal **Molecular & Cellular Proteomics**, researchers in Bernard Kuster's lab at the Technical University of Munich report a new approach to determining the lifespan of a great many proteins, and their alternative isoforms, in large data sets.

"Plenty of research has demonstrated that cancer, neurodegenerative diseases, age-related diseases and even aging per se are associated with altered lifespans of single proteins or a global dysregulation of the cellular recycling machinery," said lead author Jana Zecha. She compares a cell in which proteins are continuously made and destroyed to "a tiny protein production and recycling machinery." With colleagues, Zecha set out to measure this factory's output, determining the rates of production and destruction of many different proteins.

The researchers combined two techniques for telling samples apart by their mass: stable isotope labeling by amino acids in cell culture, or



SILAC for short, and tandem mass tag labeling, or TMT. The primary SILAC label enabled a pulse-chase experiment, a way of measuring how much of a new amino acid is taken up after it is added to cells. By combining SILAC with TMT, the researchers could achieve high proteome coverage with high reproducibility and accurate counts of each protein. Then they looked for trends over time. For example, a protein's rate of synthesis can be measured by how much of the new SILAC label appears over time in its spectrum, and degradation is measured by how much the old label disappears.

Other scientists previously had combined the SILAC and TMT methods, but this data set gave an unusually thorough look at protein lifetimes. The researchers found substantial variability among splice variants of proteins, which no one

had yet measured in a data set of this size. Because two splice variants from the same gene have many peptides in common, a data set with many measurements at the peptide level was required.

The approach could offer a better way of understanding the basic biology of disease states with altered protein turnover. The researchers also are interested in modifications occurring after translation that may alter turnover rates.

"A proteome-wide measurement of turnover rates of modified peptides is the next logical step for us," Zecha said.

DOI: 10.1074/mcp.RA118.000583



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From the journals

By Sasha Mushegian & Laurel Oldach

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**.

Molecular secrets of bacterial signaling

Cyclic di-adenosine monophosphate is an essential bacterial signaling molecule, the functions of which are still incompletely understood. Angelika Gründling and colleagues at Imperial College London examined the role of c-di-AMP in the pathogen *Staphylococcus aureus*, which is unable to grow without c-di-AMP in rich medium but able to in minimal medium. Their experiments suggested that c-di-AMP is required for regulating osmolyte intake. Furthermore, they showed that methicillin-resistant *S. aureus* strains lacking c-di-AMP were hypersensitive to a beta-lactam antibiotic, suggesting that targeting c-di-AMP may be a strategy for treat-

ing drug-resistant staph infections. The findings were published in the **Journal of Biological Chemistry**.

DOI: 10.1074/jbc.M117.818716

Fatty acid addition lets a parasite stick

Trichomonas vaginalis, commonly known as trich, is the most common curable sexually transmitted disease, and the vast majority of people with the disease — upward of 70 percent — do not experience symptoms, according to the Centers for Disease Control and Prevention. However, the protozoan parasite can increase an infected person's risk of contracting HIV or developing cancer and can cause preterm labor in pregnant women. In other parasites, a protein modification called palmitoylation, the addition of a 16-carbon saturated fatty acid to cysteine residues of a protein, regulates infectivity. In a new paper in the journal **Molecular & Cellular Proteomics**, research-

ers at the Instituto Tecnológico de Chascomus in Buenos Aires and the University of California, Los Angeles, enriched palmitoylated proteins from *T. vaginalis* and found numerous palmitoylation sites in pathogenesis-related proteins. Yesica Nievas and colleagues report that disrupting palmitoylation reduced the protist's self-aggregation and adhesion to host cells. This work establishes the importance of palmitoylation in *T. vaginalis* proteins for infection and suggests that palmitoylation enzyme inhibitors may help treat the infection.

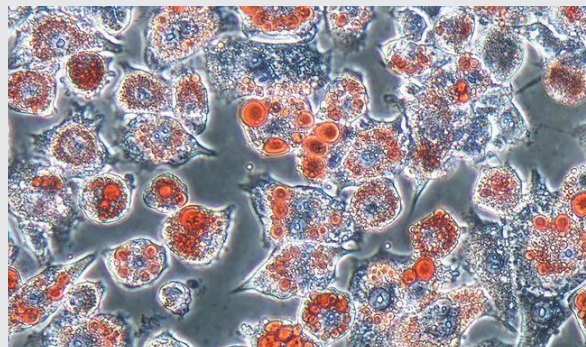
DOI: 10.1074/mcp.RA117.000018

Fat can cause selective insulin resistance

Ordinarily, insulin causes cells in the liver to switch energy sources by turning down the activity of enzymes that make new glucose and increasing the activity of genes that govern lipid synthesis. This switch lets cells store energy when blood glucose is

MicroRNAs promote fat cell apoptosis

Weight loss can be hard to sustain. The total mass of adipose tissue depends both on the number of fat cells, or adipocytes, and their average size. During weight loss, the amount of fat stored in each cell drops, but the total number of cells stays the same, making it easy to regain weight when a caloric surplus is available. Therefore, being able to selectively kill adipocytes or their precursor cells, preadipocytes, may be a way to make weight loss last. In a paper in the **Journal of Lipid Research**, Zhenzhen Zhang and colleagues at Northwest A&F University in Shaanxi, China, reported that in a model for apoptosis in fat cells, two microRNAs are important drivers of the programmed cell death pathway. These microRNAs, miR-103 and 107, suppress the production of a protein called wnt3a that reduces apoptosis. Overall, the microRNAs led to more programmed cell death.



COURTESY OF M. OKTAR GOLUGLU/WIKIMEDIA

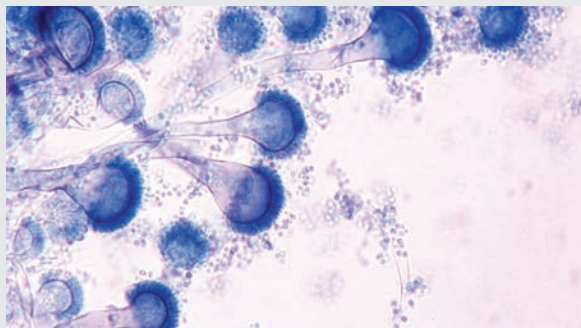
A micrograph of fat cells stained with Oil Red O shows their lipid vesicle contents.

Targeting these microRNAs could someday become a route to killing adipocytes.

DOI: 10.1194/jlr.M082602

How a fungus outfoxes the macrophage

Aspergillus fumigatus is an opportunistic pathogen in the lung. People with compromised immune systems, either from disease or immune-suppression therapy, are especially vulnerable to the airborne mold spores called conidia. In a healthy person, macrophages in the alveoli take up the fungus, and normally an acidic organelle called the phagolysosome destroys it. Conidia from *A. fumigatus*, however, disrupt acidification of the phagolysosome and prevent the infected macrophage from committing suicide through apoptosis. Researchers at the Leibniz Institute for Natural Product Research and Infection Biology in Germany investigated the immune evasion strategies the pathogen uses by infecting cultured macrophages with magnetically tagged *Aspergillus* conidia from a virulent strain or a less infectious mutant strain. Hella Schmidt and colleagues then extracted phagolysosomes from macrophages infected with each strain and compared their proteomes. In a paper in the journal **Molecular & Cellular Proteomics**, the team reported



COURTESY OF LIFE WORLDWIDE/NIH FLICKR

An illustration of *Aspergillus fumigatus*.

that the more virulent strain reduces maturation of the phagolysosome and proinflammatory immune signaling. These disruptions ensured that the more virulent strain had a comfortable place to survive inside the host.

DOI: 10.1074/mcp.RA117.000069

abundant. But in diabetes, a paradox occurs: Insulin fails to shut off gluconeogenesis while still stimulating lipid synthesis. To find out how this phenomenon, called selective insulin resistance, can arise, researchers at Harvard University and the Broad Institute reduced the complexity of the problem by studying the effects of the fatty acid palmitate on insulin signaling in cultured liver cells. The researchers, Zhihuan Li and colleagues, reported in the journal **Molecular & Cellular Proteomics** that the presence of palmitate increased glycerolipid levels and disrupted a small number of proteins that normally would respond to insulin, including the transcription factors FoxO1 and NFkappaB and the kinase GSK3. The researchers also identified many previously unknown insulin-induced phosphorylation sites. They propose that their comprehensive data set may be useful for generating hypotheses about how insulin signaling is controlled in the more complex environment of the liver.

DOI: 10.1074/mcp.RA117.000560

Primate tau problems

Defects in the protein tau, which is abundant in the central nervous system, are associated with both Alzheimer's and Parkinson's disease. The tau protein of primates has an N-terminal motif that is absent in tau from other mammals. Arne Ittner and colleagues at the University of New South Wales investigated whether this region may be responsible for humans' increased susceptibility to tau-related disorders compared with other animals. They found that this region mediates interactions with several neuronal proteins. Because protein interactions affect tau pathology, this motif may be critical for understanding neurodegenerative diseases. The research was published in the **Journal of Biological Chemistry**.

DOI: 10.1074/jbc.RA118.001784

A potential oncogene for gastric cancer

Gastric cancer has one of the highest mortality rates among cancers, but its mechanisms and biomarkers remain poorly understood. Zheng-

sheng Wu and colleagues at Anhui Medical University in China showed that the proline-rich protein GSE1, which previously was known to have an oncogenic role in breast cancer, promotes gastric cancer proliferation, invasion and metastasis both in vitro and in mouse models. Its expression correlated with patterns of survival and relapse in gastric cancer patients. GSE1's cancer-promoting role appeared to involve the amino acid transporter SLC7A5, which was upregulated when GSE1 stabilized the SLC7A5 transcript. The research was published in the **Journal of Biological Chemistry**.

DOI: 10.1074/jbc.RA117.001103

Eicosanoid profile in cultured cells

Cultured cells depend on media for many essential nutrients, among them polyunsaturated fatty acids. Researchers observed that cells' production of signaling lipids derived from PUFAs by cultured macrophages changes over time between media changes as the cells exhaust the available essential

Healthy octogenarians with high CEC

Many scoring methods designed to help doctors predict whether a patient is at risk for cardiovascular disease are not accurate in elderly adults. As life expectancy grows longer around the world, the search is on for new ways to measure risk beyond the traditional cholesterol test and life history. In a recent study in the **Journal of Lipid Research**, Francesca Zimetti and colleagues at the University of Parma in Italy and the State University of Campinas, Brazil, set out to determine if cholesterol efflux capacity, or CEC, should be considered a risk factor in healthy adults aged 80 or older. CEC is shorthand for the ability of arterial macrophages to release excess cholesterol, preventing it from accumulating on artery walls. In younger adults, high CEC correlates with a reduction in early signs of atherosclerosis. While this association did not hold in a group of Brazilian adults who had reached their 80s in good health, the octogenarians had significantly higher cholesterol efflux capacity than their middle-aged counterparts. The authors caution that the healthy elderly patients should be compared to patients over 80 with cardiovascular disease to be certain, but suggest that high CEC may promote longevity.

DOI: 10.1194/jlr.P079525



COURTESY OF ADAM JONES/WIKIMEDIA

A study of healthy Brazilian octogenarians, such as this man in Paraty, Brazil, showed that they have higher cholesterol efflux capacity than their middle-aged counterparts.

PUFAs. In an article in the **Journal of Lipid Research**, Toshiaki Okuno and colleagues from Jutendo University in Japan and the University of Colorado in Denver quantified the changes to various lipids. In addition to fluctuating lipid levels, they observed that the number of days since the previous media change dramatically altered tumor necrosis factor secretion in response to lipopolysaccharide, an inflammation mediator. The study suggests that cell feeding schedules may introduce variability among in vitro experiments, which could be reduced by flow-through culture.

DOI: 10.1194/jlr.M083030

Phases of aggregation in Huntington's disease

In Huntington's disease patients, the huntingtin protein has extended lengths of repeated glutamines at one end, which cause the protein to form

neurotoxic aggregates. In a paper in the **Journal of Biological Chemistry**, Rohit Pappu and colleagues at Washington University in St. Louis found that these aggregates fall into three distinct categories delineated by concentration thresholds, sizes and morphologies. They also found that profilin, an actin-binding protein known to reduce huntingtin aggregation, interacts with aggregates in one specific phase. Understanding the phase behavior of huntingtin and other aggregation-prone proteins may be important for developing therapies.

DOI: 10.1074/jbc.RA117.000357

How calcium pump rates relate to skin health

Darier disease is a rare autosomal dominant disorder of the skin characterized by severe rashes or lesions caused by mutations in a particular

isoform of the sarcoendoplasmic reticulum calcium transport ATPase, or SERCA. Jens Peter Andersen and colleagues at Aarhus University in Denmark reported in the **Journal of Biological Chemistry** that a Darier disease mutation affected the interaction between an isoform-specific cytoplasmic loop and other regions of the protein. This change increased SERCA's calcium transport rate, which could activate a stress response and induce apoptosis, perhaps explaining its role in Darier disease pathology.

DOI: 10.1074/jbc.RA117.000941



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Upcoming ASBMB events and deadlines

JUNE Alzheimer's & Brain Awareness Month

1: Marion B. Sewer Distinguished Scholarship for Undergraduates deadline

14–16: IMAGE grant-writing workshop

21: Frontiers in RAS Pathobiology and Drug Discovery oral abstract deadline

JULY

10: Frontiers in RAS Pathobiology and Drug Discovery early registration deadline

19: Transcriptional Regulation by Chromatin and RNA Polymerase II oral abstract deadline

20: Frontiers in RAS Pathobiology and Drug Discovery poster deadline

28: World Hepatitis Day

AUGUST

August is for Advocacy Month

9: Frontiers in RAS Pathobiology and Drug Discovery registration deadline

13–17: Fungal Disease Awareness Week

14: Transcriptional Regulation by Chromatin and RNA Polymerase II early registration deadline

30: Transcriptional Regulation by Chromatin and RNA Polymerase II poster deadline



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FEATURE

THE GUT-BRAIN CONNECTION

Puzzling out Parkinson's disease

By John Arnst & Laurel Oldach

Benjamin Stecher was living in Shanghai when he first noticed the tremor. He had moved to



STECHER

China not long after college and landed a job teaching English at a company called San Li Around America. Within a couple of years, he was a managing partner. Meanwhile, the rigidity and shaking in his right foot and hand slowly got worse.

During a trip home to Canada in 2013, he saw a movement-disorder specialist who quickly diagnosed the problem as a symptom of early-onset Parkinson's disease. Stecher was just 29 years old.

Experts estimate that by the time a Parkinson's diagnosis is made, more than half of the dopaminergic neurons in a section of the brain controlling movement already have died. Aggregates of the protein alpha-synuclein form clumps known as Lewy bodies that disrupt neuronal function and eventually kill the cells. While some treatments, such as the drug levodopa, control patients' tremors, there are currently no methods to block the ongoing damage (see sidebar: The shaking palsy). As neurodegeneration spreads, patients suffer a gradual loss of movement and independence.

"It's not easy figuring out how to move on with life as a young man faced with that kind of fate," Stecher said.

He tried to work around his symptoms, but they continued to worsen. At age 32, he moved home to Toronto to focus on his health.

Stecher asked his doctor a lot of questions. Then he started asking other experts. Soon, he found himself immersed in Parkinson's research, reading studies and visiting labs all over the world. He hadn't taken a biology class since high school, but he learned fast.

"I was able to draw upon my understanding of how to learn a language, and that really helped me dive into the world of biology," he said.

Stecher started a blog to share his insights into Parkinson's research with other patients. Some of his readers are where he was when he started: excited about research, but unfamiliar with the day-to-day of basic science. Stecher works to bridge the gap in his blog, *Tomorrow Edition*, where he posts transcripts of his conversations with experts in all areas of Parkinson's research.

For those experts, the anatomists, neurologists and life scientists of every ilk who have been analyzing Parkinson's disease for the past 200 years, the disease has proved frustrating. A "snowflake disease," with no two patients looking quite the same, Parkinson's manifests in an array of motor and non-motor symptoms — including blocked bowels, nocturnal convulsions and a diminished sense of smell — that one patient may experience to far greater degrees than another.

But the symptoms all stem from the aggregation of misfolded alpha-synuclein. Preventing or disrupting its misfolding may be the best chance researchers have for stopping and treating the disease — which has doubled in prevalence over the past 15 years to affect more than 7 million people worldwide.

Before the tremors

Journalist Dave Iverson, who has Parkinson's, is a patient advisor and contributing editor for the Michael



IVERSON

J. Fox Foundation, a nonprofit engaged in funding and advocacy for the disease. At the Parkinson's Policy Forum, a recent advocacy event sponsored by Fox and the Parkinson's Foundation, he moderated a panel discussion updating



COURTESY OF BENJAMIN STECHER

Parkinson's patient and reporter Benjamin Stecher (right) looks at induced pluripotent stem cells (iPSCs) with Tilo Kunath, whose lab at the University of Edinburgh was one stop on his "world tour" of Parkinson's research groups.

The shaking palsy

The constipation, disrupted sleep and creeping decline in motor function that mark the disease were first described in 1817 in a monograph by the English surgeon James Parkinson, who called it “the shaking palsy.”

Nearly 100 years later, the neurologist Frederic Lewy discovered that proteins aggregated in the neurons of Parkinson’s patients. These spherical aggregates were later found to be responsible for the death of dopamine-signaling, or dopaminergic, neurons in the substantia nigra, a part of the mid-brain involved in motion and reward.

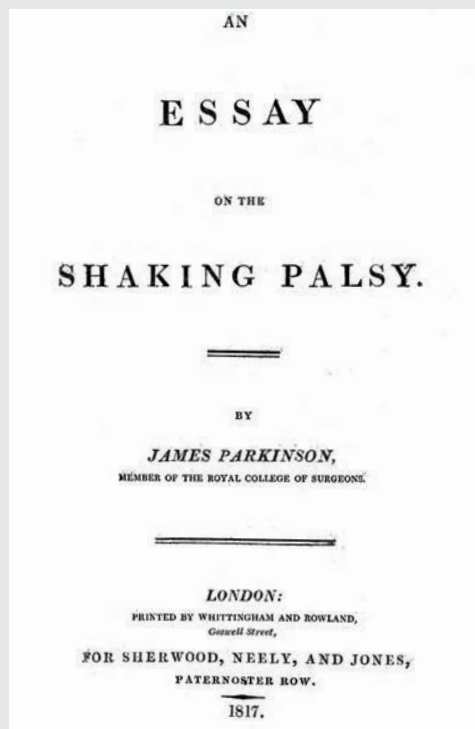
In 1957, the Swedish scientist Arvid Carlsson found that when dopamine was depleted



CARLSSON

from rabbit brains, a Parkinson’s-like phenotype could result. The disease could be reversed by administering levodopa, which was approved for human Parkinson’s patients in 1967. The drug, which acts by replacing a patient’s depleted dopamine, remains the most widely prescribed treatment for the disease, but does nothing to halt the march of neurodegeneration. Levodopa, a mirror image of dopamine, crosses the blood-brain barrier, an obstacle that made direct dopamine replacement impossible. Once in the brain, it rapidly converts to dopamine, which reduces tremors and shakes and improves a patient’s motor control. However, levodopa’s quick metabolism gives patients only a brief window of relief before symptoms return.

Ben Stecher, who was diagnosed



COURTESY OF WIKIMEDIA COMMONS

“An Essay on the Shaking Palsy,” by James Parkinson, was originally published as a monograph in 1817.

with Parkinson’s at age 29 and who blogs about the disease, started taking levodopa after milder drugs for tremor, such as dopamine breakdown inhibitors, didn’t work for him.

“The on/off of levodopa has become the metronome of my life,” Stecher said, describing an “on” that can last from 20 minutes to two hours before slipping away. “When I’m off, I feel as though I’m stuck in the mud, not just my body, but to some extent my mind as well.”

Over the long term, levodopa can cause dyskinesia, a clinical term for jerky, involuntary movements. And although replacing the missing dopamine can relieve symptoms, it does nothing to prevent further spread of alpha-synuclein throughout the brain.

A less-common treatment for

late-stage Parkinson’s is deep-brain stimulation, in which micro-electrodes are implanted into one of three regions of



VAN HULSTEYN

the brain’s basal ganglia, depending on symptoms. Peggy van Hulsteyn, a writer living in Santa Fe, was diagnosed 18 years ago and had DBS surgery in 2009.

“I have to admit, when I first heard about DBS, I was horrified,” van Hulsteyn said. “My steadfast and affable neurologist, Scott Sherman, was the constant cheerleader for this scary surgery.”

Looking back, van Hulsteyn describes the surgery as the best thing she’s done to manage her Parkinson’s. DBS does not work for every patient and can be risky especially for older patients; however, in patients for whom it works, the suppression of motor symptoms with DBS compared to levodopa alone can last for 10 years or more.

The implanted micro-electrodes are connected by a subcutaneous wire to a battery-powered pacemaker placed below the collarbone. With an external remote control, a patient can turn the system on or off once it has been programmed by their physician. The system can complement levodopa treatment, allowing a patient to take smaller doses of the drug, and it counteracts some of the dyskinesia that can occur with higher doses. DBS can be an effective treatment for late-stage Parkinson’s, but like levodopa, it has no effect on the progression of alpha-synuclein.

patient-advocate attendees on recent research.

“We used to think that if we could just fix the dopamine supply, we’d be good to go,” Iverson said in his opening remarks. “But now we know it’s a more complicated disease; there are problems with everything from cognition to constipation.”

Almost all patients experience slowing and rigidity of movement, with seven out of 10 exhibiting a tremor at rest in one or more limbs. Many patients also find that their handwriting gets smaller, their voices softer and their faces less expressive. Some develop low blood pressure; others, sleep problems; still others, mood disorders.

Many of these symptoms, including constipation and anosmia, or the loss of sense of smell, develop before the signature tremor.

“Ninety percent of us have no sense of smell,” said A.C. Woolnough, a retired high-school principal from Sandpoint, Idaho, who is a patient and active advocate. “I can’t tell the difference between Coke, root beer and Dr. Pepper.”

Anosmia is caused by the death of olfactory neurons and can have pernicious effects on a person’s quality of life. Edward Burton, a neurology professor at the University of Pittsburgh who treats patients in the movement disorders clinic and also runs a lab, points out that the loss does not just affect one’s enjoyment of food.

“Not being able to smell whether your clothes are clean? Whether you left the gas on?” he said. “These things are kind of disabling.”

Many people think of constipation as a normal part of getting older or eating an unbalanced diet. Few realize that it can be an early warning sign of Parkinson’s development; more than 50 percent of patients

suffer from constipation for several years before motor symptoms become apparent.

The seemingly disparate symptoms were linked in 2003, when the German anatomist Heiko Braak published a new model of the disease’s progression.



BRAAK

Braak had performed a series of autopsies on brains comparing patients with symptoms of Parkinson’s to those displaying asymptomatic aggregation of alpha-synuclein into Lewy bodies. Braak and his colleagues noted that Lewy bodies began to accumulate in the anterior olfactory nucleus, which is responsible for processing smells, before they appeared in the substantia nigra, which was known to show neurodegeneration in Parkinson’s. They also found that in some people whose brains had Lewy bodies, motor symptoms never developed. In these cases, the substantia nigra remained intact.

The researchers proposed a staged model wherein aggregation of alpha-synuclein started in the olfactory bulb and spread through connections between neurons into the brain. According to the model, when the spread reached the substantia nigra, where dopaminergic neurons are the densest, patients’ ability to move would begin to decline.

In 2007, Braak and his colleagues came up with a new model, known as the dual-hit hypothesis, which introduced the gut as a second possible starting place for alpha-synuclein aggregation.

Both the nose and the gut have abundant nervous tissue, and in both places these neurons are exposed to microbes and other possible aggregation triggers from the environment. The researchers were unsure how alpha-synuclein aggregation passed from one cell to another, and they proposed that a neuron-specific virus

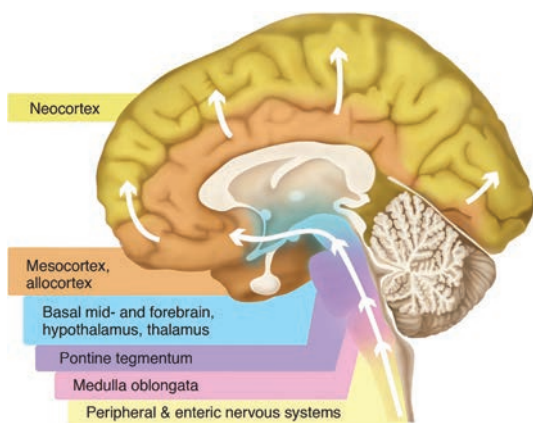


LAUREL OLDACH/ASBMB

A.C. Woolnough, a retired high school principal from northern Idaho, wears a shirt promoting the World Parkinson’s Conference, an international meeting that brings together doctors and patient advocates from all over the world.

Below: This stuffed raccoon, the conference mascot, has hot-pink medical tape around its paw to show support for research.





VISANJI ET AL./ACTA NEUROPATHOLOGICA COMMUNICATIONS

A diagram illustrates the temporal progression of alpha-synuclein aggregates starting in the peripheral nervous system. The motor symptoms of Parkinson's disease usually begin when aggregation and neurodegeneration occur in the substantia nigra, in between the blue and purple regions.

might be to blame.

The mechanism remains in question, but in general, the model has held up. Early aggregation of alpha-synuclein in the peripheral nervous system, as proposed in the Braak hypothesis, has become widely accepted as a model for the disease's progression and appears to occur in about 80 percent of patients, based on autopsy findings.

According to Braak's hypothesis, if alpha-synuclein pathology begins in the gut, it needs to reach the brain via the vagus nerve, which connects the stomach, intestines and other organs to the brain. Evidence recently gathered from medical records in Denmark and Sweden suggests that patients with a severed vagus nerve developed Parkinson's at a lower rate than the general population. The procedure, known as a vagotomy, was popular in the 1970s as a treatment for severe peptic ulcers, which later were discovered to be caused by bacterial infection.

While both the Danish and Swedish studies found that performing a vagotomy led to a reduction in the occurrence of Parkinson's disease at both five and 10 years after the surgery, the procedure also severs the nerve's connection to the stomach, liver, gallbladder and pancreas — making it far from practical as a preventative measure. The results of both analyses, however, do provide credence to a role for the gut-brain axis in Parkinson's disease.

Some researchers believe that disruption to the intestinal wall, perhaps caused by inflammation, may be a



SHANNON

factor in triggering alpha-synuclein aggregation. Kathleen Shannon, a neurologist at the University of Wisconsin-Madison specializing in movement disorders, is searching for biomarkers of disrupted intestinal membrane integrity in

patients with Parkinson's.

The U.S. Food and Drug Administration has approved no therapies to halt or disrupt alpha-synuclein aggregation. Shannon and other experts hope to develop treatments that will stop neurodegeneration at early stages. To make that happen, they must identify patients much earlier, before the dopaminergic die-off begins.

"The thought is: Are there things that you can detect in people five to 10 years before onset and intervene then?" Shannon said. "That's where the whole field is moving right now."

The genes

If Parkinson's disease were a product of a single malfunctioning gene, like Huntington's disease, diagnosing the disorder would be relatively easy, but fewer than 10 percent of Parkinson's cases have a single-gene cause. Still, recent identification of genetic risk factors may shed light on the various points where aberrant biochemical behavior can give rise to the disease.

"Fifteen or twenty years ago, we didn't think genetics was involved in Parkinson's disease at all," Dave Iversen of the Fox Foundation said.

But genome-wide association surveys and studies of families with a high incidence of the disease have turned up some genetic risk factors. The most common are variants in the lysosomal kinase LRRK2, believed to play a role in the development of 2 percent of all known cases of Parkinson's, and the lysosomal enzyme glucocerebrosidase A, or GBA, which affects about 5 percent of patients, including Benjamin Stecher.

"We're coming pretty close to understanding how that mutation actually leads to the disease," said Stecher, who is participating in research on targeted therapies specifically for patients with the GBA mutation.

Scientists suspect that in cells

with pre-existing lysosomal problems, aggregates of alpha-synuclein cannot be cleared effectively.

Aside from lysosomal enzymes like LRRK2 and GBA, some 26 other genes also impart a degree of risk; most do not cause Parkinson's in every person who carries them, and just one in 10 patients has a known genetic mutation. Experts do not expect to find major new genetic contributors, but research into these mutations ultimately may help every patient by allowing clinicians to extrapolate to treatments targeting shared pathways in the disease.

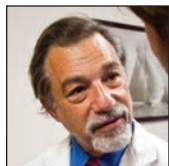
Some members in the Parkinson's community are fond of the saying, "The genes load the gun, but the environment pulls the trigger." While a complex constellation of genetic factors may put a person at risk of Parkinson's disease, genetics alone cannot account for every case. Experts think that alpha-synuclein begins to aggregate because the environment introduces a stressor.

The twisted protein

Alpha-synuclein typically is found within the presynaptic terminal of neurons and binds to lipids. It may affect the fusion of synaptic vesicles, helping to deliver neurotransmitters to the synapse. It also has been found to misfold and aggregate after viral infection in the brain or traumatic brain injury.

Preliminary results suggest that alpha-synuclein also may play a role in mediating intestinal inflammation.

In a 2017 paper in the *Journal of Innate Immunity*, Michael Zasloff, an immunologist at Georgetown



ZASLOFF

University, and his colleagues noted high levels of alpha-synuclein in neurons in endoscopic biopsies taken from 42 children with acute or chronic gastrointestinal infections. The researchers believe the pro-

tein's presence during infections suggests a role as part of a gastrointestinal immune response. The researchers also found that alpha-synuclein acted as a chemoattractant for monocytes and neutrophils, essential components of an immune response.

"What we imagine is that in certain settings ... where the infection is chronic, and alpha-synuclein is constantly being produced, or in a setting where your genetics is such that the equipment needed to clear alpha-synuclein from the nerve or the surrounding tissue is impaired, alpha-synuclein begins to accumulate," Zasloff said. "And when it accumulates, for example in the nerve (cells), you start to see pathology."

Levels of alpha-synuclein expression are highest in the dopamine neurons of the substantia nigra, which is why they are thought to be most sensitive to the prion-like spread of alpha-synuclein aggregation. However, it isn't clear quite how the problem goes from a single fibril to a systemic invasion — whether, for instance, aggregates get deposited by dead or dying cells and taken up by other cells.

"I think everybody in the field more or less agrees that there are intrinsic factors in some neurons that make them more susceptible (to alpha-synuclein aggregation)," said Burton, the Pittsburgh-based physician-scientist. "The question is whether the temporal cascade of pathology is spreading physically, or whether there is a systemic problem that affects each population of neurons in order of their susceptibility."

In either case, the first fibril of alpha-synuclein must form somewhere, and researchers have identified potential culprits.

"If environmental factors involved in Parkinson's disease trigger alpha-synuclein pathology, the gastrointestinal tract is a really good candidate for the site of initial aggregation," Burton said. "The gut presents a huge surface area that could be exposed to environmental toxicants."

A short-chain puzzle

Acetate, propionate and butyrate, the three short-chain fatty acids Sarkis Mazmanian's Caltech lab added to the water of germ-free mice, are products created when microbes break down dietary fiber. In that study, feeding germ-free mice predisposed to Parkinson's disease short-chain fatty acids tended to trigger Parkinson's-like symptoms.

Studies in humans show an inverse correlation between levels of short-chain fatty acids and Parkinson's and generally find a reduction in levels of the molecules in stool samples from people with the disease. Fiber, which is broken down into short-chain fatty acids, has been proposed to play a role in the lower age-specific prevalence of Parkinson's disease in Africa and India, where consumption of vegetables is higher. Some work has linked butyrate to neuroprotection and diminished symptoms in mouse and fly models of Parkinson's, though early clinical studies of a butyrate derivative for Parkinson's patients have no reported success.

Acetate appears to be the odd chain out. While butyrate and propionate are known to activate a subset of G-protein coupled receptors, inhibit histone deacetylases and suppress inflammation through regulatory T cell, acetate doesn't share these roles. Short-chain fatty acids are known to promote intestinal contraction and affect immune signaling and gene expression.

The contradiction between Mazmanian's finding and other studies has yet to be explained.

The environment

Researchers have identified an array of molecules, including pesticides and bacterial byproducts, that can trigger symptoms of Parkinson's in animal models. While it is not clear why giving each of these molecules to rodents induces alpha-synuclein aggregation, they reliably cause both Lewy body formation and motor symptoms similar to those observed in Parkinson's patients. Several mechanisms have been proposed.

"It's quite possible there are multiple different ways you can enter the pathophysiological cascade" that leads to spreading alpha-synuclein pathology, Burton explained.

Some of the chemicals also have been linked to the disease in humans.

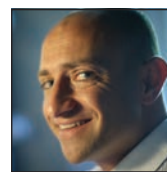
One such pesticide, paraquat, is a precursor to a neurotoxin that resembles dopamine. Once metabolized into the neurotoxin, the molecule enters cells through a dopamine transporter and kills them.

Another precursor to the same toxin is a chemical byproduct of opioid synthesis. Its neurotoxic effect was discovered after a drug user, who was also a graduate student in chemistry, injected himself with an impure home brew and developed Parkinson's symptoms just days later. The man suffered from Parkinson's for the rest of his life; an autopsy found alpha-synuclein aggregates in his brain.

Another pesticide, rotenone, was commercially available until an epidemiological study published in 2011 showed that exposure to it increased farm workers' risk of Parkinson's. Although rotenone, which blocks mitochondrial respiration, is in principle available to every cell in the body, dopaminergic cells seem the most sensitive to the stress of coping with the toxin.

Man-made compounds in the environment may not be the only culprit.

In a 2016 study published in the journal *Cell*, researchers from Sarkis Mazmanian's lab at the California



MAZMANIAN

Institute of Technology showed that while overexpression of alpha-synuclein can predispose mice to Parkinson's, keeping the mice in germ-free conditions protected them.

"If mice received microbiota from a human donor, they had worse motor symptoms than mice that received microbiota from a health control," Mazmanian said. These results suggested that a bacterial product in, or from, the gut might cause the first seed to form in a host cell.

A variety of bacterial products have been proposed. One possibility is that one or more prion-like bacterial proteins may act as a seed. Alpha-synuclein is just one of many proteins, termed amylogenic, that tend to misfold and aggregate into amyloid fibrils. Matthew Chapman,



CHAPMAN

a microbiologist at the University of Michigan who began collaborating with Mazmanian's group after their 2016 paper, studies

proteins in bacteria that share many of alpha-synuclein's structural properties.

"It's possible that functional amyloids made by things in the microbiome could 'seed' human proteins," Chapman said. "Therefore, it is possible that a seed provided by a bacterial functional amyloid could be the trigger or nucleator."

Other researchers, including a South Korean team headed by Myung Sook Oh, have proposed that a non-protein molecule from bacteria in the gut may trigger alpha-synuclein aggregation. Lipopolysaccharides are a broad class of sugar-linked lipids from the outer membrane of many bacteria and are well-known triggers for inflammation. Biochemical experiments showed that when lipopolysaccharides were mixed with purified

alpha-synuclein, toxic fibrils formed more readily than they would in a solution of alpha-synuclein alone.

Lipopolysaccharides also have been shown to trigger Parkinson's in animals, potentially due to long-term low-grade neuroinflammation after they are introduced to the eye or the gut. Oh's lab reported in January in the journal *Scientific Reports* that in several pesticide-induced mouse models of Parkinson's, they found upregulation of a single gut microbe, *Proteus mirabilis*.

The researchers isolated lipopolysaccharide from the bug and added the molecules to mice that had been exposed to a pesticide level previously too low to develop Parkinson's symptoms. The addition caused the mice to develop symptoms.

Likewise, Mazmanian's group found that mice bred to over-express alpha-synuclein could be pushed to develop Parkinson's symptoms by receiving a fecal transplant from a Parkinson's patient.

However, their study also found that feeding the mice a sterile mixture of three bacterial metabolites known as short-chain fatty acids could trigger the motor and non-motor symptoms of the disease — even though, unlike lipopolysaccharide, the short-chain fatty acids could not seed aggregation independently.

These metabolites are not exotic; every person's gut has microbes that make short-chain fatty acids. This finding also appears to be at odds with studies in humans demonstrating that short-chain fatty acids are helpful, not harmful, in the onset of Parkinson's (see sidebar: "The short-chain conundrum").

Interestingly, Mazmanian's group also found that germ-free mice that received a specific mixture of short-chain fatty acids seemed to have neuroinflammation triggered by the activation of microglia in the brain — another role for the molecules at odds with their regular function.

Brain inflammation

The main immune cells governing neuroinflammation are microglia, a strain of glia that are derived from the same stem cells as macrophages. Like macrophages throughout the body, microglia are tissue-resident cells that can sense infectious agents and eliminate them through phagocytosis.

Marina Romero-Ramos, a neurobiologist who studies microglia at Aarhus University in Denmark,



ROMERO-RAMOS

noted that in animal models of Parkinson's disease, activated microglia cluster in areas where Lewy bodies are especially dense.

This immune response mimics the response found in autopsies of Parkinson's patients and seems to suggest that the microglia are responding to the neuronal event initiated by alpha-synuclein, she said.

"For many years, it was thought that microglial activation came as a consequence of initial cell death of neurons," Romero-Ramos said.

In this classic view, microglia were activated by dying neurons and responded harshly with a neuroinflammatory response that did further damage to surviving cells. However, researchers now know that microglial activation starts much earlier. Romero-Ramos said that, because they constantly survey the tissue around them, microglia respond early to very small changes in neurons. In other words, they may get involved before neurons begin to die.

Mazmanian's study did not examine whether microglia were activated directly by the bacterial metabolites; they may have been responding to immune events initiated by the metabolites elsewhere in the body. But Romero-Ramos allows that, because the molecules are lipid-soluble, "in theory, (SCFAs from the gut) could reach any cell in the body. They could reach neurons, or they could



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Sarkis Mazmanian and his colleagues at the California Institute of Technology are currently attempting to identify a single microbe, or microbes, that may be responsible for the aggregation of alpha-synuclein in the human gut.

reach immune cells.”

Inhibiting microglia using a small molecule, minocycline, reduced inflammation in the brain and delayed the onset of Parkinson’s-like symptoms in Mazmanian’s study. So, should inhibition of microglia be regarded as a promising treatment for Parkinson’s? It’s a complicated question, Romero–Ramos said.

Research by prominent glia biologists in the last decade has shown that microglia are key contributors to synapse pruning and neuronal circuit formation during development and also may be important for cognition in adults. And even when activated and releasing cytokines, the protein factors that drive inflammation, the immune cells can release pro-survival factors that keep neurons alive. Moreover, a study of how cells degrade external alpha-synuclein aggregates found that microglia can remove and destroy the aggregates more efficiently than any other brain cell type.

“Many of the studies up to now were very focused on quieting microglia, and that has proved not too successful ... I think it’s because we knew very little about the microglia,” Romero–Ramos said. She believes that future Parkinson’s treatments will modulate microglial activity, but that before such treatments can be developed, we need to understand the cells better.

“In the future, most likely, treatments will combine something that is focused on neurons, with probably a second drug that is focused on the immune cells as well,” she said. “Unless we really find the cue to why alpha-synuclein aggregates, I am pretty sure that our therapy will be a combined therapy.”

The search for a drug

As researchers propose possible future treatments, the Parkinson’s patient community is instrumental in helping test these therapies in clinical trials. By Woolnough’s count, he has

participated in 21 studies.

“If I see something that I’m eligible for and that fits my timeline, I’m ready to jump all over it,” the retired high school principal said. “I’ve got two sons and three grandsons. That’s why I do it.”

Woolnough likes to say that Parkinson’s gave him a part-time job to keep busy in retirement. Besides participating in research, he writes a column for a local newspaper and serves as a patient member of grant review committees for the Parkinson’s Foundation and the Department of Defense. Last year, he joined fellow patients and a few llamas on a fundraising hike, an endeavor he wryly refers to as “60 miles on the Pacific Crest Trail that nearly killed me.”

He has volunteered for a number of observational trials, which aim to deepen understanding of the disease without interfering with the ordinary course of treatment. One research group sent him an accelerometer-enhanced smart watch to monitor his tremors continuously from home. Another took a spinal tap, blood samples, and biopsies from his salivary gland and colon to establish whether alpha-synuclein aggregates reliably appear outside the brain during disease, and if so, where within one person a diagnostic should be targeted.

Woolnough isn’t involved in any tests of new drugs at the moment. But several clinical trials for Parkinson’s are underway, some aimed at improving quality of life and others testing interventions that scientists hope will stop the spread of alpha-synuclein aggregates. These include immunization or monoclonal antibodies against alpha-synuclein. Another trial, due to be completed in 2019, tests a calcium channel blocker that currently is used to control blood pressure, on the hypothesis that it may protect dopaminergic neurons.

In contrast to therapy to block the progression of Parkinson’s, which

has proved elusive, new therapies to improve patients' quality of life have become increasingly available. For example, several supplementary drugs to treat side effects of levodopa, the most commonly prescribed drug for Parkinson's, became available last year.

Many molecules have failed, however, at disease modification — so many that some major pharmaceutical companies are cutting their investment in research and development for neurodegenerative disorders. Earlier this year, Pfizer announced that it would drop funding for its neurodegeneration programs; AstraZeneca sharply reduced its neurosciences division in 2016.

Some of this disinvestment is informed by failures of drugs to treat Alzheimer's disease, which is more common than Parkinson's and has a similar neurodegenerative mechanism driven by protein aggregation. Over the last two decades, Pfizer sponsored close to 100 clinical trials for 24 potential drugs to treat Alzheimer's, only one of which ultimately was approved. That drug, Aricept, is used to treat the dementia that the disease brings, rather than targeting the beta-amyloid plaques responsible for neurodegeneration.

Despite this news, Gregory Petsko, a biochemist at Weill Cornell Medical College, is hopeful about the future



PETSKO

of Parkinson's treatment.

"In a sense, this is easier to deal with than cancer," he said, "You've got to kill every cancer

cell, or you know what could happen. But, here, if you delayed the onset of Parkinson's disease by 20 years, on average, we wouldn't be having this conversation, because this would no longer be a major health problem."

A handful of startup drug companies are looking to tackle Parkinson's disease in the gut.

Enterin, a pharmaceutical company Georgetown's Zasloff founded in 2014, recently concluded a clinical trial assessing the safety and tolerability of a synthetic squalamine derivative, ENT-01, in patients with Parkinson's disease. Squalamine is an antimicrobial originally isolated from dogfish sharks in 1993 in Zasloff's lab. The company hopes to show that ENT-01 is useful for treating Parkinson's-related constipation.

Like squalamine, ENT-01 prevents aggregates from forming in purified alpha-synuclein samples. In cultured cells, squalamine has been shown to displace aggregates of alpha-synuclein from the lipid membranes of neurons. In a model of Parkinson's disease in the roundworm *Caenorhabditis elegans*, it was shown to inhibit the formation of toxic alpha-synuclein aggregates and prevent the onset of paralysis.

Zasloff believes the alpha-synuclein that aggregates in the gut is a product of the body's immune response to gastrointestinal infections.

"In the normal, day-to-day life of the gut's nervous system, it is expressing alpha-synuclein to either protect itself or the local milieu that it lies within, within the wall of the gut, and it does so by calling in a variety of white blood cells and by alerting the immune system," Zasloff said.

In an unusual move for a trial testing an intervention for neurodegeneration, Enterin's clinical trial did not try to measure neurodegeneration or changes in movement among patients. Instead, it focused tightly on the gut, looking for a change in constipation.

"The trial was meant to test the hypothesis that (the squalamine derivative) could reverse the functionally inactive enteric nervous system of an individual with Parkinson's," Zasloff said.

The investigators also watched for effects of ENT-01 on the motor symptoms, mood changes, sleep dis-

Parkinson's in women

Another quirk of one of the most complicated human diseases turns out to be its higher incidence in men than in women. On average, men have 1.5 times the risk of developing Parkinson's as women, and women tend to develop Parkinson's two years later than men; however, no definitive explanation exists for this disparity. One hotly debated hypothesis involves levels of estrogen, which are believed to play a role in dopamine synthesis and help modulate dopamine receptor function. Other hypotheses involve genetic risk factors that are X chromosome-linked, which makes the genes more likely to be inherited in men. Disparity in careers that put workers at a higher risk of head trauma or increase exposure to environmental toxins may also be to blame.

ruptions and hallucinations associated with the disease.

Data from this clinical trial are still being analyzed. Zasloff and his colleagues are planning a more rigorous clinical trial early next year, in which a larger group of patients with severe constipation will receive the drug for several months.

This isn't the first time Zasloff has gone through clinical trials with derivatives of squalamine. His first drug company, Genaera Corp., founded in 1989 as Magainin, conducted, but ultimately halted clinical trials exploring squalamine's ability to treat prostate cancer and a severe form of macular degeneration by blocking blood vessel growth.

Zasloff is optimistic that squalamine can be used to treat a number of complex neurological conditions, including schizophrenia and autism; he and Enterin are slated to begin early trials with ENT-01 for both disorders in 2019.

Mazmanian, at Caltech, also has a startup exploring the role of the gut-brain axis in Parkinson's disease. In 2013, Mazmanian helped found Axial Biotherapeutics, based on earlier work from his lab that attributed autism-like symptoms in mice to a deficiency of either the bacteria *Bacteroides fragilis* or its metabolites. Last fall, the company's CEO stated that they intend to bring at least one therapy for autism to early clinical trials this year, and the company has indicated that it is developing a Parkinson's therapy based on work from Mazmanian's lab. Like Enterin, Axial aims first to measure the effects of its interventions on patients' GI function rather than the movement symptoms that are more typically used to measure the disease.

While drug companies inch forward, patients have attempted to take treatment into their own hands with nutrition — and less savory actors have sought to take advantage of them.

Nutrition and snake oil

"When I go to my neurologist — and I know this is the case for the vast majority of patients—there's no talk of nutrition," Stecher said.

Doctors rarely make nutritional recommendations to patients with Parkinson's, and reputable patient-education groups issue the mildest of healthy-eating guidelines, recommending a balanced diet with plenty of fiber and water.

Stecher rattled off a list of supplements, including vitamin D and coenzyme Q10, that have been tested based on promising preclinical data but failed to show a consistent effect in patients.

"There are so many things that have been associated with having a neuroprotective effect," he said. "But actually identifying which ones are truly neuroprotective and which ones people should be taking? We're not there yet."

Epidemiologists have found some habits, such as cigarette smoking and coffee drinking, that dramatically reduce the risk of developing Parkinson's disease. However, large-scale clinical trials testing whether nicotine or caffeine could help patients proved futile.

There may be no clear data on proper nutrition with Parkinson's, but a wealth of questionably sourced diet books purport to have the answers, according to Michael Okun, the chair of the University of Florida's neurology department and the medical director of the Parkinson's Foundation.

"Just like every disease, there's a cottage industry," Okun said. "The harsh reality in Parkinson's disease,



OKUN

in my opinion, is the businesses have popped up before the data and the science is really there."

Plenty of patients, credulous or desperate, don't

want to wait for randomized controlled trials. In A.C. Woolnough's support group, he said, patients often pass along rumors about supplements or alternative treatments.

"I say, 'You know what? Show me a randomized double-blind study with a placebo, (and) I might take your word for it,'" he said. "It may be perfectly true. But can it be replicated?"

Okun takes a similar attitude. Much of his time both in the clinic and on the Parkinson's Foundation website, where he runs an "Ask the Doctor" forum, is devoted to pointing patients toward reliable sources of information. He acknowledges that patients eager to try alternative therapies may be on to something, but cautions that they may be taken advantage of.

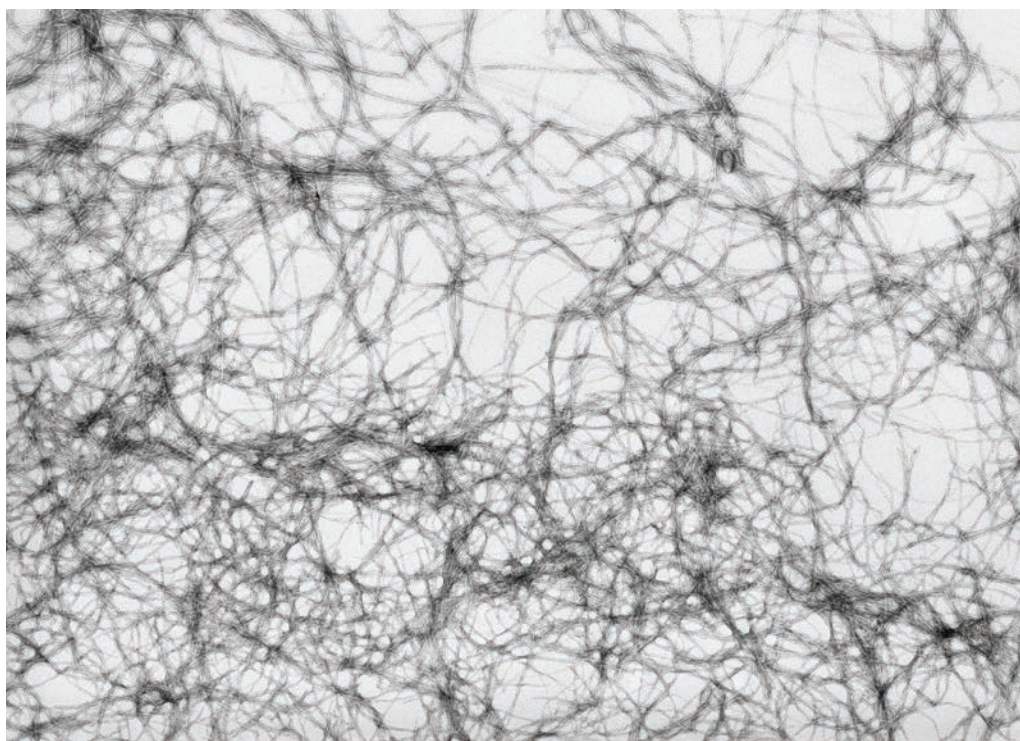
"There's oftentimes a sales pitch that goes with (an alternative therapy), that you've got to keep going with the vitamins or keep going with the nutraceuticals," he said. "We've seen people drain their savings."

A bag of chemicals and cells

Scientists have their work cut out for them determining why alpha-synuclein misfolds and how it can be prevented. Mazmanian and his colleagues are currently sharpening their focus on single microbes that may cause the onset of sporadic cases of Parkinson's.

In the meantime, researchers are walking a high-wire, balancing optimism for the possibilities of new treatment on one side with overselling their findings on the other.

"Because there's nothing for these diseases, this field is really susceptible to fads, so many things have failed, right?" Petsko said. "Anything new that comes along, people jump on like crazy in the hope that it might work. That sounds like a criticism, but it isn't."



COURTESY OF CHAPMAN LABORATORY

But the research enterprise itself is fascinating. Just ask Stecher.

While he writes his blog primarily as a service to other patients, the work seems to do Stecher a lot of good, too. "Even though Parkinson's itself sucks, and daily it can be quite a hassle, I am somewhat thankful that it's opened my eyes to the world of biology.

"At the end of the day, we are just a bag of chemicals and cells and proteins that kind of chaotically interact with the environment and the world around us. Prior to being diagnosed with Parkinson's and delving into all this research, I had no real basis for appreciating that. Now that I do, it's something that fills me with awe and wonder."

One potential hypothesis for the aggregation of alpha-synuclein is that bacterial amyloid fibers provide a 'seed' that triggers misfolding of the protein.



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Sinking goals and skating on cellular surfaces

A new associate editor at the Journal of Biological Chemistry interrogates bacterial polysaccharides and sustains football fandom

By John Arnst

As the medical landscape rapidly runs out of effective antibiotics, novel treatments for pathogenic bacteria will need to pick up the slack. At the University of Guelph in Ontario, Canada, Christopher Whitfield and colleagues are investigating therapeutic approaches that focus on the myriad polysaccharides that can cover the surfaces of bacteria.

A professor in the university's department of molecular and cellular biology, Whitfield was born and educated in the United Kingdom, where he earned his bachelor of science in bacteriology from the University of Newcastle upon Tyne in 1976 and his Ph.D. in microbiology from the University of Edinburgh in 1979. After completing postdoctoral fellowships at the University of California, Davis and the University of Calgary, Whitfield started his lab at the University of Guelph, where his group works on the structure and assembly of bacterial cell surfaces.

Whitfield joined the ranks of associate editors at the Journal of Biological Chemistry in January 2017. He spoke with John Arnst, ASBMB Today's science writer, about his work.

The interview has been edited for clarity and length.

What is your group focused on?

We are interested in how bacteria assemble complex carbohydrates on their surfaces. Carbohydrate structures play pivotal roles in host-pathogen interactions, so they are potential points for therapeutic intervention, but these kinds of applications have to start with a fundamental understanding of bacterial physiology and cell biology.

One strategy would be to use small-molecule inhibitors to turn off production and render the bacteria susceptible to our normal immune defenses. We are investigating compounds coming from high-throughput screens we performed as part of a collaborative team within GlycoNet, a cross-Canada National Centre of Excellence focusing on glycomics. The cellular targets are found in a range of important pathogens including extraintestinal *Escherichia coli* and were identified and prioritized

through discovery-based research.

An equally important approach is through vaccines. Surface carbohydrate-based vaccines have had a huge influence on global health — the pneumococcal vaccine is a great example. One of the challenges with vaccine approaches is knowing how many structural variations exist in nature. If you're going to make a vaccine, how many components does it have to have in order for it to offer protection against a bacterial species that's a bit more variable?

Take pneumococcus as an example: There are 90-odd capsular polysaccharide types, potentially more due to recombination. If you wanted to protect against everything, you'd need so many different elements in the vaccine cocktail that it wouldn't be feasible. So researchers end up looking at what is the least number of capsular polysaccharide types that will give you the best possible coverage. But to do that, you need information about the structures that exist and what's represented in large clinical collections; asking those kinds of questions starts with good carbohydrate chemistry, knowledge of assembly pathways and access to high-throughput sequencing approaches.

One organism we're quite interested in at the moment is *Klebsiella pneumoniae*, which causes a variety of different infections, including lung infections, urinary tract infections and bloodstream infections.

Klebsiella infections have been treated with broad-spectrum antibiotics, but because of the spread of antibiotic resistance, new approaches are needed. Immunotherapies become much more important under these circumstances. One possibility being pursued in the field is giving people antibodies to protect them (known as passive immunization). We are looking at candidate polysaccharides and mechanisms by which they might vary.

Another one of the organisms



Christopher Whitfield

we're doing a lot of work with at the moment is a *Salmonella* serovar that causes typhoid fever. We're looking at it from a different perspective; there already are vaccines available, and a surface polysaccharide is an important component, but the way in which the cells produce that polysaccharide is quite different from what we would have anticipated. We're trying to unravel the details of how those polysaccharides are made.

What was your academic background and research training?

My undergraduate program at the University of Newcastle gave me my first exposure to microbiology and led me to change degrees. On graduation, I was considering a job opportunity as a government scientist, but a Ph.D. offered me a chance to follow my scientific interests. I studied the production of xanthan gum, a bacterial polysaccharide used as a food additive, among other things. During that program, I had become interested in biochemical approaches to investigate such systems and was really impressed by a paper published by Rick Troy and colleagues — in *JBC* — and that led me to apply to Rick's lab at the University of California, Davis, as

a postdoc. It didn't hurt that, after so long in the north of England and Scotland, I was looking for something in a better climate.

I followed that with a postdoc at the University of Calgary, where I was able to start building some genetic tools. The first cloning and heterologous expression of a gene cluster for bacterial polysaccharide synthesis had just been reported, and it was clear this would transform the field. From there, I moved to a faculty position at Guelph.

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

A lot of it was following my interests. And great opportunities seemed to come along at the right time. I was lucky in that respect. The climate is now so much more demanding, and the level of planning needs to be much higher to have success. Certainly, the excitement of seeing the first results from my own work led me to being hooked on scientific research. Even if it is now more of a vicarious experience, through the work of my group, the opportunity to work with bright young scientists is, without doubt, an aspect that keeps me motivated.

When did you first become involved with JBC?

I published in JBC as a postdoc and first became an editorial board member in 2001. After one term, I took a break for a while, rejoining in 2013, and Lila (Gierasch, JBC editor-in-chief) persuaded me to become an associate editor. Last year, my son published his first JBC paper. His research focuses on exercise physiology and mitochondrial function. He's now a postdoc at Australian Catholic University.

What does it mean to you on a personal level to be an associate editor of JBC?

It's rewarding to be so closely associated with a journal that has the history of JBC. My goal is to see JBC become home for more of the excellent microbial biochemistry and cell biology research that is going on. As a bonus, I get to see a broad range of fascinating work in areas I might not read otherwise and interact with a great bunch of people on the board and among the staff of JBC.

There is a feeling of responsibility with this position. People are trusting you with their work, and I think you feel the responsibility to make sure you do the job fairly and rigorously. You'd like to believe you got the decisions right every time, but that is occasionally not the case. In any kind of area where you're judging things, you certainly don't want to be in a position where you made the wrong decision because you didn't put the work in.

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

My wife would laugh at that question. Balance? We are both devoted fans of football — the real one. My wife is a Chelsea fan, and I support Newcastle. We have very different positions in league standing at the moment, and unfortunately I don't hold bragging rights. I still play somewhat competitively, depending who you ask, and we are season ticket holders for Toronto FC. We also have a couple of energetic dogs that demand our attention.

One of the unanticipated benefits of this career has been the opportunity to travel. With our kids now out on their own and doing well, we



COURTESY OF CHRIS WHITFIELD

Chris Whitfield often enjoys time outdoors with his Australian shepherds Callie (left, 6 years old) and Jake (right, 5 years old).

have had more opportunity to travel together. We like Australia a lot and are planning another trip, and we've always had a really good time there. Italy we liked a lot, and we go to the U.K. at least once a year or so.

For scientists in training, do you have any words of wisdom?

First of all, pursue a scientific field because you are passionate about it and not because of a perception of what is trendy. It's hard to predict where the next great breakthrough will come from. Who would have pre-

dicted the impact of CRISPR-Cas9? More importantly, if you aren't happy and motivated, success will be hard to achieve.

Recognize that the communication, problem solving, critical thinking and perseverance skills you learn as a researcher all have value beyond being an academic scientist. Former members of my group are pursuing a lot of different avenues leading to satisfying careers.



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

How to serve up a killer research seminar

By Bill Sullivan

The introductory remarks are over, and the lights have dimmed.

You settle into your chair with cookie and coffee in hand, waiting to be wowed by today's seminar speaker. Less than 10 minutes into the hour, you realize this speaker is going to be a disappointment. The talk is incoherent, you're suffocating under an avalanche of data and a hypothesis is nowhere to be found. As if that's not bad enough, you accidentally took an oatmeal-raisin cookie instead of chocolate chip.

There's only one thing worse than sitting through a mind-numbing seminar, and that's delivering a mind-numbing seminar. To avoid this fate, I've developed a formula for science communication that should help you dazzle the audience every time. This formula is not only useful for research seminars but also works for other forms of science communication, including grants, papers, blog posts and popular science articles.

The trick is to be a good server.

When I go out to enjoy a meal, the quality of the experience is not limited to the cuisine. Whether it will be a night to remember or one I can't wait to forget is largely influenced by my waiter or waitress. From the moment you open a blank PowerPoint file to the moment you step down from the podium, that is the role you should assume. Your science is the entrée, and it is your job to serve it up so the audience will walk away satisfied.



The appetizer

The best meals are prefaced by a starter plate that pairs well with the main dish. Ideally, the appetizer should be tasty but small, leaving the patron salivating for more. The best appetizer in a research talk presents an unsolved problem. Everyone loves a good mystery, so this is a delectable way to pose your research question. Some examples: How does protein X contribute to the development of disease? How does cellular stress increase expression of gene X? How does compound X kill cancer cells? How do parasites modify their host's behavior? The data you present during the main course will later be savored as clues in your detective story.

Keep in mind that we scientists study small but important pieces of larger puzzles. When setting up your seminar, it is imperative to orient the audience to your specific puzzle piece, not so much the larger puzzle. For example, everyone knows how

nasty cancer is, but we are less likely to know the details concerning the gene or pathway you decided to study. If you fail to educate the audience about your system at the get-go, you will lose them to daydreams. Virtually any research question will captivate an audience if you frame it as a mystery.

Like a good server who patiently describes unfamiliar items on the menu, be sure to define jargon early. It is preferable to leave alphabet soup off your menu, but if you must use some biotech babble, it is your job to explain it carefully and clearly.

Take care not to fill a patron's stomach to capacity before you get to the main course; keep the appetizer light. A common mistake is to present overwhelming extraneous details right out of the gate. Stop and think: Does the audience really need to know this to understand my specific research question? If not, leave it out. What you must include are details relevant to the formulation of your hypothesis.

If you set the stage properly, your audience should be able to guess your hypothesis before you state it.

Take no more than 10 minutes to complete the appetizer.

The main course

In the finest restaurants, the entrée is simple and elegant, not an all-you-can-eat jumble of 30 different foods thoughtlessly piled on top of one another. The latter, called a “data dump,” is another common mistake in research seminars. You want to avoid stuffing your audience with a buffet of data. Present only the cream of the crop, not every single experiment you’ve done in the last few years. There is no need to show results that have little to do with the specific research question your seminar is addressing. By cutting out the fat, you’ll have sufficient time to walk people through each experiment so they understand the assay well enough to interpret the data on their own.

Remember that people want to feel satisfied after a meal. No one enjoys the indigestion that results from eating too much too fast. Instead of trying to cram too much down your audience’s gullet, focus on select pieces of evidence in greater detail. Describe how these results shed light on the mystery (or how they complicate it). Rather than feeling the need for a cognitive antacid, your audience should walk away from your talk with a sense of satisfaction, a sense that

they learned something.

Some people like to incorporate humor into their research seminar to spice things up a bit. No problem. However, treat humor like dinner wine. In moderation, it can enhance the meal’s flavors, but too much dampens the taste buds. A few laughs can season a talk to perfection, but excessive humor becomes distracting. Similarly, small doses of humor can loosen up the audience, but too much and you’ll look like a goof.

Take about 25 minutes to complete the main course.

Dessert

It’s the moment we’ve all been waiting for. Time to solve the mystery you presented at the outset. If you have an experimental finding that unequivocally addresses the hypothesis, now is the time to show it. If you don’t, it is time to review the evidence you’ve amassed so far. Either way, by discussing your results in the context of the appetizing research question, you will give your seminar a memorable finish.

The best way to conclude your seminar is to restate the mystery (your research question), summarize the clues (your experimental findings), and construct a model that solves the mystery (or at least gets you closer to an answer).

Take no more than 10 minutes to complete the dessert — it should be short and sweet.

Service with a smile

Frustratingly, many seminars drag on beyond the allotted period and leave little time for questions. You don’t want to deprive your colleagues of the chance to ask questions, and you don’t want to miss hearing what they think. Limiting yourself to a 45-minute talk leaves ample time for questions.

As with a good server, professionalism and courtesy continue to be of utmost importance. Do not interrupt the audience member by rushing to answer. Taking a moment to repeat the question is helpful for two reasons: one, it ensures that you’ve correctly captured what is being asked, and two, it helps others in the audience who could not hear the question. As you address the question, it is critical to be polite and unassuming; never be condescending and arrogant.

Finally, never slam the reviewer comments of your grants or papers during your talk; those folks might be in the audience.

If you follow these simple tips and serve up your research question like a good meal, you can bet people will request you the next time they have a hankering for science. They may even tip you with an honorarium.



Bill Sullivan (wjsullivan@iu.edu) is a professor at the Indiana University School of Medicine. Follow him on twitter @wjsullivan.

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Bridging the gap between research and treatment

By Michelle L. Gumz

I found the papers on PubMed six months too late. It was July 2008, and my mom, after having received the news that she was in “complete pharmacological remission” a month prior, had just been diagnosed with multiple brain metastases from triple-negative breast cancer. The papers I found showed that TNBC was much more likely to metastasize to the brain than other forms of breast cancer. If I had seen these reports sooner, I would have demanded that my mom get a brain MRI, and maybe they would have caught it sooner. My mom died on Sept. 1 at the age of 53.

I have since made peace with the fact that I couldn't save my mom. I did take an important lesson from this tragedy.

My mom's initial diagnosis came just six months after I had a radical hysterectomy for a rare form of cancer. Having completed postdoctoral training in cancer biology in 2006, my anxiety levels were through the roof. I remembered quite well the molecular biology horror show that is a cancer cell. Although my lymph nodes had come back clear and I didn't require additional therapy beyond surgery, I worried about the clonal theory — that just one cell might be hiding somewhere and would later result in a recurrence. My cancer was stage IB, and all of my doctors assured me the chance of a



COURTESY OF JESSE JONES/UNIVERSITY OF FLORIDA HEALTH

Michelle Gumz is shown in her lab at the University of Florida where she researches molecular circadian control of renal function.

recurrence was extremely remote.

Following her breast cancer diagnosis, I assured my mom she would be fine. There are targeted therapies for breast cancer, I told her. If you have to have cancer, this is the kind you want, I tried to comfort her. The TNBC diagnosis came a month later. I had never heard of it. There was no targeted therapy.

Still, I made a conscious decision to trust my mom's doctor. She was being treated at a premier cancer hospital, ranked in the top 20 nationally, and we were sure she was in the best hands.

Her oncologist was surprised at the brain metastasis articles I found in

PubMed, because the prevailing understanding at the time was that Her2neu-positive tumors were the “worst” type of breast cancer. My mom received the neoadjuvant standard-of-care treatment at the time: doxorubicin, cyclophosphamide and paclitaxel. She could feel the tumor shrinking on a weekly basis, and her doctor assured us the treatment course was going well. We celebrated after her surgery when she was given a clean bill of health.

The blinding headaches, inexplicable vomiting and debilitating pain in her limbs began just a few weeks later. Looking back, I know these were clear signs of CNS involvement, yet her doctors assured her she was just experiencing the aftereffects of the chemotherapy leaving her system.

By the time she had a brain MRI, it was too late. Despite receiving whole-brain radiotherapy in addition to intrathecal chemotherapy for seven metastatic lesions on her brain, my mom went on hospice toward the end of August 2008 and died a short time later.

We will never know if a brain MRI early on would have saved my mom's life. What I do know is that physicians can't know everything there is to know about each subtype of each of the diseases they are treating. Although they are trained to tailor treatment for individual patients,

physicians operate within guidelines that are based on established, population-level data rather than the very latest findings from basic and clinical research.

Doctors increasingly spend more and more time fighting insurance companies and seeing as many patients as possible due to decreasing reimbursement rates, making it impossible to stay on top of the very latest advances that haven't yet made their way into clinical practice guidelines.

They need our help.

Nothing can bring my mom back, but after her death I vowed that I would never again bury my head in the sand instead of using my training to investigate the most recent findings in medicine on behalf of my loved ones.

I lucked out with an amazing oncologist when my cancer recurred in 2011. He had done postdoctoral training at the National Institutes of Health and was truly an outside-the-box thinker. At first, none of my other doctors agreed with his plan for me. He argued that my cancer was unusual and needed to be treated as such. I received truly personalized medicine before that phrase became popular. I firmly believe I am alive today because of it. A year or two later, I ran into one of the doctors who had argued that all I needed was standard-of-care treatment. That doctor was obviously surprised to see that I was alive and well.

My novel course of treatment included a chemotherapy regimen very similar to what is used for ovarian cancer. I received carboplatin plus Taxotere in a sandwich design bracketing the standard-of-care treatment, which at the time was cisplatin plus radiotherapy.



COURTESY OF MICHELLE GUMZ

In this family photo taken in November 2007, Michelle Gumz sits between her mother, Mary Lou "NuNu" Miller, on the left, and her sister, Melanie Lindquist. The three women were diagnosed at different times with different forms of cancer.

During my treatment, my oncologist set me up on a "chemo date" with a woman fighting ovarian cancer who was close to my age. We were the youngest people in the infusion center, and we became fast friends.

After our physician-scientist oncologist retired, my friend had to switch to a different oncologist who was, unfortunately, an inside-the-box thinker. When my friend's ovarian cancer recurred, the only option her team offered was doxorubicin, which is considered a drug of last resort for that type of cancer and is associated with severe side effects that drastically reduce quality of life. I reached out to a former colleague working in industry drug development for female cancers and learned about the newly approved PARP inhibitor oliparib, sold as Lynparza.

Had my friend received the doxorubicin regimen, according to the population-level outcomes, she would have been expected to have about 12 months to live. Although her medical team never even mentioned the availability of a brand-new FDA-approved drug with outstanding clinical trial results, she asked for and received Lynparza, which she qualified for due to her BRCA status and previous response to other therapies. Two

years later, her disease is stable and she is enjoying a full life. She did her own research and basically demanded that she receive personalized medical treatment.

As scientists, this is something we can help our friends and family with. For the lay public, the difference between a Google search and a PubMed search may mean the difference between spiraling into a morass of misinformation on nonmedical and nonscientific websites

versus accessing the most recent state-of-the-art findings at the forefront of medical research.

Cancer hit close to home once again last summer with my sister's diagnosis of a rare form of uterine cancer. I went to the literature to check the treatments she was being offered, and I reached out to my former colleagues in cancer research and my wider network from my own training period. What I found was that my sister was being offered the best possible treatment course. I traded PubMed articles with my sister's oncologist, who was perhaps not overly thrilled at my involvement, but I needed to do my due diligence.

As a principal investigator of a biomedical research lab, I emphasize the importance of networking for the career development of my students and postdoctoral trainees. This was an important part of my own training, and although I never doubted the importance of my network for the advancement of my career, I never imagined how important that network would become in terms of its lifesaving potential.

Michelle L. Gumz (michelle.gumz@medicine.ufl.edu) is an assistant professor of medicine at the University of Florida.

His career is all in the timing

At the University at Buffalo, D. Fernando Estrada, an assistant professor in the biochemistry department, and his lab study the structure and function of class I cytochrome P450 enzymes, with special emphasis on those that affect vitamin D availability.

Estrada earned his associate's degree at Dodge City Community College, his bachelor's in biochemistry at Kansas State University and his Ph.D. in biochemistry at the University of Kansas.

In this month's Research Spotlight, he talks about finding his way to science, serving as an officer in the U.S. Army and becoming an academic researcher. The interview has been edited for length, style and clarity.

How did you first become interested in science?

I was definitely a late bloomer. In high school and for most of the first two years attending a community college, I still didn't know what it was that I wanted to do. I first became interested in becoming a science major when I took an organic chemistry course from a professor named Ron Albrecht. At the end of the course, the last section covered biomolecules, and it was easily the most fascinating to me. That's when I knew what I needed to major in. But even then, I had a different career in the military before I started toward a career in science. I think there's a conception out there that all scientists are struck with an early curiosity about the world and know right away that science is for them, but of course that isn't true. Many people in science come to it on their own terms and in their own time.

What key experiences and decisions got you where you are?

First, my particular career path included a seven-year tour of duty as an active-duty Army officer. In hindsight, those years I spent away from science turned into a significant growth period for me. When I returned to science for graduate school, I felt I had gained important perspective and was a much better student and researcher than I would have been otherwise.

I was also fortunate to have been involved in a training program while at the University of Kansas called the Madison and Lila Self Graduate Fellowship. This program seeks to develop graduate students outside of the lab in areas such as entrepreneurship, project management, negotiation, and communication skills, among others.

I also have been in training environments where I've always been encouraged to apply for independent funding. This was very important, because it allowed me to experience firsthand the cycle of applying and reapplying for grant funding during a time when the stakes were low. Without this period, I don't know that I would have had the confidence to fund my own research now, when the stakes are clearly much higher.

When faced with failures, how did you regroup and get back on track?

When I first transferred to a four-year institution as an undergraduate, I definitely took on more than I could handle. I was involved in student organizations, Army ROTC, and I

held a part-time job in addition to a full course load. As a result of being stretched too thin, my academics suffered. I graduated with a grade point average that I wasn't proud of and that probably wasn't competitive for most graduate schools. It also left me with some uncertainty about following science as a career.

It wasn't until after I had spent some time away from science in a different career path that I finally realized that my previous academic performance wasn't due at all to my acumen but rather to my inexperience in time management. When I returned for my Ph.D. training, I was a completely different student and performed far better.

When I look back now I realize that I probably wasn't ready to pursue graduate school right away — I needed to step away and grow as a person first. I still feel this is an important lesson today that I try to keep in mind. Just because I am not ready to do something right now doesn't mean I won't be at some point, so I try to keep my options open about the future.

What advice do you have for underrepresented students interested in a career like yours?

Don't self-eliminate. An academic career path is fraught with rejection. Most experiments don't give us the results we expect, most manuscripts don't get accepted by journals on the first or second submission, and most proposals don't get funded. It's easy to get discouraged or to think you don't measure up, and as a result, it's easy to take yourself out of the running for the graduate program or the job

that you want, or not to apply for a funding opportunity that you may be competitive for. I feel this is more prevalent among young people from underrepresented backgrounds.

What are your hobbies?

I have two young children at home, so what free time I have I try and spend with them. We like to explore hiking trails in western New York (More people should know how naturally beautiful this state is!) or just hit the open road for a good old-fashioned family road trip.

Who are your heroes, mentors or role models?

My parents certainly have been role models for me. They risked everything to emigrate from Mexico to start a new life in the U.S. while my siblings and I were all very young. They didn't speak the language or have a trade, but they still managed to build a happy childhood for all of us. Today, on the occasion that I feel overwhelmed in my career or at home, I am reminded that my worries



D. Fernando Estrada.

don't compare to those of my parents, and suddenly it all feels eminently manageable. I am very grateful to them for that perspective.

Professionally, I have had the enormous benefit of working with and for some amazing people. The U.S. Army has excellent leaders from the junior sergeant level on up, and I'd like to think that I've learned something from working with each of those soldiers. But I also have benefited from incredible mentorship in my Ph.D. and postdoc positions as well.

What keeps you working hard every day?

It's definitely the thrill of discovery, and getting to share that feeling with other people, that keeps me working hard every day. I've learned that one good day in research can fuel all of the days in between when the rewards are harder to find.

About the Research Spotlight

The American Society for Biochemistry and Molecular Biology's Research Spotlight highlights distinguished biomolecular and biomedical scientists from diverse backgrounds as a way to inspire up-and-coming scientists to pursue careers in the molecular life sciences. Eligible candidates include Ph.D. students, postdoctoral fellows, and new or established faculty and researchers. To nominate a colleague for this feature, contact education@asbmb.org.

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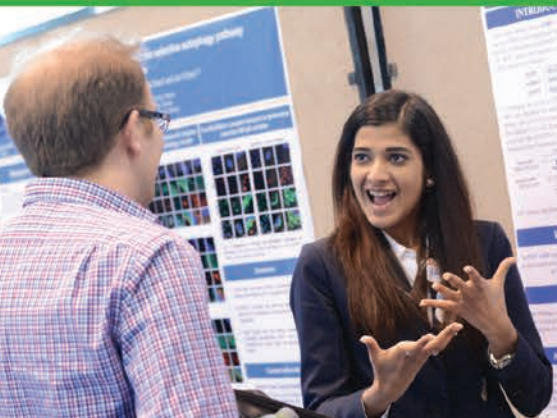
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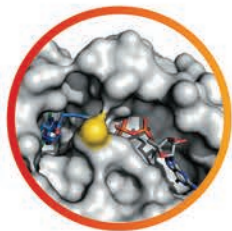
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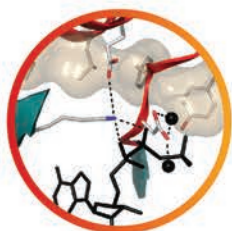
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