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ASBMB TODAY

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

THE ANTIBODY PATENT QUESTION

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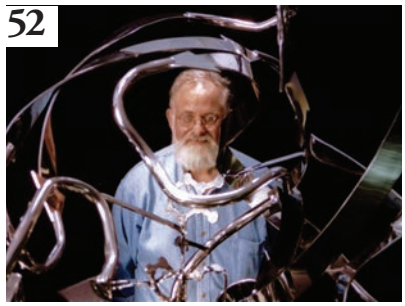

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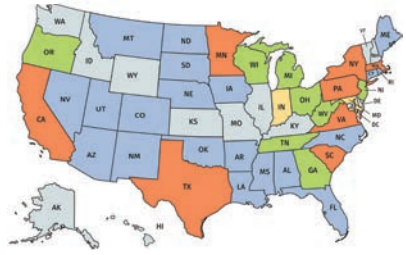

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Science surges in the House

By John Arnst

Again this month, I'm ceding this space to science writer John Arnst, who offers something weightier than my holiday baking tips.
— Comfort Dorn, managing editor

When the dust settled after this year's midterm elections, six of 22 first-time Congressional candidates with science backgrounds had won their races, including Sean Casten, a former biochemist who will represent Illinois' sixth district.

What's more, for the first time since 1995, it looks like the U.S. House science committee will be overseen by a member of Congress with a scientific background.


JOHNSON

U.S. Rep. Eddie Bernice Johnson, D-Texas, a former nurse who was first elected to Congress in 1992 and became the first female and first African-American ranking member of the committee in 2010, is poised to take over the committee in January, when chairs are elected. The last representative with a scientific background to hold the position was George Brown, a former engineer from California who chaired the committee from 1991 to1995.

The House Committee on Science, Space and Technology oversees NASA, the National Oceanic and Atmospheric Administration, the National Institute of Standards and Technology, the Department of Energy, the National Science Foundation, the Environmental Protection Agency, the Agency for Toxic Substances and Disease Registry, the Federal Aviation Administration and the Federal Emergency Management Agency.

The outgoing chairman, Rep. Lamar Smith, R-Texas, is known for espousing disbelief in climate science. He used his position to subpoena NOAA officials for data related to climate change research and subpoena state attorneys general and members of the Union of Concerned Scientists for correspondence about investigations into the fossil fuel industry.

In a statement released on election night, Johnson laid out three priorities, should she be elected to lead the committee: to support science, technology, engineering and mathematics education and federal research funding; to address the challenge of climate change; and to restore the credibility of the science committee as a place where science is respected and recognized as a crucial input to policymaking.

"I am heartened that Democrats will be in the majority in the 116th Congress, and I cannot wait to get to work," she stated. "If I am fortunate enough to be elected chair of the Committee on Science, Space, and Technology, a committee that I like to call the 'Committee of the Future,' I know that there is much that we can accomplish as Democrats and Republicans working together for the good of the nation."

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

2018 in review

By Benjamin Corb

December is a great time to take stock of the year that is ending. Here is a summary of some of the policy-related news that broke in 2018.

NIH budget growth

Whereas the early 2010s were marked by fiscal austerity and flat budgets across the federal science sector, 2018 continued a four-year trend of increases to the National Institutes of Health's budget. The NIH saw a $2 billion increase this year, and, for the first time since the 1990s, the NIH's budget was approved on time, without the delays in new funding that had been the norm for two decades. The same cannot be said for most other science funding agencies (including the National Science Foundation), which remain under a continuing resolution through early December.

Sexual harassment

The National Academies of Sciences published in June a report highlighting the systemic and often underreported harassment of women in the scientific enterprise. One woman out of every two in science has been a target of sexual harassment or misconduct. The NAS investigated harassment in the scientific workforce and published a series of recommendations to combat sexual harassment and create a safe work environment at science funding agencies, universities and scientific organizations.

In response to the NAS report, the National Science Foundation and other federal agencies have taken action, with the NSF blazing the trail for federal responsiveness. Institutions receiving NSF grants now must notify the NSF of reported harassment. The NSF will review the information and work with the institutions to determine appropriate action and, if it is deemed necessary, may remove grant funding.

Organizations, including the American Association for the Advancement of Science, are convening scientific society officials to develop policies to combat harassment in the laboratory as well as during scientific meetings and conferences. Here at the American Society for Biochemistry and Molecular Biology, we published an in-depth article about sexual harassment in ASBMB Today, and the Public Affairs Advisory Committee created an anti-harassment working group to advocate for policy changes that will make the scientific enterprise inclusive and safe for all scientists.

The next generation

The NAS published a report in April identifying policies to support the next generation of biomedical and behavioral science researchers. Included in the 18 recommendations are suggestions that Congress create a Biomedical Research Enterprise Council, increase the NIH budget with set-asides to support the report's recommendations and expand professional-development opportunities for young scientists.

After the report was published, the NIH developed a Next Generation Researchers Initiative working group, which has met to discuss steps the agency can take to support new and at-risk investigators. The ASBMB solicited input from its members and has provided recommendations to the working group. The PAAC will continue to monitor and comment on this important work in the next year.

Finally, a science adviser

In August, after a historically long delay, the White House named Kelvin Droegemeier to head the Office of Science and Technology Policy. Droegemeier, a research meteorologist, had been the vice president for research at Oklahoma University. The scientific community lauded his nomination, and the Senate Commerce Committee unanimously approved it. The nomination still needs to be approved by the full Senate.

Closer to home

In 2018, the ASBMB launched the Advocacy Training Program for scientists seeking formalized preparation to become science advocates. Ten ASBMB members from across the country participated in the inaugural class, and the second cohort will start training in January. Finally, the public affairs staff introduced "Pipettes and Politics," a science policy podcast.

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

Interested in science policy?

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

Member update

By Erik Chaulk

Vanderbilt chair honors Armstrong

A $1 million gift to Vanderbilt University has established a new faculty chair named in honor of the late biochemist Richard Armstrong.


ARMSTRONG

The Richard N. Armstrong, Ph.D., chair for innovation in biochemistry will support a faculty researcher in the school of medicine's division of basic sciences.

Endowed by Armstrong's family, the chair was created as part of the Chancellor's Chair Challenge, during which the university is investing $30 million to support endowed chairs.

Armstrong passed away in 2015 at the age of 66. He had served since 1995 on the Vanderbilt faculty, where he was a professor of biochemistry and chemistry. His research career focused on understanding detoxification enzymes.

He also served as editor-in-chief of the journal Biochemistry for 12 years and held an adjunct professorship at the Karolinska Institute.

Bassler wins Schering prize

Molecular biologist Bonnie Bassler received the 2018 Ernst Schering Prize for her research on quorum sensing.


BASSLER

One of the most prestigious German science honors, the award is issued annually to a scientist who has done outstanding biomedical research.

Quorum sensing is the process of cell-to-cell communication in bacteria. Bassler was honored for describing the universal use of chemical communication among bacteria, transforming our view of bacteria.

She is Princeton's Squibb professor in molecular biology and an investigator with the Howard Hughes Medical Institute.

The award carries a €50,000 prize.

McReynolds receives Hanna Gray fellowship

Melanie McReynolds is among 15 early-career scientists to receive Hanna Gray Fellowships from the Howard Hughes Medical Institute. The program seeks to promote diversity in the biomedical research community by supporting scientists who come from backgrounds underrepresented in the life sciences.


McREYNOLDS

McReynolds is a postdoctoral research assistant in the lab of Joshua Rabinowitz at Princeton University. Her research focuses on the diseases of aging and on understanding how the molecule NAD+ is produced and used.

Each fellow receives up to $1.4 million in funding over eight years, supporting them from early postdoctoral training through obtaining a faculty position.

In addition to funding, the program supports career development through mentoring and networking with other scientists.

Berger appointed Hopkins director

James Berger has been appointed director of the Institute for Basic Biomedical Sciences at Johns Hopkins University.


BERGER

Berger's appointment is part of the university's Betting Big on Basic Science initiative, which will invest $100 million over the next five years to hire new faculty and support core programs.

He will be tasked with developing interdisciplinary as well as translational and collaborative research programs at IBBS.

Berger is a professor of biophysics and biophysical chemistry at John Hopkins University School of Medicine and co-director of the cancer chemical and structural biology program at the Johns Hopkins Kimmel Cancer Center.

A structural biologist, Berger studies the fundamental mechanisms of enzymes that control cell proliferation.

Cornett promoted to associate professor

Jonathan Cornett is among seven Lee University faculty members to be promoted from assistant professor to associate professor.


CORNETT

Cornett received his undergraduate degree at Lee University in Tennessee, where he was named a Centennial Scholar and a Ledford Scholar,

won the E.K. Hamilton Scholarship in Math and Sciences, and received the departmental biochemistry award.

Cornett earned his doctorate in genetics and molecular biology from Emory University and completed postdoctoral studies at the Yale University School of Medicine.

He joined the Lee University faculty full time in 2012.

Jewell earns Gilman scholarship

Salisbury University undergraduate student Mollie Jewell received the Benjamin A. Gilman International Scholarship at the university's annual honors convention.

JEWELL

The Gilman scholarship, a grant program through the U.S. Department of State, provides financial support to study or intern abroad. With it, Jewell took a summer course titled Bioscience for Global Health at the University of Glasgow in Scotland.

The program is open to undergraduates who are U.S. citizens receiving federal Pell Grant funding at two-year or four-year colleges.

A senior biology major at the university in Maryland, Jewell serves as president of the Delta Alpha Pi international honor society and as co-president for Salisbury's American Society for Biochemistry and Molecular Biology Student Chapter. She is also a member of the Phi Kappa Phi and Beta Beta Beta honor societies.

In memoriam: Lewis Lukens

Lewis Nelson Lukens, a former Wesleyan University biochemistry professor, passed away at his home in Middletown, Connecticut, on Sept. 8. He was 91.

LUKENS

Born Jan. 21, 1927, Lukens earned his bachelor's degree from Harvard University in 1949 and his Ph.D. in biochemistry from the University of Pennsylvania in 1954.

Lukens was a postdoctoral fellow at Columbia University and later joined the faculty at Yale Medical School. In 1966, he joined the faculty at Wesleyan, where he stayed until his retirement in 1999.

Lukens was a founding member of the department of molecular biology and biochemistry at Wesleyan. His research focused on the regulation of gene expression by eukaryotic cells, specifically the genes for type I and type II collagen.

He also served as chairman of the biology department, on the committee on graduate instruction and as program director of the university's biomedical research support grant.

He is survived by his wife, Ellen, and their four children, Katherine Lukens, Marie Lukens Hansen, Ellen Lukens Sisson and Lewis Lukens Jr.

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!

Martha Vaughan (1926–2018)

By Edward Korn & Joel Moss

Like many great scientists who spend their careers at the National Institutes of Health, Martha Vaughan possessed a quiet humility that sometimes concealed her immense contributions to the field of biochemistry.

Gentle, unassuming yet omnipresent in the corridors of the NIH for more than 65 years, Martha devoted her time to understanding the molecular basis of intracellular signaling. She conducted some of the earliest research on insulin signaling, which helped to reveal the insulin receptor, and spent six decades largely focused on G proteins and metabolic regulation.

A member of the National Academy of Sciences since 1985, Martha conducted seminal studies that elucidated the role of cyclic nucleotides and G proteins in regulation of lipolysis in fat cells. Later in her career, she investigated the control of intracellular vesicular trafficking by ARFs, a family of low molecular weight G proteins, and their regulatory partners.

Little did her colleagues imagine when they celebrated her 75th birthday with a two-day symposium at the NIH in 2001 — an event that drew no fewer than three Nobel laureates as speakers, including Ferid Murad, whom she mentored — that Martha still had more than a decade ahead of solid research findings, such as how the G protein activators BIG1 and BIG2, discovered in her lab, regulate cell migration. She retired in 2012 and was named NIH scientist emerita, a position that allowed her to continue her scientific pursuits and her mentoring, which she cherished above all.

BILL BRANSON/OFFICE OF NIH HISTORY, NIH

Martha Vaughan worked for more than six decades at the National Institutes of Health and was an associate editor at the Journal of Biological Chemistry for more than 20 years.

Martha, our dear friend for many years at the NIH, died peacefully Sept. 10 at the age of 92.

Martha's soft-spoken demeanor could be traced to her Wisconsin roots and a modest upbringing; her family lost much of their wealth in the Great Depression. She earned a bachelor's degree from the University of Chicago in 1944, part of a cohort of stellar female scientists that included the geneticist Janet Davison Rowley.

In 1949, Martha received her M.D. from the Yale School of Medicine and soon began her research career as a postdoctoral fellow in Yale's department of physiological chem-

istry. At Yale, Martha revealed her commitment to human rights, joining the Yale chapter of the Association of Internes and Medical Students, which concerned itself with then-progressive ideas such as universal health insurance, racial equality in medical education, vivisection and the draft.

While at Yale, she also met her future husband, the charismatic Jack Orloff, a brilliant scientist who died in 1988. In many ways, the boisterous Jack was Martha's polar opposite; yet, as the saying goes, opposites attract. Jack adored Martha. He arrived at the NIH and the newly established National Heart Institute in 1950, and Martha joined him two years later (after a yearlong stint as a fellow working with the great diabetes researcher William C. Stadie at the University of Pennsylvania).

Recruited to the NHI by Christian Anfinsen, Martha worked in the now-legendary Building 3 with an elite core of researchers, a mind-boggling collection of scientific talent that included Anfinsen, Julius Axelrod, Robert Berliner, Robert Bowman, Nina Braunwald, Bernard Brodie, Donald Fredrickson, Leon Heppel, Edward Korn, Arthur Kornberg, James Shannon, Thressa and Earl Stadtman (another power couple), and James Wyngaarden.

The 1950s were crazy, fun times at the NIH and particularly in Building 3, which Martha later recalled as being home to lab animals that included cats, dogs, cows, pigs, sheep and chickens; it was not uncommon for her to ride the elevator with four-footed and winged colleagues. Many of the scientists, including Martha, had moved over to the newly built NIH Clinical Center, Building 10, by the mid-1950s.

Early in her career, Martha worked closely with Anfinsen, whose studies of the essential building blocks for making proteins and their three-dimensional folding earned him a Nobel Prize in 1972. She rose to the position of chief of the National Heart, Lung and Blood Institute's Laboratory of Cellular Metabolism and head of the Section of Metabolic Regulation. She made lasting contributions toward understanding fundamental signal transduction mechanisms.

As her 1985 NAS citation reads, "Vaughan's pioneering studies on adipose tissue metabolism, her elucidation of the mechanism of action of cholera toxin on the adenylate cyclase system, and her brilliant work on the phosphodieseterases have had a major influence of current concepts of metabolic regulation."

We can add that Martha was way ahead of the curve on her cholera research using adipose tissue instead of intestinal tissue; the editors of the journal Nature were not at all convinced by the unconventional approach but eventually acquiesced and published what is now considered a landmark paper.

Martha authored or co-authored more than 365 papers and book chapters and was a generous citizen-scientist, serving in editorial positions with several research journals including more than 20 years with the Journal of Biological Chemistry. She also served on the NAS Committee on Human Rights from 1992 to 1998 and was a president (1988–1990) and board member (1979–2007) of the Foundation for Advanced Education in the Sciences, which sponsors academic courses, job-related training, cultural events and services for NIH staff. Martha also was a medical officer with the U.S. Public Health Service from 1954 to 1989.

Throughout her life, Martha was a survivor, as quiet as she was fierce. She struggled to pay for her college education. She survived breast cancer in the late 1950s as well as a traumatic brain injury from a fall in the 1990s that left her in a coma for several days. After that injury, doctors were convinced she'd never regain her cognitive abilities, but Martha, then a recent widow, did so in spades.

We visited her at the hospital and found her casually reading a newspaper — upside-down. She was faking it, pretending she could read and not wanting us to worry about her condition. This funny anecdote captures Martha's spirit, but it was worrisome to us then, for sure.

A few years after this, a terrific derecho windstorm blew over a massive tree that leveled Martha's house and car. This was on a Friday. On Saturday she bought a new car and found an apartment to rent; on Monday she was back at work. She never returned to that house.

Martha was renowned for her mentorship of young scientists. In his Nobel autobiography, Murad singled her out as an "excellent mentor" who offered sage advice and "considerable freedom." Martha mentored scores of postdoctoral fellows, many of whom are now in prominent academic and government positions.

After her retirement, Martha spent most of her time at her second home, the NIH, attending lectures and asking pointed questions. We wonder how many of the young postdoctoral fellows in attendance at these lectures understood the greatness of this soft-spoken woman.

Martha was preceded in death by her husband, Jack, in 1988 and her son David in 2015. She is survived by her sister, Margaret Cox, of Onancock, Virginia; her sons Jonathan Orloff of Washington, D.C., and Gregory Orloff of Bethesda, Maryland; and six grandchildren.

The authors acknowledge Christopher Wanjek at the NIH for his help in composing this tribute.

Edward Korn (korned2@nhlbi.nih.gov) is scientist emeritus at the NIH National Heart, Lung, and Blood Institute.

Joel Moss (mossj@nhlbi.nih.gov) is a senior investigator in the NHLBI Laboratory of Translational Research.

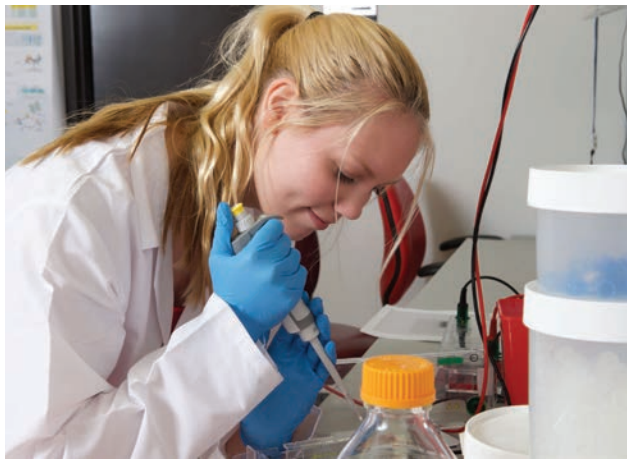
Chapter president inspired by mother's diagnosis

By Kerri Beth Slaughter

When she learned that her mother had been diagnosed with colon cancer, Amanda Duplan changed her plans.

Duplan was a freshman at Grand View University in Iowa, more than 1,700 miles from her family home in Sacramento, California, when she got the news three years ago.

"Instead of getting depressed, I've been inspired to help others going through similar situations," she said.



COURTESY OF AMANDA DUPLAN

Amanda Duplan, a senior at Grand View University, plans to pursue a Ph.D. in biochemistry and molecular biology with an interest in immunotherapy.

Duplan has always loved science, she said, but her mother's diagnosis inspired her to get involved in research. Duplan started her freshman year on a premed track, but she found that her true passion was to study the underlying cause of disease.

Her undergraduate research focuses on engineering a PETase that will break down PET plastic more efficiently. Bonnie Hall, an assistant professor of chemistry, has played a major role in Duplan's education at Grand View. Duplan started her research in Hall's lab during her sophomore year, and Hall chose Duplan to work with her at the University of Iowa during a research fellowship last summer.

"She has been great at helping me through the bad times," Duplan said of Hall. "She is an amazing person and an amazing professor."

Hall also had a role in the founding of the American Society for Biochemistry and Molecular Biology Student Chapter at Grand View. Hall first learned about Student Chapters at an ASBMB annual meeting. She brought the idea back to campus and started the chapter with the help of Duplan and other students. She serves as the faculty adviser for the chapter.

This year, Duplan became the chapter president. She has worked to encourage involvement in the chapter by planning fun events such as a liquid nitrogen ice cream social. Duplan had wanted to make ice cream ever since she discovered the liquid nitrogen used for NMR experiments on campus. Chapter members worked as a team and invited fellow students to participate.

The chapter continues to grow, and science outreach is a major focus, Duplan said. "I like having a common goal of doing something for other people."

Duplan also serves as her chapter's student mentor for the Connect Researchers, Educators and Students, or CREST, group. Her group will design a physical model of a protein and present it at the ASBMB annual meeting in Orlando.

Duplan's experience as chapter president has helped her become a better organizer and delegator, she said. She has strengthened her leadership skills by serving as a peer leader for science classes, a senior research mentor and the captain of the women's bowling team. Her optimism and determination in the face of challenges have been instrumental to her success at Grand View.

Duplan's mother is receiving treatment and continues her fight against cancer. "I've had to deal with many setbacks, but my family has encouraged me to keep going," Duplan said.

Duplan will graduate from Grand View in May. She plans to apply for postbaccalaureate programs before entering a Ph.D. program in biochemistry and molecular biology with an interest in immunotherapy. Her goal is to be a professor so she can teach young scientists and do research.

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

Looking ahead, looking back

Meet the Sewer scholarship recipients

By Stephanie Paxson

The Marion B. Sewer Distinguished Scholarship for Undergraduates is named in honor of a member of the American Society for Biochemistry and Molecular Biology who passed away in 2016.

Throughout her education and career as a researcher, Marion Sewer promoted diversity and inclusivity within the scientific community. As a member of the ASBMB Minority Affairs Committee, she founded the society's grant-writing workshop and mentorship program to help support early-career scientists from underrepresented minority groups. That program evolved into Interactive Mentoring Activities for Grantsmanship Enhancement, or IMAGE.

The mission of the committee is "to increase cultural diversity in fields of biochemistry and molecular biology by increasing participation, visibility and status of minorities within ASBMB." This scholarship (formerly the Distinguished Undergraduate Scholarship) was created to provide financial support for students who demonstrate an interest in these fields and enhance the diversity of science.

Each year, the MAC and the Student Chapters Steering Committee select up to five undergraduates to receive up to $2,000 toward tuition. Applicants provide statements about significant barriers they have faced and their commitment to promoting diversity on campus and in the scientific community.

Here, the 2018 Sewer recipients introduce themselves, and we take a look back at the 2017 recipients and find out how some of them benefited from this scholarship. Their comments have been edited for length and style.

2018 recipients

ARROYO

Vidal Arroyo

Chapman University (Orange, California)

After completing my undergraduate degree in biochemistry and molecular biology, I will pursue an M.D./Ph.D. dual degree in biomedical informatics so I can serve society as an oncologist, cancer researcher and mentor of students from disadvantaged backgrounds. With my research, I hope to advance the field of oncology by building computational tools that can be used by physicians. Specifically, I wish to develop clinical support tools that can be used to partition certain cancer treatments based on a patient's genetic and clinical characteristics. With this work, I will reduce the late effects seen among survivors of pediatric cancer by bettering how we treat children with cancer.

FLORES

Mauricio Flores

University of California, Riverside

I plan to go to graduate school to pursue a Ph.D. in molecular biology for biomedical research to help develop new forms of treatment to combat illnesses and disorders that affect millions of people every day. This is mostly due to my experience growing up in a lower-socio-economic community and watching sick people suffer because they were unable to afford healthcare.

Finding effective and cheaper forms of treatment would be my way of giving back to the community that raised me.

PIERRE

Tanya Pierre

Agnes Scott College (Decatur, Georgia)

I want to pursue a career in biomedical research that allows me to work with my research interests in the disciplines of genetics, molecular biology, immunology and toxicology. Although I am not entirely sure what my future career will look like, I know that I want the flexibility to interact with young scientists in my community through mentoring and volunteering programs.

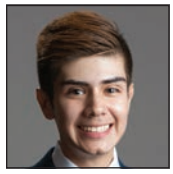
TAHSEEN

Danyal Tahseen

Trinity University (San Antonio)

I aspire to work in academic medicine so I can see patients in a teaching hospital while mentoring students and residents, while also participating in

research and delivering lectures. Within that framework of academic medicine, I want to choose a specialty like dermatology that has a large scope for research as well as long-term doctor-patient relationships so I can accompany my patients on their medical journey from both emotional and physiological perspectives. I would love to do research on diseases like vitiligo, the differing perceptions of those diseases in various cultures and how that affects patient care, as well as more wet lab projects exploring the molecular pathways of novel drugs targeted toward these diseases. Lastly, I want a facet of my career to involve inspiring young students from minority groups that don't think being a physician is a possibility for them. This would let me do my part in diversifying the future medical workforce by showing first-generation students the steps to becoming a doctor and/or researcher and that it's awesome to dream big.


ZEPEDA

Francisco Zepeda
Massachusetts Institute of Technology (Cambridge, Massachusetts)

I am a second-year bioengineering student with experience in cell culture, histology and immunology. I love biology because it is such a multifaceted discipline and has limitless possibilities for collaborations with individuals from other fields. Recently, I have been working on building a robust set of electrical engineering techniques to help solve the problems I come across in lab. Outside of science, I am involved with cultural and political groups, and I have a passion for youth outreach. I plan to pursue an M.D. and develop a pediatric specialty. A more immediate goal of mine is to secure an internship that fits my skill set. I believe my persistence, quick learning and ability to work in teams would make me a great coworker.

2017 recipients


AGUBOKWU

Nnedi Agubokwu
Lincoln University (Oxford, Pennsylvania)

Nnedi Agubokwu earned her B.S. in biochemistry and molecular biology in May 2018. In high school, she did biomedical research at the Children's Research Institute and completed an 80-hour training program to educate her peers on studying for the SAT, applying to colleges and receiving scholarships. At Lincoln University, she was a mentor for the empowerment of young black women. She also completed research internships at Lincoln and at the Sidney Kimmel Cancer Center of Thomas Jefferson University, where she investigated a mutation in men with prostate cancer with the aim of expanding genetic testing.

An update from Nnedi:

I am working toward becoming a part of a program that encourages and enables young girls to pursue careers in STEM. It is based in my hometown in Prince George's County, Maryland, a predominately black area, and will allow these girls to increase their interest in academic areas where they are not seen as the normal demographic. I serve as a role model for younger women who are interested in pursuing careers in STEM. At my institution, I helped young women I mentored to find and apply for internships.

I experienced a high level of stress throughout my time in college due to coursework, balancing extracurricular activities and working multiple jobs. With the help of this scholarship, my senior year was much less stressful. I was able to attend research conferences to present my research, such as ASBMB's annual meeting, and focus more on my academic and future professional endeavors. Being in these spaces allowed me to connect with my peers and those who have achieved the goals I am working toward.


FAISON

Edgar Maxwell Faison
University of North Carolina at Chapel Hill

Edgar Faison is a first-year graduate student at UNC Chapel Hill who is interested in the physics and chemistry behind protein structure, stability and interaction. The most direct application of this is studying disease etiology as it relates to protein misfolding or abhorrent interactions within the cell. Alternatively, a deep understanding of protein physics can be applied to protein engineering. After graduate training, he would like to mentor students and work to increase diversity in the STEM field, creating a more representative and robust scientific community. This includes outreach to communities and high schools that may not be able to encourage young people to pursue science.

An update from Edgar:

The Marion B. Sewer scholarship helped me through my senior year, which included my hardest fall semester. I was not only taking undergraduate coursework but also a graduate-level class and about 20 to 30 hours a week of research in Dr. Nikolay Dokholyan's lab for my honors thesis. The work was daunting, but earning the scholarship afforded the confidence I needed not only to accomplish all of the above but also to apply to graduate school.

As an undergraduate, I was heavily involved in the Chancellor's Science Scholars, a program aimed at increasing minority representation in the sciences and higher learning in general. The Sewer scholarship helped me encourage minority excellence at Carolina by serving as an example for my younger peers and as a point of contact for anyone else who was interested in applying for the award. I believe the Sewer award helped me encourage their success and journey through science.

MASON

Miranda Mason

University of Louisville (Kentucky)

Now a senior at the University of Louisville, Miranda Mason is pursuing an individualized major in medicine and society with minors in biology and political science. After graduation, she intends to study medicine and then pursue a pathology residency so as to work behind the scenes of medicine as a "doctor's doctor" with opportunities to better study the mechanisms of disease.

An update from Miranda:

I am now helping to plan a series of science-related presentations to Kentucky Refugee Ministries and acting as a host on campus, introducing students of various backgrounds to the college experience.

With the financial support of the Sewer scholarship, I was able to take part in research instead of taking another job. I could afford rent and supplies without the support of my family, thus not only relieving financial pressure but also allowing me to act independently of my family's expectations. This has enabled me to be more outspoken on issues and causes I care about that they do not support.

GOMEZ ZUBIETA

Daniela Gomez Zubieta

University of Michigan–Dearborn

As an undergraduate, Daniela Gomez Zubieta followed her passion for human rights through service work at a free clinic in Detroit and overseas work in Honduras. These experiences exposed her to economic injustice that drove her to pursue medicine with the goal of becoming a physician serving as an advocate for underserved populations. She wants to work toward closing gaps between access to healthcare and minority groups as a scientist and physician, possibly by obtaining an M.D./Ph.D. She planned to continue basic research in neuroscience and molecular and cell biology, using her dual degree to treat patients while working to better their treatment options and knowledge of their pathologies. Her goal is to answer scientific questions such as "How can we better treat neurodegenerative disorders?" as well as social questions such as "Why does the burden of pathologies such as Alzheimer's disease and dementia fall so harshly on minority groups?"

PABÓN CRUZ

Alexander Pabón Cruz

University of Puerto Rico–Bayamón

When he applied for the Sewer scholarship, Alexander Pabón Cruz's short-term academic goal was to complete his bachelor's degree in human biology. His long-term academic goals were to complete a doctorate in pharmacy and then work as a professor and researcher in the area of pharmacy.

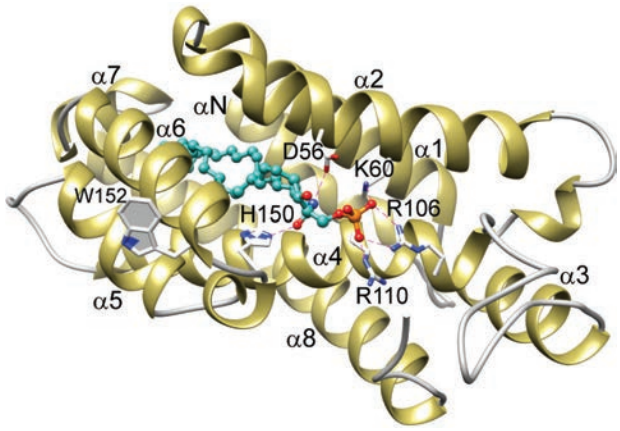
Stephanie Paxson (spaxson@asbmb.org) is the ASBMB's diversity and undergraduate education coordinator. Follow her on Twitter @stephaniepaxson.

The many roles of CPTPs

By Rhoderick E. Brown

Ceramide-1-phosphate transfer proteins, or CPTPs, burst onto the scientific landscape about five years ago. Ceramide-1-phosphate, or C1P, is a sphingolipid consisting of nonpolar ceramide connected to a polar anionic phosphomonoester headgroup. C1P exerts many bioactive effects including induction of cell proliferation, stem cell mobilization, macrophage migration and activation of IVA phospholipase A2 for eicosanoid production. Prior to the discovery of CPTPs, insights into C1P intracellular transport were sparse.

Human CPTP first emerged from in silico annotative predictions of the Human Genome Database; an ortholog found in plants and capable of regulating accelerated cell death, ACD11, had been identified a decade earlier with sphingolipid transfer ability. Recent structure–function studies of CPTP and ACD11 reveal global folds highly similar to glycolipid transfer protein, a two-layer, all-alpha-helical fold for binding complex sphingolipids in a sandwichlike fashion. C1P specificity originates from a few key residues in the sphingolipid headgroup recognition center which connects to a hydrophobic pocket that ensheaths the nonpolar SL aliphatic chains of the ceramide moiety. A surprising aspect of CPTP is its complete lack of structural homology with ceramide transfer protein.



PROTEIN DATA BANK: 4K84

In this crystal structure of the CPTP/16:0-C1P complex, a surface-located cationic residue triad (R60, R106, R110) provides selectivity for the phosphate headgroup of C1P. D56 and H150 interact with the ceramide amide linkage to provide sphingolipid selectivity. The C1P hydrocarbon chains are ensheathed in an interior hydrophobic pocket.

Regulation

Potential cellular mechanisms for regulation of CPTPs now are emerging. C1P intermembrane transfer rates by ACD11 and CPTP increase in the presence of phosphatidylserine, or PS. Other anionic phosphoglycerides, such as phosphatidic acid or phosphatidylglycerol, have the opposite effect of PS and depress C1P transfer rates.

The evidence suggests that PS increases membrane partitioning in a way that may either optimize protein orientation for C1P uptake during initial membrane contact or facilitate protein release from membranes after C1P acquisition. To explain how PS embedded in the membrane could enhance and facilitate a favorably oriented interaction by ACD11 or CPTP, the existence of a PS headgroup-specific site on the surface of ACD11/CPTP near the C1P binding site has been hypothesized. Still, the mechanistic details defining exactly how C1P transfer is sped up are in need of clarification.

In any case, intracellular membranes containing cytoplasmically exposed PS, such as the plasma membrane and trans-Golgi network, seem to be targeted hot spots for ACD11 and CPTP action in cells. A regulatory role for certain phosphoinositides also recently has been reported by our lab. The recent findings support earlier immunocytochemical localization showing that human CPTP is present in the cytosol but targets to distinct cellular regions.

Roles

CPTP downregulation or expression of CPTP point mutants with ablated C1P binding sites affects cells in two major ways: first, C1P levels increase in subcellular fractions enriched in trans-Golgi but decrease in fractions enriched in plasma membranes, and second, arachidonic acid and pro-inflammatory eicosanoid levels increase. The findings are consistent with CPTP acting as a C1P sensor and mediator of C1P transport from the trans-Golgi production site to the plasma membrane.

When CPTP is downregulated, the accumulated C1P in the trans-Golgi membranes can enhance translocation of IVA phospholipase A2 via its C1P-

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Journal of Lipid Research names new editors-in-chief

Pair to broaden journal's editorial scope to include more clinical research

By Angela Hopp

The American Society for Biochemistry and Molecular Biology announced in late October that Kerry-Anne Rye of the University of New South Wales Sydney and Nicholas O. Davidson of Washington University in St. Louis will be the next editors-in-chief of the **Journal of Lipid Research**.

Rye runs the lipid research group at the School of Medical Sciences in the Faculty of Medicine at UNSW Sydney. She has been an associate editor for JLR since 2008. Davidson leads the gastroenterology division and the digestive disease research center at Wash U's medical school and has been an associate editor for JLR since 2011. Their joint five-year term as co-editors will begin Jan. 1.

"Kerry-Anne and Nick have prepared a thoughtful and detailed proposal to advance the journal in the future," said Gerald Hart, president of the ASBMB and an eminent scholar at the University of Georgia. "We are confident that the two of them will attract the kinds of papers that will most benefit JLR's impact."

While JLR already publishes some patient-oriented studies, Rye and Davidson have developed a plan for broadening the scope of the journal to include additional clinical research, including studies examining microbial taxa in lipid homeostasis, lipid mediators in human diseases (including atherosclerosis, inflammatory bowel disease, Alzheimer's disease and liver disease), the role of noncoding RNAs in lipid metabolism, and epigenetic regulation of lipid metabolism.

Rye earned her Ph.D. at Flinders University in South Australia and completed postdoctoral training at the University of Illinois at Urbana–Champaign. She has been a research professor since 2013 at UNSW, where she serves as the deputy head of the School of Medical Sciences and studies atherosclerosis and diabetes.

> *"(I) have great faith that Kerry-Anne and Nick will continue the long tradition of publishing the most outstanding biochemical and biomedical lipid research and lead the JLR to new heights."*
>
> **— EDWARD DENNIS**

RYE

DAVIDSON

Davidson earned his medical degree at King's College Hospital Medical School in London. He then entered the clinical scholar track at The Rockefeller University in New York before completing his gastroenterology fellowship and research training at Columbia–Presbyterian Medical Center. He has been at WUSTL since 1998 and holds professorships there in the departments of medicine and developmental biology.

The pair will take the reins from the journal's current co-editors, Edward Dennis of the University of California, San Diego, and William Smith of the University of Michigan. Dennis has steered the journal since 2003. For most of that time, Joseph Witztum, also at UCSD, was co-editor. Witztum stepped down in 2016, at which point Smith stepped in to complete Witztum's term.

"In 2019, JLR will celebrate its 60th year as the premier journal devoted to both basic biochemical and clinical lipid research, and after some 20 years of association with the JLR — including 15 years as editor-in-chief — I felt it was time for new leadership to take the helm," Dennis said. "We have 22 outstanding associate editors of the journal, and Kerry-Anne and Nick have been among the most devoted of them. I am very pleased with their selection and have great faith that Kerry-Anne and Nick will continue the long tradition of publishing the most outstanding biochemical and biomedical lipid research and lead the JLR to new heights."

JLR was founded in 1959 by a group of lipid scientists at the National Institutes of Health. They called their organization Lipid Research Inc. When the NIH reduced financial support for the group in the late 1960s, the journal's editors began exploring partnerships to sustain the publication.

Beginning in 1971, the Federation of American Societies for Experimen-

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specific binding site. The ensuing arachidonic acid release enables production of pro-inflammatory eicosanoids. In our lab, CPTP knockdown has been found to upregulate IVA cPLA2 transcript.

Recently, exciting medical insights have begun emerging for CPTP. Patients with severe acute pancreatitis who exhibit downregulated expression of proteins needed for viable tight junctions in intestinal mucosal epithelial cells also have lowered CPTP and elevated IVA cPLA2 expression. Thus, proper CPTP expression may protect tight junction proteins and intestinal mucosa from inflammatory damage linked to IVA cPLA2.

In another recent study, autophagy induction and inflammasome assembly and activation have been linked to CPTP expression. WT-CPTP overexpression protects against starvation-induced autophagy. CPTP downregulation or expression of C1P binding-site point mutants triggers an eight- to tenfold increase in autophagosomes, organelles that degrade nonessential cell components and delay cell death in response to stressful events. CPTP depletion helps increase formation of nascent membranes needed for autophagosome assembly by a mechanism that includes increased ATG9A-vesicle release from the Golgi. This finding is consistent with the hypervesiculation and disruption of Golgi cisternae stacks noted earlier by CPTP knockdown.

In macrophagelike cells, CPTP depletion increases pro-inflammatory interleukin release and pyroptotic cell death through an autophagy-dependent inflammasome-mediated pathway. Elevation of intracellular C1P by exogenous C1P treatment rather than by CPTP depletion also induces autophagy and IL-1-beta release.

The new findings provide mechanistic insights that could help decipher disease-related microarray analyses involving previously reported CPTP expression changes. For example, CPTP downregulation has been observed in age-related macular degeneration, and the CPTP genetic locus, chromosome 1p36, is deleted in a genetic disorder that causes intellectual disability, delayed growth and other symptoms.

Together, these findings are beginning to shed light on mechanisms that cells can use to regulate CPTPs in humans and plants, while also revealing the emerging translational medical importance of these proteins in human health and disease.

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tal Biology took over the day-to-day management of the journal, and in 1999 officials at Lipid Research Inc. approached Dennis, then the head of the ASBMB Publications Committee, about transferring first management and eventually ownership of the journal to the society. The two parties struck a deal, and the journal has been a part of the ASBMB publishing portfolio ever since.

Barbara Gordon, executive director of the ASBMB, praised the journal editors' leadership over the years.

"The original agreement between the society and JLR's previous owner says: 'ASBMB intends to work to maintain JLR as the premier journal in the lipid field, to broaden its appeal to authors, and to increase its impact even more,'" she said. "Ed has been committed to fulfilling this promise each day of his tenure. I can't thank him, along with Joe Witztum and Bill Smith, enough for their steady, capable administration over the past almost two decades."

Hart, president of the ASBMB, said the society's officials have full confidence in the new editors: "We have no doubt that they will be outstanding leaders in keeping JLR as the top journal in the lipid field."

Davidson has worked extensively with national and international academic communities in digestive and liver disease and is an associate editor for the journal Hepatology and chairman of the board of editors for the journal Gastroenterology.

"I'm excited to work with Kerry to expand the reach of the Journal of Lipid Research into new communities while building on the great legacy created by Drs. Dennis, Smith and Witztum," Davidson said. "We are also grateful to all the current associate editors for their support and insights on behalf of the journal."

Rye has extensive links in the international cardiovascular community. She is an associate editor for the journals Arteriosclerosis Thrombosis and Vascular Biology, Circulation Research and the Journal of the American Heart Association.

"We are honored to be given the opportunity to expand the scope of the Journal of Lipid Research while remaining committed to the current focus of all aspects of lipids in science," she said.

Angela Hopp (ahopp@asbmb.org) is executive editor of ASBMB Today and communications director for the ASBMB. Follow her on Twitter @angelahopp.

Linking virus sensing with gene expression, a plant immune system course-corrects

By Sasha Mushegian

Plant immune systems, like those of humans and animals, face a difficult balancing act: They must mount responses against ever-evolving pathogens, but they must not overdo it. Immune responses require energy and resources and often involve plants killing their own infected cells to prevent the pathogens from spreading.

Researchers at Durham University in England have identified a crucial link in the process by which plants regulate their anti-viral responses. The research was published in the **Journal of Biological Chemistry**.

Martin Cann's lab at Durham, in collaboration with the laboratories of Aska Goverse at Wageningen University and Frank Takken at the University of Amsterdam, studied a receptor protein called Rx1, which is found in potato plants and detects infection by a virus called potato virus X.

SCOTT BAUER/USDA

Researchers at labs in the UK and the Netherlands studied a receptor protein found in potato plants like this one that detects infection by a virus called potato virus X.

Binding to a protein from the virus activates Rx1 and starts a chain of events that results in the plant mounting an immune response. But the exact sequence of cellular events — and how Rx1 activation was translated into action by the rest of the cell — was unknown.

"Our study revealed an exciting, and unexpected, link between pathogen attack and plant DNA," Cann said.

Specifically, the study showed that Rx1 joins forces with a protein called Glk1. Glk1 is a transcription factor, meaning it binds to specific regions of DNA and activates genes involved in cell death and other plant immune responses. The team found that when Glk1 bound to virus-activated Rx1, it was able to turn on the appropriate defense genes.

When the viral protein was absent, Rx1 seemed to have the opposite effect — actually keeping Glk1 from binding to DNA. In this way, it prevented an inappropriate immune response.

"The immune response involves reprogramming the entire cell and also often the entire plant," Cann said. "An important part of this regulatory process is not only allowing activation but also making sure the entire system is switched off in the absence of infection."

More than one-third of the potential global crop harvest is lost to pathogens and pests each year, so breeding plants with better immune systems is an important challenge. Understanding how this immune system is regulated at the appropriate level of activity gives the researchers more ideas of points in the immune signaling pathway that could be targeted to increase the plant's baseline ability to resist disease.

"To increase (crop) yield, there is an urgent need for new varieties that are resilient to these stresses," Cann said. "A mechanistic understanding of how plants resist or overcome pathogen attack is crucial to develop new strategies for crop protection."

DOI: 10.1074/jbc.RA117.000485

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Seeking an off switch for celiac disease

Researchers at Stanford have discovered how a disease-associated protein gets inactivated, opening the door to possible new treatments

By Sasha Mushegian

Celiac disease is an autoimmune disorder that affects, by some estimates, nearly one in 100 people. Celiac symptoms ar triggered by gluten, a protein found in wheat and related plants, but gluten doesn't act alone to cause the digestive problems that patients suffer. Rather, gluten induces an overactive immune response when it's modified by the enzyme transglutaminase 2, or TG2, in the small intestine.

Research published in the **Journal of Biological Chemistry** identifies an enzyme that turns off TG2, potentially paving the way for new treatments for celiac disease. Michael Yi, a chemical engineering graduate student at Stanford University, led the study.

"Currently, therapies to treat people with celiac disease are lacking," Yi said. "The best approach right now is just a strict adherence to a lifelong gluten-free diet. Perhaps the reason behind this is our relatively poor understanding of TG2."

The biochemistry of how TG2 interacts with gluten and induces an immune response has been well studied, but more basic mysteries remain, such as how TG2 behaves in people without celiac disease. Chaitan Khosla, the Stanford professor and director of Stanford Chemistry, Engineering & Medicine for Human Health, who oversaw the new study, has done research showing that TG2 can be active or inactive, depending on the forming or breaking of a specific chemical bond, called a disulfide bond, between two amino acids in the enzyme.

NACHO JANKOWSKI/THE NOUN PROJECT

This icon represents celiac disease, an autoimmune disorder triggered by gluten, a protein found in wheat.

"Even though there's a lot of transglutaminase 2 protein in the (small intestine), it's all inactive," Khosla said. "When it became clear that even though the protein was abundant, its activity was nonexistent in a healthy organ, the question became 'What turns the protein on, and then what turns the protein off?'"

In 2011, Khosla's team identified the enzyme that activates TG2 by breaking its disulfide bond. In the new paper, the researchers did experiments in cell cultures and found an enzyme that re-forms this bond, inactivating TG2. This enzyme, ERp57, is known mainly for helping fold proteins inside the cell. When it turns off TG2, it does so outside of cells, raising more questions about its functions in healthy people.

"Nobody really understands how (Erp57) gets outside the cell," Khosla said. "The general thinking is that it's exported from the cell in small quantities; this particular observation suggests that it actually does have a biological role outside the cell."

TG2 is now the first protein known to have a reversible disulfide bond on/off switch of this type.

"This is a very different kind of on-and-off chemistry than the kind that medicinal chemists would (typically) use," Khosla said.

Understanding this mechanism has led the team to investigate whether any drugs approved by the Food and Drug Administration could target the switch directly. Because previous studies have suggested that lack of TG2 doesn't seem to affect the health of mice negatively, blocking TG2 is a promising avenue for treating celiac disease patients without requiring lifelong dietary changes.

DOI: 10.1074/jbc.RA117.001382

"Currently, therapies to treat people with celiac disease are lacking. The best approach right now is just a strict adherence to a lifelong gluten-free diet. Perhaps the reason behind this is our relatively poor understanding of TG2."

—MICHAEL YEE

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A close-up of the lipids in Niemann–Pick disease

By Laurel Oldach

Researchers at the University of Illinois at Chicago have used mass spectrometry imaging to map lipid accumulation in Niemann–Pick disease with unprecedented detail. Their results were published in a recent issue of the **Journal of Lipid Research**.

There are three major forms of Niemann–Pick disease. All are genetic and rare. Type C, or NPC, results in accumulation of cholesterol and complex lipids known as gangliosides in the endosomes and lysosomes of cells. This accumulation leads to neurodegeneration, killing patients when they are young. Many die before they're 10. It's rare for one to live to 40.

Based on the way movement and cognition problems emerge in NPC, it seems that different brain regions degenerate at varying stages of the disease. To understand this staging better, it would be useful to visualize lipid accumulation in specific brain regions. This isn't easy to do with traditional methods, because antibodies against gangliosides are not very specific, so most studies of lipid accumulation in Niemann–Pick disease use homogenized tissue samples from mice with the disease and measure bulk lipids by mass spectrometry.

To achieve greater spatial accuracy, researchers in Stephanie Cologna's lab used mass spectrometry imaging to look closely at lipids in specific regions of the cerebellum in mice with early-stage NPC. Mass spectrometry imaging, which does not require antibodies or chemical labeling, works by representing small areas of a tissue sample as pixels. The researcher coats a tissue sample in a matrix that helps it to ionize and then collects mass spectra from many tiny areas within that sample.

Each spectrum from one pixel includes information about the abundance of many lipid species. The team used the information about different molecules to make images representing the distribution of lipids across the cerebellum.

Mindful of variations in the intensity of matrix-assisted laser desorption/ionization spectra that can arise from uneven application of the matrix or variability among samples, the team, led by graduate student Fernando Tobias, also devised an algorithm to evaluate the most abundant signals. The algorithm let them filter out noise and compare measurements of wild-type and NPC brain samples more reliably with many replicates.

Once they compared lipid distributions across the cerebellum, the team made the interesting observation that, while two types of ganglioside (GM2 and GM3) are drastically higher in the NPC mouse's cerebellum, GM1 seems to go up throughout the brain. Also, GM2 elevation is very tightly localized in a part of the cerebellum called lobule X, but it's not yet clear what that might mean.

The researchers intend to continue using mass spectrometry imaging to get a more granular picture of the disease course.

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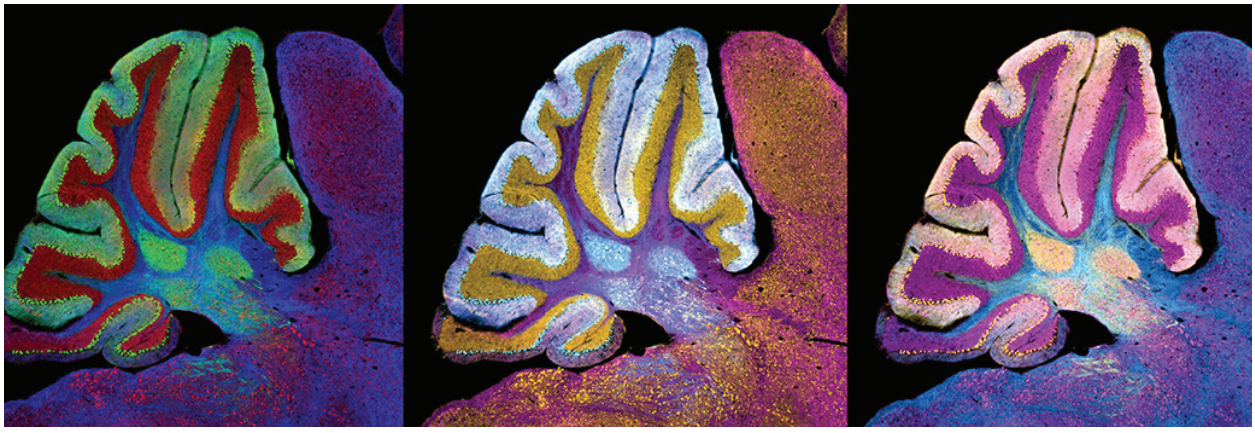

WILLIAMS/NICHD

This image of a cerebellum from a mouse with Niemann–Pick C was generated using fluorescence immunolabeling, which is an effective technique for determining protein distribution but cannot capture the location of gangliosides and other lipids that accumulate and cause the disease.

A royal legacy

Researchers delve into sugar modifications to proteins in honeybees' royal jelly

By Laurel Oldach

Katharina Paschinger's father, a conservation chemist in Vienna, was a devoted beekeeper. Paschinger remembers fondly that he would bring royal jelly, an important food for bee larvae, as a gift on visits to her maternal grandmother.

"He would feed it to my grandma and tell her it was for long life and beauty," Paschinger said. "And actually, she lived to be 98."

Royal jelly is widely believed to have health benefits, although the medical evidence is scarce (and doctors caution that some people have severe allergic reactions). One thing the substance certainly does is promote caste development in honeybees, causing genetically identical larvae to develop into very different adults. All bee larvae eat royal jelly secreted by worker bees for the first few days of life, but those selected to be queens continue to eat it until they pupate and beyond, whereas those that will become workers switch to honey and pollen. Biologists believe molecular signals in royal jelly drive larval bees to develop into queens, but the details of that signaling — including what molecule is most important and how it is recognized — are not yet clear.

Such questions brought Katharina Paschinger, a chemist, to revisit royal jelly this year in research published in the journal **Molecular & Cellular Proteomics**. Paschinger and colleagues in Iain Wilson's lab at the University of Natural Resources and Life Sciences in Vienna focus on glycoproteins, proteins to which a chain of sugar molecules is attached. These sugar chains, called glycans, can affect proteins' binding and signaling activities dramatically.

Previous studies of royal jelly glycoproteins mostly had found classes of glycans known as oligomannosidic and simple hybrids. As these contain no special recognition elements, they could not explain the unique effect of royal jelly on larval fate. But Paschinger, her colleagues and other scientists recently began to find more complex glycan structures in several insect species, such as mosquitoes and moths. Their data, Paschinger said, challenged "a really long-held belief that insects only synthesize oligomannosidic glycans. You see these statements everywhere. It's a nightmare to read such simplifications."

WAUGSBERG/WIKIMEDIA COMMONS

These two queen cells were opened to show queen larvae of the Western honey bee floating in royal jelly.

The diversity in other insects' glycans was a reason to suspect that royal jelly glycoproteins also had hidden depth. Royal jelly, available in bulk at health food stores, was a good candidate for a combined glycomic and glycoproteomic analysis, first author Alba Hykollari said.

"If you have a sample and you want to start with glycomics, the first question is how much you have and how pure is it," Hykollari said. "We were quite lucky; we got a lot of royal jelly, and it was very pure."

To determine the structure of the glycans in royal jelly, Hykollari used enzymes to isolate the glycans from proteins and added chemical tags. She separated the tagged glycans using liquid chromatography and analyzed them using a mass spectrometer.

Paschinger analyzed the data to draw conclusions about the glycan structures. First, she compared fragmentation patterns to precursor molecules, making inferences about the glycans' structures from how they broke apart. Then she suggested specific chemical or enzymatic treatments to test those hypotheses.

Because glycans are modular chains, like Legos, breaking off one unit at a time can give a good idea of how the whole fits together. For example, phosphoethanolamine, a subunit the team observed in royal jelly, blocks digestion by some

enzymes, but it can be removed using hydrofluoric acid. If glycan fragments of a certain mass appeared after treatment with hydrofluoric acid, it was a clue that phosphoethanolamine was present.

"I would say that the N-glycome of royal jelly was definitely underestimated," Hykollari said.

Of the approximately 100 glycan structures the team defined, many had not been observed before in bees. Their laboratory's exclusive focus on glycan biochemistry and their extremely sensitive mass spectrometer helped the researchers determine the identity of scarce glycans, Hykollari said. "We have worked (on glycans) for many years, so I would say our workflow is optimized."

Knowing these structures could help future scientists understand the activity of glycosylated proteins in royal jelly — either how they designate larval bees as future queens or how they trip allergic alarms in the human immune system. For example, said Paschinger, a researcher could synthesize a glycan from royal jelly to see how it interacts with signaling proteins in the larva. Their own plans moving forward are to tackle the glycome of another species.

"Our driving force is understanding glycoevolution," Paschinger said. "But very often we're also driven by the element of challenge."

Paschinger said the research team dedicated their manuscript to her father, the chemist-beekeeper. "I am sure he would have been very happy to see something scientific come out of his beekeeping hobby."

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Upcoming ASBMB events and deadlines

DEC

1: World AIDS Day
4: ASBMB–Deuel Conference on Lipids early registration deadline
9–12: Special Symposium: The Many Faces of Kinases and Pseudokinases
10: Advocacy Training Program application deadline

JAN

2: Science communication course application period begins
22: ASBMB–Deuel Conference on Lipids abstract deadline
30: Annual meeting late-breaking abstract and early registration deadline
31: ASBMB Honor Society application deadline

FEB

1: ASBMB–Deuel Conference on Lipids registration deadline
16: Annual meeting Outstanding Student Chapters Award deadline

From the journals

By Courtney Chandler, Isha Dey, 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**.

Seeking new ways to lower cholesterol

ApoE is a key transporter of extracellular cholesterol in humans. ApoE mimetics such as Ac-hE18-NH2 have undergone clinical trials as cholesterol-lowering agents. Roger White and colleagues at the University of Alabama at Birmingham recently developed new analogs by linking different chemical groups to Ac-hE18-NH2 and investigating their ability to lower cholesterol in mice and macaques. Of the three analogs investigated, one in particular was the most effective at reducing plasma cholesterol in mice that lacked apoE and were fed a standard or high-fat diet. This analog was synthesized by linking a 12-carbon myristic acid chain to Ac-hE18-NH2. This analog also was used to treat macaques that had elevated plasma cholesterol levels. A single administration of the analog was enough to reduce cholesterol in the plasma for up to one week, depending on the dose. Cholesterol in low-density lipoproteins also was reduced significantly after treatment and did not return to baseline until one week after treatment. This work, published in the **Journal of Lipid Research**, may have implications for developing better cholesterol-lowering therapeutics.

DOI: 10.1194/jlr.M085985

Breaking up a pair of Alzheimer's troublemakers

During Alzheimer's disease, the protein amyloid-beta aggregates in the brain into insoluble fibrils and soluble oligomers. Amyloid-beta oligo-

Early screening improves disease outcome

Cerebrotendinous xanthomatosis, or CTX, is a rare autosomal recessive genetic disorder characterized by abnormal storage of fats in the body. The disease is caused by a mutation in a gene that converts cholesterol to bile acid. Accumulation of fats within the brain can lead to neurological symptoms, and people with this disorder often also suffer from jaundice, tendon inflexibility and progressively brittle bones. Certain populations, including Moroccan Jews and the Israeli Druze community, have higher incidence of CTX. The disease can be functionally cured by early diagnosis and treatment from birth onward. Quality of life and success of treatment are diminished when a diagnosis is delayed.

Researchers led by Tzipora Falik–Zaccai of the Galilee Medical Center conducted a prospective study on dried blood spot, or DBS, samples collected from newborns to detect characteristic CTX-associated markers. They also collected samples high-risk Israeli newborns. Falik–Zaccai and colleagues used a two-tiered approach to identify CTX-positive samples. In the first tier, they used flow-injection tandem mass spectrometry to analyze all DBS samples. This approach detected CTX-positive newborns with 100 percent sensitivity and a low false-positive rate. As the second-tier test, they used liquid chromatography mass spectrometry, which detected CTX-positive samples with 100 percent specificity and 100 percent sensitivity. The team's research, recently published in the **Journal of Lipid Research**, describes the feasibility of a two-tiered screening process to diagnose CTX in newborns using DBS samples. This type of screening could improve early diagnosis of CTX, thereby ensuring early treatment and improving quality of life.

ZIVYA/WIKIMEDIA COMMONS

A rare genetic disorder characterized by abnormal storage of fats in the body can be functionally cured by screening newborns and treating them immediately.

DOI: 10.1194/jlr.M087999

— Courtney Chandler

Obesity study connects genes, brains and immune cells

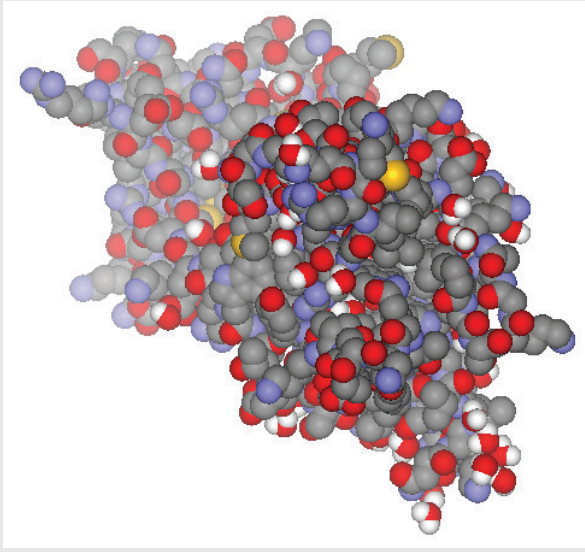
Researchers from the Burke Medical Research Institute and Weill Cornell Medical College have connected a genetic risk factor for obesity to an immune cell receptor, uncovering a pathway that may pave the way for more precise treatments for metabolic disorders. Their work was published in the **Journal of Biological Chemistry**.

A particular variant in the gene encoding brain-derived neurotrophic factor, or BDNF, causes humans and mice to become extremely obese when fed a high-fat diet. BDNF plays several important roles in the brain, including regulating emotions such as anxiety and aggression as well as appetite. The obesity-associated BDNF variant is very common, present in up to 30 percent of Americans and 70 percent of Asians. Sunghee Cho, a professor of neuroscience at Weill Cornell, wanted to know how fat metabolism worked in the population of people carrying this variant.

Her team found that, in mice carrying the human obesity-associated BDNF mutation, another multifunctional protein was implicated: the receptor CD36. When expressed in taste receptors in the tongue, CD36 is responsible for our love of the flavor of fat. (Knockout mice lacking CD36 do not exhibit their typical preference for fatty foods.) When expressed in monocytes and macrophages, CD36 takes up long-chain fatty acids, which provide energy for these long-lived immune cells.

"(CD36) is heavily involved in lipid metabolism," Cho said. "When it sees a nutrient, it uptakes it."

When mice with the obesity-associated BDNF gene variant were treated with an inhibitor of CD36, they did not gain as much weight on a high-fat diet and had less insulin resistance and less inflammation. However, the inhibitor did not affect weight gain in mice with the other BDNF variant, suggesting that CD36 is uniquely important in populations that are genetically obesity-prone.



JACOPO WERTHER/PROTEIN DATA BANK

Brain-derived neurotrophic factor, or BDNF, regulates both emotions and appetite.

"The import of the findings is that we can manipulate CD36 based on an individual's genetic makeup," Cho said.

DOI: 10.1074/jbc.RA118.002405

— Sasha Mushegian

mers bind to membrane-associated prion protein. This binding leads to hallmarks of disease like over-phosphorylation of tau protein and destabilization of dendritic spines. In a paper in the **Journal of Biological Chemistry**, Nadine Rösener and colleagues at Heinrich-Heine-Universität Düsseldorf characterized the complex containing amyloid-beta and prion protein and showed that a D-enantiomeric peptide, identified in a previous screen of potential drug candidates, could inhibit the formation of this complex.

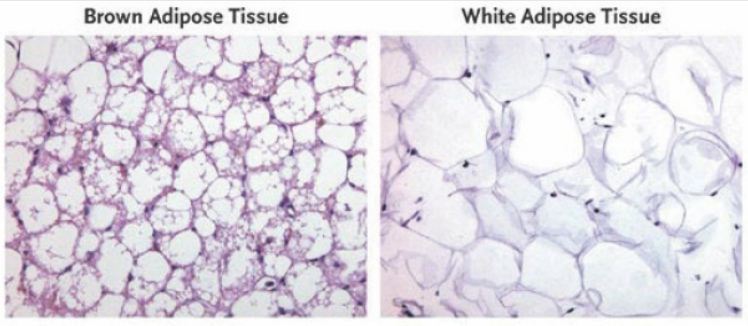
DOI: 10.1074/jbc.RA118.003116

What determines protein complex stability?

Most of the time, individual proteins perform important functions in our systems as part of a larger complex of multiple proteins. A protein's function is determined by certain moieties or functional groups that are attached to it after it has been synthesized from RNA. Such additions are called post-translational modifications, or PTMs. The location of such modifications within a protein determines its binding affinity with other proteins and the stability of protein–protein interactions under different conditions. A recent collaborative study by Nikolina Šoštarić and researchers in labs across three countries in Europe has identified certain PTMs that stabilize or destabilize protein complexes purified from budding yeast, or Saccharomyces cerevisiae. They focused on the evolutionarily conserved PTMs at a protein–protein interface and used various computational approaches to determine the effect of these PTMs in regulating protein-protein interactions. Their findings, published in the journal **Molecular & Cellular Proteomics**, suggest that acetylated lysine residues play a stabilizing role

Comparing the content of white and brown fat cells

Fat-producing adipose tissue plays an important role in our bodies by making fats, storing them when they are not needed and metabolizing them to release energy under various conditions. The tissue consists of two kinds of cells: white adipocytes that provide insulation between organs and release energy in times of starvation and brown adipocytes, mainly present in newborns, that produce heat by consuming energy. Recent evidence indicates other systemic functions of these cells, a lot of them regulated by hormones, but details of this regulation are not understood.



VAN MARKEN LICHTENBELT ET AL/DIAPEDIA

In adipose tissue stained with hematoxylin and eosin, brown adipose tissue is seen to contain multiple lipid droplets (white areas) and mitochondria (purple lining).

Recent multidisciplinary work by Asrar Ali Khan and researchers at several institutes in Germany, published in the journal **Molecular & Cellular Proteomics**, compares the secretome of mouse-derived white and brown adipocytes with or without hormonal stimulation. According to this study, while unstimulated brown adipocytes secrete a variety of proteins, unstimulated white adipocytes mainly secrete carbohydrate metabolism-regulating proteins. When the authors stimulated these cells with the hormone norepinephrine (essential for many physiological functions), they found that the brown adipocytes released many novel cytokines (cell-signaling proteins), while white adipocytes secreted more known cytokines. Interestingly, brown adipocytes showed a marked change in their secretome upon hormonal activation.

Overall, norepinephrine stimulation triggered the adipocytes to secrete a diverse range of proteins regulating various processes apart from carbohydrate metabolism, namely lipid metabolism and adipogenesis. Increased secretion of proteins conferring resistance to oxidative stress also was observed.

This study sheds some light on the response of fat-processing cells to hormonal regulation. Moreover, brown adipose tissue has been identified as a target for the treatment and prevention of obesity and obesity-associated diseases such as Type 2 diabetes. This study provides an archive of the potential biomarkers of activated brown adipocytes, which could be exploited for treating brown adipocyte-associated diseases.
DOI: 10.1074/mcp.RA118.000704

— Isha Dey

while phosphorylated residues play a destabilizing role in protein complexes. Though this study broadens our understanding of the functional role of PTMs, it remains to be seen how these findings from purified protein complexes repeat within developing cells and extrapolate to other organisms.
DOI: 10.1074/mcp.RA118.000892

If you had a nickel for every UTI

E. coli and other bacteria that cause urinary tract infections sometimes carry the gene encoding the metallophore yersiniabactin, or Ybt. Ybt previously was shown to chelate iron and copper ions. In research published in the **Journal of Biological Chemistry**, Anne Robinson and colleagues at Washington University School of Medicine showed that Ybt additionally scavenges nickel from the extracellular environment and imports it into nickel-requiring enzymes in the bacterium. Nickel-requiring enzymes like urease have been associated with uropathogenicity, suggesting that this nickel-scavenging pathway may be important for understanding UTIs.
DOI: 10.1074/jbc.RA118.004483

More than one strategy against cancer

Immunotherapy is a promising strategy against cancer, but immune responses against cancer must be quantified and controlled to avoid dangerous side effects from hyper-inflammation. Christian Backes and colleagues at Saarland University wrote in the **Journal of Biological Chemistry** about developing a time-resolved single-cell assay for monitoring the kinetics and mechanisms of how natural killer cells cause target cell death. They found that a single NK cell could kill cancer cells via

Mitochondrial proteins take a hit in a mouse model of fatty liver

Kwangwon Lee and a team of researchers at Northeast Ohio Medical University studied the lifespan of mitochondrial proteins in a mouse model of fatty liver disease. Comparing the amount of protein between healthy mice and a mouse model of nonalcoholic fatty liver disease gave them an estimate of each protein's half-life.

Their findings, published in the journal **Molecular & Cellular Proteomics**, show that many proteins involved in mitochondrial function, especially those directly involved in making ATP, are broken down more quickly than usual in a fatty liver. Not only does this reduce the number of proteins, but the remaining proteins are also less active.

The insult to ATP-producing proteins damaged the mitochondria. In an apparent effort to get rid of dysfunctional mitochondria, cells from fatty livers showed more evidence of digesting their mitochondria but did not increase production of new ones. As a result, the authors observed mitochondrial and ATP shortages in the cells of mice with fatty liver.

The authors proposed that because the overloaded liver cells used fatty acids instead of glucose to make energy, they might have created more reactive oxygen byproducts, which damaged proteins.

DOI:10.1074/mcp.RA118.000961

— Laurel Oldach

different mechanisms, either inducing apoptosis or causing membrane disruption and lysis (necrosis). Because these different types of cell death have different effects on the surrounding tumor microenvironment, this variation should be taken into account to fine-tune NK cell-based immunotherapy.

DOI: 10.1074/jbc.RA118.004549

Synthetic surfactants stick around longer

Pulmonary surfactants are protein–phospholipid mixtures secreted into the alveolar space that reduce surface tension where air and liquid meet. Substitutes have been developed to treat patients who need surfactant supplementation, including preterm infants. A paper in the **Journal of Lipid Research** describes the differences in metabolism between synthetic and animal-derived exogenous surfactants. Anthony Postle and colleagues at the University of Southampton in the U.K. used mice to compare the metabolism of Curosurf, an animal-derived surfactant used by doctors, with that of CHF5633, a synthetic surfactant in clinical trials. Both were labeled with a carbon isotype-containing tracer and introduced to mice intranasally. The researchers extracted lipids from lung lobes harvested at various time points after introduction, and they dectected the tracer using electrospray ionization mass spectrometry. By tracking the hydrolysis products of each surfactant, Postle and colleagues were able to compare their catabolism profiles. They observed that catabolism of synthetic CHF5633 was delayed compared with that of animal-derived Curosurf, although the pathways used for metabolism were similar. They also observed enhanced recycling of the hydrolysis products of CHF5633 into new phospholipid species. Their findings have implications for how the metabolism of new synthetic pulmonary surfactants will be evaluated during clinical trials.

DOI: 10.1194/jlr.M085431

An alternative pathway in brain mitochondria

The mitochondrial calcium uniporter, or MCU, mediates calcium influx into mitochondria, regulating calcium-dependent processes including mitochondrial respiration. James Hamilton and colleagues at Indiana University School of Medicine

showed that the role of this transporter may be different in brain-cell mitochondria than in other cell types. Whereas knocking out MCU in liver, heart and skeletal muscle mitochondria completely inhibited calcium uptake, it only slowed but did not completely inhibit uptake in mitochondria from glial cells. This suggests that another, MCU-independent calcium uptake pathway exists in brain mitochondria and may explain why ischemia-reperfusion injury has brain-specific effects. This research was published in the **Journal of Biological Chemistry**.
DOI: 10.1074/jbc.RA118.002926

Chaos and flexibility in elastin

Elastins are the proteins that allow lungs, arteries and skin to stretch and bend. To understand these essential proteins' mechanical properties and resilience, we need to know how the network of elastin fibers is cross-linked. In research published in the **Journal of Biological Chemistry**, Christoph Schräder and colleagues at Martin Luther University Halle-Wittenberg characterized these cross-links in detail in mature bovine elastin. Contrary to the previous assumption that these proteins are assembled in an orderly array, Schräder and colleagues showed that elastin formed an unordered, randomly cross-linked network.
DOI: 10.1074/jbc.RA118.004322

Of dual-coding genes: database revision needed

A gene is a piece of DNA that codes for a protein. It contains a nucleotide sequence called the open reading frame, or ORF, which the RNA polymerase reads and then translates the codons (sets of three bases coding for one amino acid) into messenger RNA, which ultimately forms the protein after some post-transcriptional processing. According to the one gene–one protein hypothesis of George Beadle and Edward Tatum, each gene codes for a single protein. However, a recent paper in the journal **Molecular & Cellular Proteomics** by Xavier Roucou and researchers from the Université de Sherbrooke in Canada in collaboration with INSERM (Institut National de la Santé et de la Recherche Médicale) in France reiterates the existence of dual-coding genes, that is, single genes coding for different proteins from different ORFs. They showed that the gene MIEF1, known to encode 463-amino-acid protein MiD51 (an important regulator of mitochondrial division), also encodes the 70-amino-acid protein altMiD51. The smaller protein is coded by an exon originally considered noncoding. In fact, in both cell lines and tissues, the smaller protein was expressed two to six times more than the bigger protein. Although expression does not correlate with function, this study means that alternate ORFs must be incorporated in a gene's coding sequence in the database.
DOI: 10.1074/mcp.RA118.000593

Understanding oddball interferons

The 16 human type I interferons, or IFNs, regulate innate and adaptive immunity. Two of them, IFN-epsilon and IFN-kappa, have very different sequences from the others and are expressed selectively in skin, mucosa and the female reproductive system. In research published in the **Journal of Biological Chemistry**, Bethany Harris and colleagues at the University of Alabama report biophysical characterizations of these two IFNs' binding interactions. They found that the two had thousandfold lower potency in signaling through the cell-surface receptor IFNAR2 than other IFNs but also had much lower affinity for an IFN-blocking viral protein. The authors speculate that these features are important for protection against viruses, including HIV, in the reproductive tract.
DOI: 10.1074/jbc.RA118.003617

Stress and iron break ribosomes

Under oxidative stress, ribosomal RNA can break. The mechanism of this breakage was incompletely understood. In research published in the **Journal of Biological Chemistry**, Jessica Zinskie and colleagues at Rowan University showed that oxidant-induced cleavage of rRNA was site-specific and mediated by cellular iron. When free iron bound to ribosomes at specific sites, its redox activity resulted in rRNA fragmentation. The authors speculate this effect could be an adaptive mechanism for fine-tuning ribosome activity under stress.
DOI: 10.1074/jbc.RA118.004174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THE ANTIBODY PATENT QUESTION

Can a drug company own every monoclonal antibody in a class — even the ones they don't know about?

By Laurel Oldach

The U.S. Supreme Court will decide in early 2019 whether to consider a patent dispute over monoclonal antibodies. At issue is whether a company, namely the pharmaceutical giant Amgen, can patent every antibody that binds a given epitope — even if there might be millions of such antibodies and not all are yet discovered.

Amgen filed the patents in question in 2008. They cover a class of antibodies that bind to the proprotein convertase subtilisin/kexin type 9, or PCSK9, and thereby lower cholesterol. Amgen markets one PCSK9 inhibitor as Repatha. The company is suing rival pharmaceutical giant Sanofi over its competing drug, Praluent, which targets the same part of PCSK9.

If Amgen goes before the high court and prevails, it will get to lay claim to a whole therapeutic approach. If it loses, patenting groups of antibodies will get much harder, especially for research teams that aren't bankrolled by pharmaceutical companies and represented by high-dollar legal teams.

But it's not clear yet that the high court will even take up the case, Amgen Inc. v. Sanofi et al. Some experts predict the precedent-loving court will send it back to the lower court. Others see it as a potentially important test case.

Fifteen years ago, PCSK9 was a barely known gene defined by homology to a family of proteases and by an interesting phenotype in a few humans with mutations. It developed with unusual speed into a drug target and a legal battleground that may set important precedent for the biotech industry.

A new genetic link to cholesterol

The story starts with the discovery that some patients with familial hypercholesterolemia, or very high levels of low-density lipoprotein cholesterol, also known as LDL, carried mutations in a newly identified gene called PCSK9. A group of French scientists led by Catherine Boileau published that finding in the journal Nature Genetics in 2003.

Scientists all over the world took notice. Within a year and a half, three groups had shown in mice that overexpression of PCSK9 in the liver raised blood levels of cholesterol because of a reduction in LDL receptors in the liver.

Tom Lagace, an American who had just finished his Ph.D. at Dalhousie University in Canada, joined one of those research groups at the University of Texas Southwestern Medical Center in 2004. He had hoped to focus on transcription factors called SREBPs, but his mentors had a different project in mind for him.

Lagace recalls a senior scientist sitting him down and saying, "'No, you're not going to work on that project. You're going to work on this, PCS, PSC' — he had to go and get a paper, then he said, 'Oh, yeah, PCSK9.'"

UTSW's department of molecular genetics had a storied history in cholesterol research. It was home to the lab of Nobel laureates Michael Brown and Joseph Goldstein, who had discovered the LDL receptor.

The receptor, expressed on the surface of liver cells, ferries low-density lipoproteins rich in cholesterol from the blood into liver cells through endocytosis. The LDL receptor then is recycled to the cell surface, while the lipoproteins are metabolized. Mutations in the receptor that disrupt this metabolic pathway are linked to high blood cholesterol. Brown and Goldstein's description of this cycle had paved the way for the development of a class of drugs called statins, and they shared a Nobel Prize for the work in 1985.

Brown and Goldstein continued to research mechanisms of cholesterol

UNIVERSITY OF OTTAWA HEART INSTITUTE

Tom Lagace is a professor at the University of Ottawa Heart Institute.

ASBMB

Michael Brown (left) and Joseph Goldstein, 1985 Nobel laureates in physiology or medicine, have long been involved in research on cholesterol metabolism.

homeostasis in a growing department at UTSW, which Goldstein chaired, staffed by many of their former trainees.

Lagace went to work for one of Brown and Goldstein's former postdocs, Jay Horton, by then a UTSW professor. Horton had come across PCSK9 independently in a study published in 2003, finding that its RNA level responded to SREBP.


HORTON

After that study and Boileau's were published, the Horton lab began to investigate mice that overexpressed PCSK9, which had higher cholesterol.

Horton shared his study results with UTSW colleagues Helen Hobbs, a physician-scientist who had also trained in the Brown and Goldstein lab, and Jonathan Cohen. Hobbs and Cohen had just established the Dallas Heart Study, using population genetics to search out rare genetic variants with significant effects on cardiovascular disease.

After hearing about the effects of PCSK9 overexpression in mice, Hobbs said, she and Cohen decided to look for mutations in PCSK9 that would kill its function. They reasoned that such mutations should appear in people with more LDL receptor activity and lower blood cholesterol.

"We went to our (heart study) population and sequenced the coding regions of PCSK9 in the individuals with the lowest LDL levels and hit pay dirt right away when we found a nonsense mutation," Hobbs told the Journal of Clinical Investigation in 2015.

The study subjects whose PCSK9 genes included a nonsense mutation had LDL levels much lower than those without the mutation. The team also discovered a missense mutation that changed a single amino acid in PCSK9. They tested the effects of these sequence variations in a different group and found that people with PCSK9 mutations had a reduced rate of heart disease.

Meanwhile, the Horton lab continued to investigate the molecular mechanisms that led to PCSK9's effect.

"I was quite lucky that a former postdoc was just leaving" the lab, Lagace said, "so I came at the right time." His predecessor left him a collection of plasmid constructs and a big question to work on: How did PCSK9 reduce cell-surface levels of the LDL receptor?

PCSK9 is a member of a family of proteases, enzymes that break down other proteins. It stood to reason, and some mechanistic work from other labs suggested, that its effect on cholesterol came through breaking down another protein — but which? What was PCSK9's substrate?

Lagace set about finding out.

'Bingo. I had it.'

He did not have much luck.

"My project was to develop a protease assay and find out what PCSK9 (was) cutting," Lagace said. "And I was getting nowhere. Now, looking back, I was getting nowhere because it's not active. But at the time … I was really struggling."

Frustrated and increasingly worried that he had nothing positive to present at the lab's weekly meeting, Lagace decided to try isolating the protein from mammalian cells instead of the bacterial or insect cells he had been using. Post-translational protein modifications are known to differ among species; perhaps, he thought, some crucial tweak to PCSK9 was missing in the protein purified from bacteria.

After setting up a system in the lab to express and purify the protein from human cells, he said, "I was really struck that the PCSK9 in the medium was much greater than the PCSK9 in the cells." That led him to hypothesize


COURTESY OF UTSW

Helen Hobbs and Jonathan Cohen, professors at the University of Texas Southwestern Medical Center, discovered that people with mutations that lowered PCSK9 had lower LDL cholesterol.

that the protein is mostly secreted — and that the previously published work suggesting PCSK9 operated inside of cells was somehow incorrect.

To test the idea, Lagace asked a nurse who worked nearby to draw some of his blood. He checked it for PCSK9; the protein was definitely in his plasma. Then he asked a colleague who processed and fractionated patient samples to run his plasma through a size-exclusion column, which separates macromolecules in a solution according to their mass.

"All I was going to do was see how big PCSK9 was (in case it oligomerized), but he also gave me the lipoprotein profiles. I was really struck that a lot of the PCSK9 was in a perfect overlap with low-density lipoprotein in the blood," Lagace said. A quick experiment using isolated proteins and lipoproteins confirmed that PCSK9 bound to low-density lipoprotein particles.

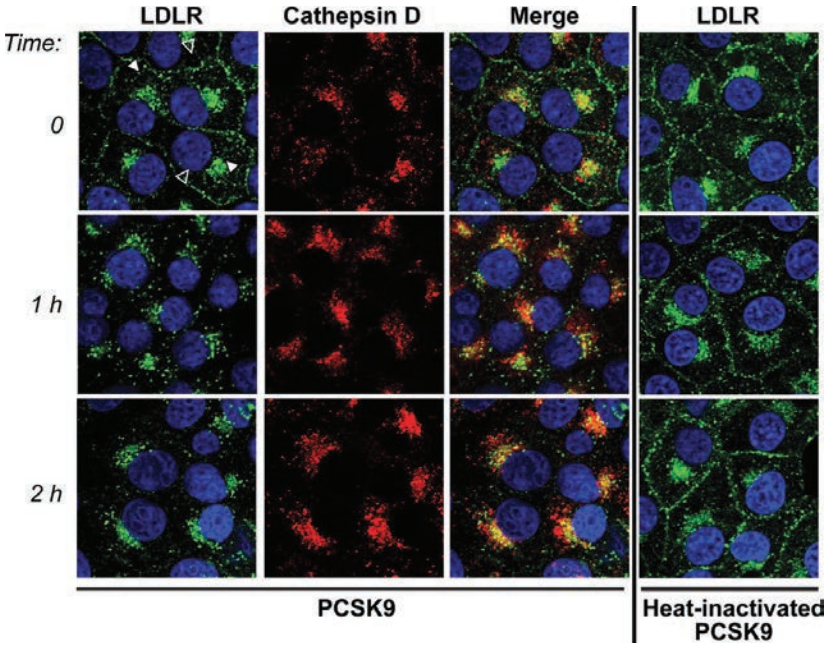
"Nobody knows this, but the first thing I ever found wasn't LDL receptor binding; it was LDL binding."

Thinking that PCSK9 might piggyback on LDL particles and attack LDL receptors once it was internalized, he set up an experiment controlled with PCSK9 alone in LDL receptor-positive and -negative cells. To his surprise, even without LDL, PCSK9 could make it into the cells — but only if the receptor was present.

"So that was it. Bingo. I had it," Lagace said. "(PCSK9) binds to the LDL receptor."

His project took off. The next steps were clear, and the Horton lab, with the Hobbs and Cohen lab, was on the way to publishing a series of papers in the Journal of Biological Chemistry defining the mechanism by which PCSK9 affects LDL receptors.

In short, circulating PCSK9 binds to the LDL receptor's extracellular domain. When the LDL receptor is internalized by endocytosis, PCSK9 directs it to the lysosome for degradation. If circulating PCSK9 is blocked, the number of LDL receptors on the surface of liver cells goes up — providing a way to remove more LDL cholesterol from the blood.



ZHANG ET AL./J OURNAL OF BIOLOGICAL CHEMISTRY

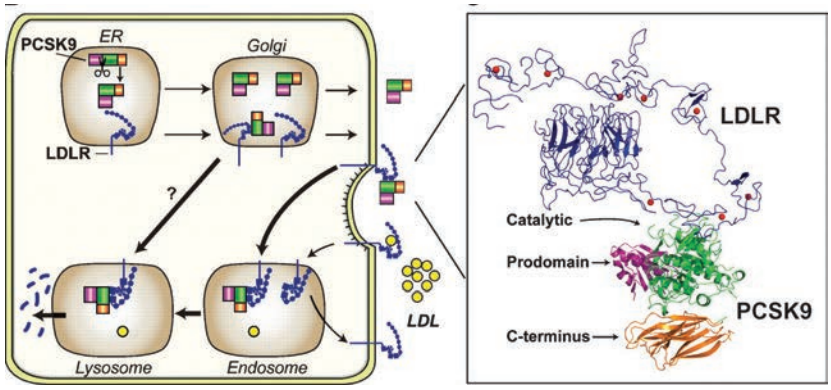
An imaging experiment from a Horton lab publication shows the effect of PCSK9 on LDL receptor internalization. The receptors (green) move into lysosomes (marked with cathepsin D, red) after PCSK9 is added. If PCSK9 is denatured (right column), the internalization does not occur.

"Because PCSK9 is secreted in the blood and works extracellularly," Horton explained in a 2015 interview, "an opportunity to create antibodies was created. These antibodies can function in the blood and block the interaction of PCSK9 with the LDL receptor, essentially resulting in an inhibitor of the PCSK9 protein."

Meanwhile, at Amgen

The potential value of a PCSK9 inhibitor was clear both to Horton and to scientists at pharmaceutical companies. When the 2003 Nature Genetics paper came out, Simon Jackson was working at a biotechnology startup called Tularik. He read the paper, chatted with his supervisor about it and put it away. It wasn't the right time, he said in court in 2016.

In 2004, Amgen bought Tularik.



HORTON ET AL./JOURNAL OF LIPID RESEARCH

A figure from a review article by Horton, Cohen and Hobbs shows how PCSK9 (green, purple and orange) promotes internalization and destruction of the LDL receptor (blue) in liver cells.

Jackson stayed on as a scientist. PCSK9 came back to his attention in 2005, when Goldstein visited Amgen and gave a lecture on findings from the Horton lab.

Horton's group had found not only that mice without PCSK9 had lower cholesterol but also that giving them blood from a mouse that did carry the gene raised cholesterol again, suggesting that PCSK9 operates in the bloodstream and not within liver cells. Hobbs and Cohen's discovery that humans with nonfunctional PCSK9 have lower cholesterol was not yet published, but Jackson saw evidence in Goldstein's talk that that reducing PCSK9 in the blood could be beneficial to patients.

"So I presented to the senior team at Amgen," Jackson testified in 2016. He earned their approval to begin research on ways to block PCSK9 activity, focusing on its hypothetical protease activity.

At around the same time Lagace was making his discoveries, Jackson and his team at Amgen were arriving at the same conclusion: PCSK9 bound directly to the LDL receptor, reducing its presence on the surface of liver cells.

Was the discovery completely independent?

At trial, Sanofi's lawyers pointed out that Horton, like Goldstein, had visited Amgen while this research was ongoing. Amgen's witnesses insisted that the scientific discussions concerned only published work. (Cohen and Goldstein both declined requests to be interviewed for this story; Horton and Hobbs did not respond.)

In any case, once it was clear that PCSK9 functioned by binding to the LDL receptor, and not as an enzyme, the next step was to come up with a protein product that could block that binding. By doing that, researchers could block LDL receptor internalization and degradation, leaving the protein able to suction more LDL out of the bloodstream. That would lower patients' risk of heart attack.

To find proteins that block PCSK9 from binding to the LDL receptor, Jackson called on Amgen's antibody team, led by Chadwick King.

"What we wanted to do was design an antibody that bound to the LDL receptor binding site (on PCSK9) and blocked that interaction," King said at trial. "What we didn't know was exactly where the site was on the molecule."

With a clever assay design, however, the team didn't need to know the exact binding location. They just needed to find out which of about 3,000 antibodies they had raised against PCSK9 in mice could block the protein from also binding the LDL receptor.

"What we were asking was, if we had PCSK9 in solution and we allowed that (experimental) antibody to bind, could that complex then bind to the LDLR on the plate?" King explained at trial.

The team found 85 antibodies that block PCSK9–LDL receptor binding. They continued to characterize that subset, looking for antibodies that would make promising drug targets.

What's in a patent?

From a lawyer's point of view, a patent is essentially a trade. An inventor tells the government what they have invented and how it's made; the federal government protects the inventor's exclusive rights to the invention for a set amount of time, usually 20 years.

What goes into the application is governed by a law that reads, in part, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same."

In most fields, that means a structural definition of the product, perhaps with some diagrams.

As anyone who has taken a biochemistry course knows, protein sequence determines structure, and protein structure determines function. So for protein inventions, applications that include the protein's amino acid sequence or its function have been accepted as reasonable proxies to structure. This is especially true for monoclonal antibodies, which are invented specifically to bind to other proteins.

Until recently, the U.S. Patent and Trademark Office would consider granting a patent application that described in detail the function of an antibody — by describing the epitope it bound. This was known as the "newly characterized antigen test." The Amgen v. Sanofi patent-infringement case, however, has forced the patent office to stop using that test.

The race to the patent office

The Amgen team was by no means the only industry research group working on PCSK9; the Amgen process is unusually public because they later disclosed it all in court. After Hobbs and Cohen published their finding that loss of PCSK9 lowered LDL cholesterol, it was clear the protein would become an important drug target. Hobbs told the Journal of Clinical Investigation, "There were a number of drug companies that picked it up."

Papers on protein crystal structures and patent applications indicate that teams at Novartis, Pfizer and Regeneron also were hard at work trying to block PCSK9. Adding urgency to their studies, everyone knew that statins, the blockbuster cholesterol-lowering drugs that included Lipitor, soon would come to the end of their patent protection and become much less profitable. (See box: What's in a patent?)

Charles Craik, a professor of pharmaceutical chemistry at the University of California, San Francisco, who doesn't work directly on PCSK9 but has followed its emergence as a drug target, said that with statins going off patent, "the whole market was wide open for something new. … There was a big race, and there was a lot of money involved."

CRAIK

Amgen won the race to the patent office. It took Jackson's team about a year and a half, from June 2006 to January 2008, to collect all the data they used in a patent filing. Beginning late in 2007, Amgen filed 30 patents for antibodies to PCSK9 with the U.S. Patent and Trademark Office, and a total of 81 worldwide.

ZYTCER

According to Ari Zytcer, an intellectual property lawyer and trained pharmacist based in Ohio who prepares patent applications, that flurry of patents is a typical strategy.

"Any time there is a drug that is this important, (lawyers) build a patent estate around it," said Zytcer, who does not represent Amgen. "You don't want to just cover the invention in a single way. You claim it in as many ways as you possibly can."

The origin of antibodies

Before scientists developed methods to produce monoclonal antibodies, researchers who needed antibody activity relied on antisera, heterogeneous mixtures of antibodies isolated from immunized animals. In 1975, Argentinian biologist César Milstein developed a method to make a single antibody species, or monoclonal antibody, by fusing a single antibody-producing cell from an immunized animal with an immortalized cancer cell. Milstein shared the 1984 Nobel Prize in Medicine for the finding.

Although the invention, called a hybridoma, spawned drug industry profits now estimated at $90 billion a year, Milstein never applied to patent it.

That decision was famous and controversial. Though Milstein did go into business with a local antiserum producer to sell monoclonals, the outfit couldn't compete with larger biotechnology companies. He developed the method while working at the Laboratory of Molecular Biology in Cambridge, England. British Prime Minister Margaret Thatcher later criticized what she called Milstein's failure to patent the invention. Milstein, who had disclosed the hybridoma technology to his funding agency before publishing it in the journal Nature, blamed the bureaucracy for not pursuing a patent.

Charles Craik, a professor of pharmacology at the University of California, San Francisco, holds 16 patents. "It's amazing that César Milstein didn't try to patent monoclonal antibodies, hybridomas," Craik said. "He just published that material, and the world benefited enormously."

UK MEDICAL RESEARCH COUNCIL

Nobel laureate César Milstein invented an efficient method for generating monoclonal antibodies, which he never patented.

The most important of Amgen's patents, filed in January 2008, described the screen that King and colleagues had performed to winnow the 3,000 antibodies to a few leading drug candidates. The patent laid claim to a class of antibodies that block PCSK9's interaction with the LDL receptor. The patent filing also included crystal structures of two of those candidates in complex with PCSK9 and amino acid sequences of about two dozen more.

The two runners-up, Regeneron and Pfizer, filed applications before the end of 2009 to patent antibodies to PCSK9 to treat high cholesterol. Regeneron, the smallest of the three companies, licensed its product to pharmaceutical giant Sanofi for clinical development and commercialization.

In the race to launch a PCSK9 inhibitor, three of the year's top 15 drug companies were now in the running.

By the fall of 2014, both Amgen and Sanofi had demonstrated that their PCSK9 inhibitor antibodies were safe and effective treatments for patients with elevated LDL cholesterol, and both companies had submitted data from large efficacy trials to the Food and Drug Administration. They expected final FDA decisions around the same time on whether they could sell the molecules as drugs. Pfizer was a few years behind them, and later scuttled its drug candidate.

That October, the patent office finally approved Amgen's 2008 application on its PCSK9 inhibitor antibody screen. Just days later, Amgen sued Sanofi for patent infringement.

Why did Amgen sue?

The patents Amgen held, the company's lawyers said, described a whole

class of antibodies — any antibody that would bind to the LDL receptor-binding region of PCSK9, often referred to in court as the protein's "sweet spot." Sanofi was preparing to market an antibody that bound exactly there, meaning it fell into the protected class. Amgen's lawyers insisted that Sanofi stop.

Sanofi hired the best possible lawyer for its particular case. Dianne Elderkin, a patent litigator in Philadelphia, had represented Janssen Biotech in an important antibody patent case settled earlier that year. Abbvie, which owned the patent on a class of antibodies against a cytokine, had sued Janssen for developing an antibody that binds to the same target. Elderkin led the legal team defending Janssen from charges of patent infringement. Her team's case convinced the jury to find Abbvie's patent invalid.

Sanofi faced a problem similar to Janssen's: It was being sued for infringing on a patent that claimed a class of antibodies. Working as lead counsel with a team of lawyers and paralegals from three law firms, Elderkin became the face of Sanofi's argument that Amgen's patent was invalid.

Squaring off against Elderkin, Amgen's lead counselors were Sarah Columbia, a Boston litigator whose prior experience tended more to devices than large molecules, and William Gaede, a colleague at Columbia's firm who was experienced in biotech. The two headed up a team of lawyers and paralegals from two law firms.

Lawyers on both sides began to review each company's laboratory records, recruit professors to serve as expert witnesses, build their arguments and dispute which evidence was admissible in court.

As the case lumbered toward a trial, the FDA approved both drugs for the treatment of high LDL cholesterol in 2015. The two drugs launched commercially, Sanofi's as Praluent and Amgen's as Repatha, about a month apart that summer. Less than six months later, the patent-infringement suit went to trial in Delaware as Amgen Inc. v. Sanofi et al.

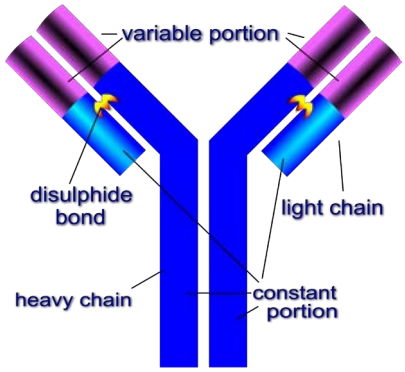
Pretrial negotiations were contentious, and neither side gave any ground. The presiding judge was Sue Robinson, a 24-year veteran of Delaware's District Court, one of the country's busiest intellectual property arenas. During a bench hearing early in the proceedings, Robinson observed to the opposing legal teams, "You all are going to appeal no matter what happens in this case, whether I stop it now, whether we go to a verdict, whatever I do with the verdict, whatever the jury does with the verdict."

The arguments

The legal issues were dense, but Amgen's core argument was simple. According to trial records, its lawyers argued that Sanofi and Regeneron had infringed on two of Amgen's patents, which protect any antibody that targets a specific LDL receptor-binding region of PCSK9. (Amgen's media relations office did not respond to a request for comment).

Sanofi's defense was not that its product didn't infringe on Amgen's patents. Instead, lawyers argued that the claims were inappropriately broad. In a statement to ASBMB Today, a Sanofi spokesperson wrote, "Amgen's patent claims essentially cover any anti-PCSK9 antibody that would work. Sanofi and Regeneron contend that these patent claims are invalid."

Everyone agreed that if the patent was valid as written, Sanofi had infringed upon it, so the issue before the jury was whether the patent was valid. In other words, did Amgen own every monoclonal antibody that binds the LDL receptor-binding region in PCSK9? To answer that question, the jury first needed to decide whether Amgen had described adequately a



WIKIMEDIA/DIGITAL SHUTTER MONKEY

Many types of antibodies, including most of the monoclonal antibodies used to treat diseases, share two polypeptides, the heavy and light chains, arranged in a Y-shaped structure. The specificity of antibody binding comes from sequence variation that leads to structural variation in the variable region, here indicated in purple.

class of antibodies and how to make them.

The law states what can't be patented: You can't patent something that's obvious, something that occurs naturally or — in most cases — an idea that hasn't been made real.

A patent needs to include a description of the product and a reasonable amount of information about how to make it, called enablement. These rules are a little relaxed for antibodies. (See box on page 31: What's in a patent?)

Also important in this case is that an inventor can patent a class of products — provided the patent application discloses enough examples in the class' written description that a colleague could see how they're related and imagine the rest of the class.

Being able to patent a class is useful in biotechnology. Otherwise, a competitor could tweak just enough of an antibody's sequence to fall outside of a patent's claims, profiting off an inventor's work. But it also raises a problem, because imagining all of the possible antibodies that could bind to a given epitope — all of the members of a class — is all but impossible.

In an influential antibody case decided in 2011, the U.S. Court of Appeals for the Federal Circuit described an epitope not as a lock with a single key, but a lock and "a ring with a million keys on it." And legal precedent, including the case Elderkin had won for Janssen, held that to own a class of antibodies, the inventor needs to describe a broad cross-section of the class, representing the diversity of those keys.

Sanofi's lawyers contended that Amgen had not provided enough information about how its family of antibodies was made or description of the antibodies themselves to qualify as a thorough description of the class. The team argued that the antibodies disclosed in the patent bound only to the edges of the PCSK9–LDL receptor binding site and, more importantly, that there was no way to envision what other antibodies would fit into the class.

Besides written description and enablement, one more important legal concept was in play. At the time Amgen had filed its patent, the part of PCSK9 that bound to the LDL receptor was not widely known. That meant Amgen's claims were also subject to a patent office assessment called the newly characterized antigen test, which protects inventors who find antibodies binding to a new and important antigen, even if the rest of the invention is routine.

For five days, the opposing legal teams and their expert witnesses argued over whether Amgen's patents fulfilled the written description and enablement requirements. (See box on page 35: Overheard in the courtroom.) Near the end of the trial, during an argument at the bench about how to phrase the jury's instructions for deliberation, Judge Robinson said, "This is the most complicated trial I've ever had."

One win each

Amgen convinced the jury that its patent claims were valid. The U.S. District Court for the District of Delaware ruled that Amgen's patent was indeed valid, and Robinson issued an injunction that would stop Sanofi from selling its PCSK9 inhibitor, Praluent. The website Law.com named Columbia and Gaede litigators of the week for the victory.

Just as Robinson had predicted, Sanofi immediately appealed. The U.S. Court of Appeals for the Federal Circuit took up the case and suspended the injunction before it went into effect. During the appeal, Sanofi parted ways with Elderkin's firm. Amgen added a few lawyers but kept its trial team otherwise intact.

Overheard in the courtroom

When Amgen Inc. v. Sanofi et al. went to trial in the District Court of Delaware, expert witnesses — many of them members of the American Society for Biochemistry and Molecular Biology — gathered at the courthouse in Dover to explain the scientific dispute to the jury and give their opinions on whether Amgen held a valid patent. A selection of their statements, in which they tried to bridge the legal and biochemical worlds, is offered below.

Sarah Columbia, attorney for Amgen:
"Would you agree with me or not that these authors … concluded that the molecular mechanism of PCSK9 action on the LDL receptor and the relationship of their observations remained to be determined?"

Jeffrey Ravetch, professor at the Rockefeller University:
"They state that. And you have to unpack that a bit because we write in jargon to each other. What they are saying is, we have identified LDLR as being an important downstream molecule for PCSK9. The precise molecular details we may need to determine. They put the second important piece in place but didn't know exactly the conclusions. That's the way science works. We build on top of prior observations."

"I'm not going to make any particular orientation here, but let's just say it binds like this. Okay? Then you can see if it does, you won't be able to get the LDL receptor in. That's what we mean by blocking. … You can see my assistant here is unable to get the LDL receptor to bind."

— Gregory Petsko, professor of neurology and neuroscience at Weill Cornell Medical College, while showing 3D printed molecule models based on the crystal structures in Amgen's patent

"I expect that there are antibodies — many, many antibodies — that will meet Amgen's claims that have nevertheless very diverse and different three-dimensional structures and primary amino acid sequences. I couldn't begin to tell you, by looking at that structure, what those particular amino acid sequences are or what those three-dimensional structures are other than the two examples that Amgen has provided in these patents."

— Michael Eck, professor of biological chemistry and molecular pharmacology, Harvard Medical School

"Granted, it is hard to get a straight answer out of experts on a general basis, but I believe he said there are different ways of doing it and he was just relying on what the inventors in this case did."

— Delaware District Court Judge Sue Robinson, ruling on whether an expert witness Donald Siegel had contradicted a prior deposition

"All this talk about 'We found a sweet spot' adds absolutely nothing to the knowledge of people of skill in the art going to make antibodies. It's just like, 'go make more, and then if you find one that binds here, great for you; that falls within our claims.' "

— Dianne Elderkin, attorney for Sanofi, during a bench conference, on whether Amgen's disclosures had enabled other scientists to generate all antibodies in the class without undue experimentation

In October 2017, the appeals court overturned parts of the lower court's ruling. It concluded that the lower court had been wrong to exclude some information that Sanofi had hoped to use to convince the jury that Amgen's written description and enablement were insufficient. That information, from Regeneron's patent application, was intended to illustrate the gap between what Amgen disclosed and the antibodies that subsequently were discovered to bind to PCSK9. It is key to a thorny question: What if a team of inventors discloses everything they have discovered, but they haven't yet discovered everything?

The appeals court also noted that experts in the trial had not agreed on whether knowing an antigen's characteristics enabled scientists to make antibodies to it. In its decision, the court wrote that "it has

been, at the least, hotly disputed that knowledge of the chemical structure of an antigen gives the required kind of structure-identifying information about the corresponding antibodies."

In light of that ongoing dispute, the appeals court ruled that describing an antigen could not suffice as written description of the antibody that binds it.

That ruling will guide the judge who hears the case if it returns to the lower court in Delaware. Judge Robinson has since retired; at the retrial, scheduled for February, the new judge cannot tell the jury that written description of an antigen suffices to describe the antibody it binds. The jury will consider the same question: Does Amgen's disclosure of 384 PCSK9 inhibitors that block the protein's interaction with the LDL receptor describe a class of antibodies well enough to claim it?


ROYZMAN

Irena Royzman is a New York patent lawyer who earned a Ph.D. in biology before law school and now litigates biotechnology cases. "The question before the court at the district court level will be whether what Amgen discloses, under the law as now clarified by the federal court, is sufficient," Royzman said. "The question is: How broad is the claim? How substantial is the disclosure in light of the breadth of the claim, and do they really have representative species?"

But whether the retrial will go forward as scheduled is uncertain. In July, Amgen appealed to the U.S. Supreme Court to review the federal appeals court's decision.

The highest court

"In Amgen's petition to the Supreme Court, they're essentially raising a new issue," Royzman said. "They're saying that the federal circuit is completely confused."

Intellectual property lawyer Ari Zytcer elaborated on Amgen's position, explaining that the company argues that the appeals court misinterpreted the patent law. Amgen's lawyers, he said, contend "that the current interpretation by the federal circuit court of a separate written description and enablement requirement is actually improper … (and) in fact it's a single requirement."

Other pharmaceutical companies, notably Bristol–Myers Squibb, weighed in with an amici curiae ("friends of the court") brief, arguing the Supreme Court should hear the case. The companies argued that the appeals court's ruling impedes innovation, because once an inventor has one antibody to an epitope, it's trivially easy to make what they called follow-on antibodies. Moreover, the brief said, compiling a "representative number of examples" could be quite subjective — just how many examples is that? — and might involve a lot of rote work.

Royzman doubts that the Supreme Court will take up the case. "(Amgen's lawyers) are arguing that there is no such thing as the written description requirement: that the Federal Circuit just came up with it and it's not grounded in a statute. I don't think that's correct."

On Nov. 19, Sanofi filed a response to Amgen's Supreme Court petition, calling the case "an exceptionally poor candidate" on the grounds that Amgen had never questioned the interpretation of patent law in the lower courts. Moreover, Sanofi argued, even if the Supreme Court did review how the appeals court is applying the law, it would not settle the central question of whether Amgen's patent is valid. Now it's

up to the Supreme Court to decide whether to intervene in the case.

Whether the case appears clear-cut could depend partly on whether a lawyer writes patents or litigates them, Zytcer noted. "From my perspective, I'd like the Supreme Court to chime in."

He sees uncertainty in how patent law is interpreted among legal practitioners and patent examiners that could be settled by a Supreme Court decision. "I think from a litigator's perspective, though, this is plain and simple." There is plenty of precedent upholding separate enablement and written description requirements for patent applications, he said.

"Amgen really did describe more than most applicants would ever put into a patent application," Zytcer said. "So the fact that their patent could be held invalid on the basis of lack of written description … that would have a chilling effect on the biotech industry."

The case has major implications for a type of patent dispute that comes up again and again — and is poised to become even more common as antibody drugs proliferate. Not long after the Delaware court's initial decision in Amgen v. Sanofi, Merck and Bristol–Myers Squibb settled a similar case over antibodies against the cancer antigen PD-1. Merck paid Squibb $625 million and will pay royalties on its drug Keytruda for the next eight years.

At least two other cases await litigation to determine whether competitors' drugs infringe on patents covering classes of antibodies defined by antigens. Bristol–Myers Squibb, one of the friends of the court advocating for the Supreme Court to hear Amgen's case, recently hired Elderkin and her team to sue AstraZeneca over PD-L1 inhibitors, which target PD-1's ligand and are also used to treat cancer. In July, Genentech filed suit against Eli Lilly and Co. over Lilly's interleukin-17 antibody just after Genentech's patent for a class of humanized monoclonal antibodies to the interleukin was granted.

A Supreme Court decision concerning Amgen v. Sanofi could reach beyond these cases, according to Anna Lukacher and Richard Kurz, who work on pharmaceutical patents in New York. The Supreme Court selects cases "with the intent to clarify the law," Kurz said. "And they tend to rule in a way that is interpreted very broadly. Any time the Supreme Court takes on a case, it usually has an impact on a wide variety of cases going forward."

According Lukacher and Kurz, the retrial at the lower court in Delaware and consideration at the Supreme Court level will proceed in parallel unless the judge in Delaware chooses to stay the trial — which Kurz said would be likely if lawyers for Amgen or Sanofi asked for a pause.

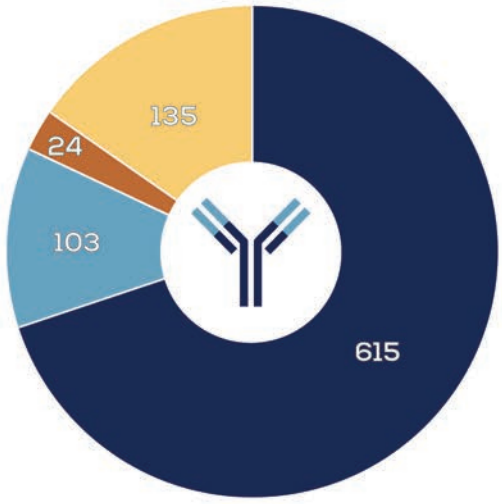
"I would say it's unlikely that the Supreme Court would get its briefing done and actually take up the case in time for the district court judge (in Delaware) to have any reason to stay the trial," he said. "That's reading the tea leaves a little bit, but that's faster than the Supreme Court usually moves."

The future of antibody patents

The U.S. Patent and Trademark Office has taken what steps it can to prevent a repeat of this battle. In a memo issued after the appeals court made its decision, the patent office instructed patent examiners that "adequate written description of a newly characterized antigen alone

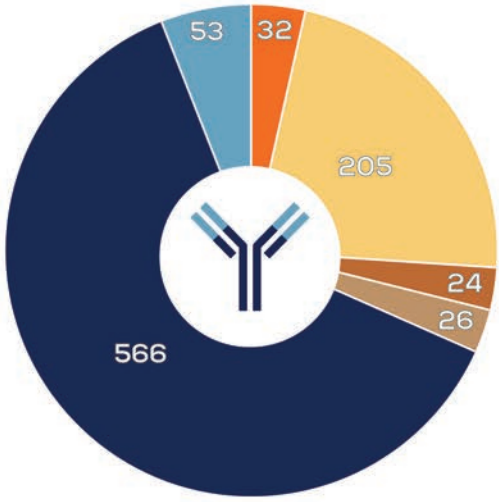
WHAT DO 2017 ANTIBODY PATENTS CLAIM?

- Antibodies (general)
- Bispecifics, chimeras, and drug conjugates
- Kits, purification approaches, etc.
- Therapeutic approaches



WHO PATENTED ANTIBODIES IN 2017?

- Academia
- Academic-commercial partnership
- Governments
- Top-25 companies
- Smaller companies
- All others



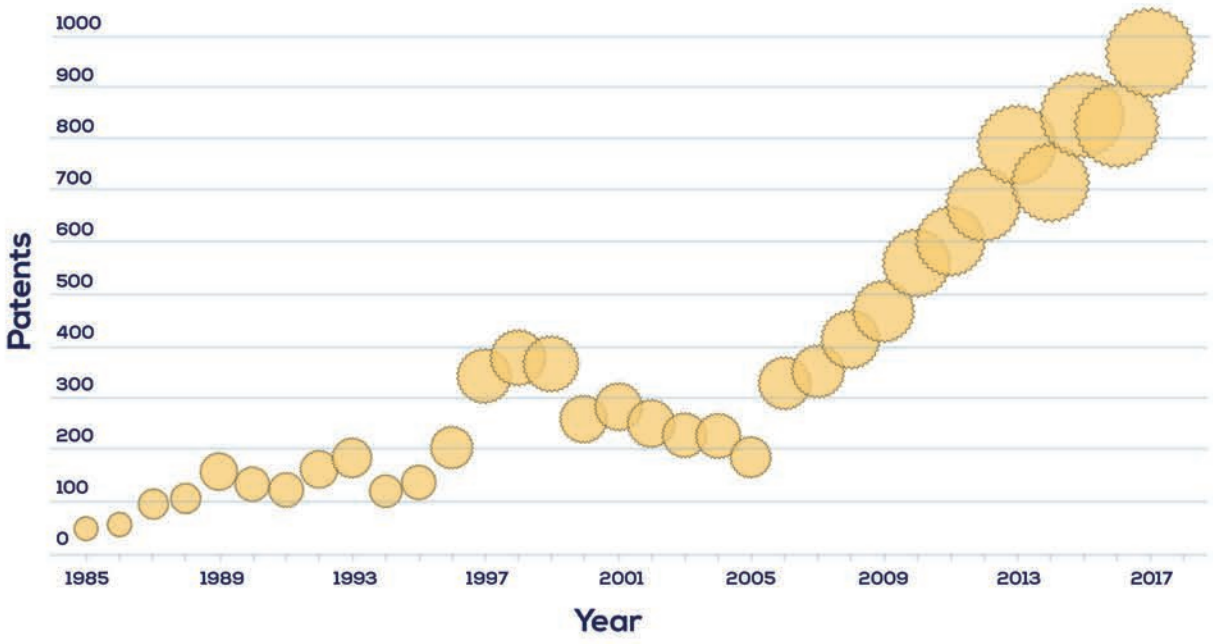
The increasingly crowded monoclonal market

As antibody drugs proliferate, there is more and more opportunity for companies' patent claims to overlap. The number of FDA-approved antibody drugs has surged in recent years, and many are in legal dispute. Challenges concerning approved drugs that target the EGF receptor, cytokine IL-12 and cancer-related receptor Her2 have shaped the patent landscape, and many infringement cases concerning drugs to other targets are ongoing.

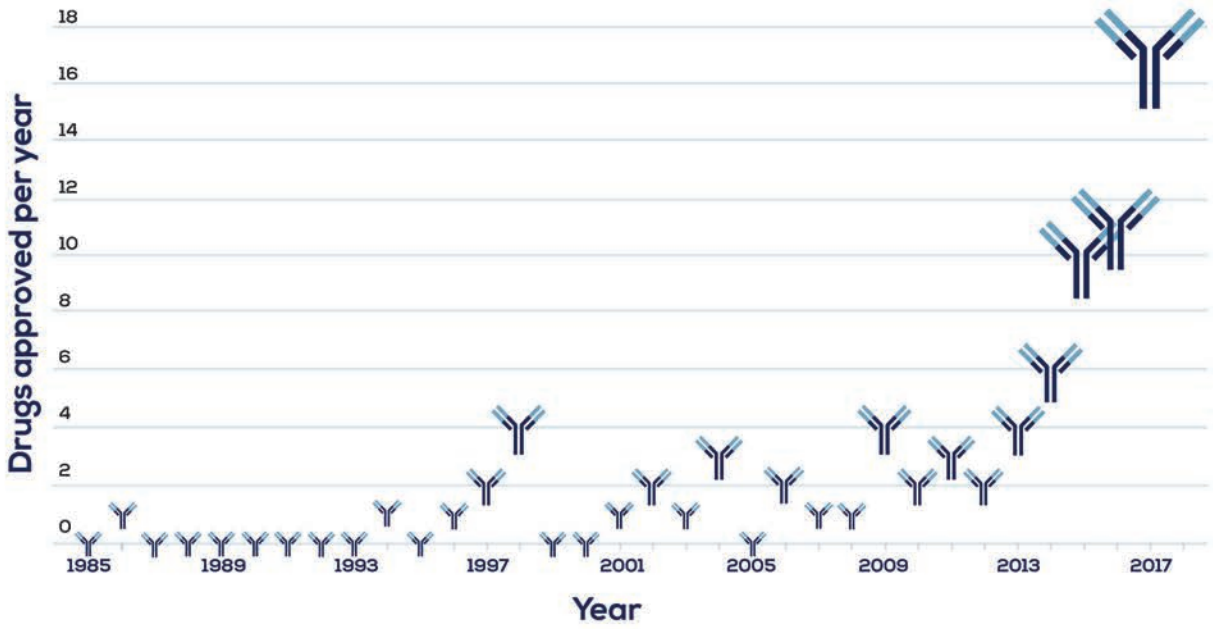
In 2017, the U.S. Patent and Trademark Office granted 964 patents with titles that contained the words "antibody" or "antibodies." Those titles sometimes described a broadly applicable method or specified a drug-antibody conjugate, but the majority simply described an antibody or group of antibodies and left the details for the claims.

Only about 2 percent of U.S. patents granted in 2017 were assigned to the world's largest pharmaceutical companies by revenue — a group to which both Amgen and Sanofi belong. About a quarter were assigned to universities or academic–commercial partnerships, and more than half went to smaller biotech and pharmaceutical companies, and in some cases individual inventors, from around the world. Academic and small commercial inventors may lack the resources to protect their intellectual property with the vigor that Amgen and Sanofi have shown in litigation.

PATENTS AWARDED WITH "ANTIBODY" AND/OR "ANTIBODIES" IN TITLE



NUMBER OF MONOCLONAL ANTIBODIES GRANTED FDA APPROVAL



should not be considered adequate written description of an antibody to that antigen," officially putting the appeals court's ruling into practice at the patent office.

However, lawyers say there is still confusion among patent examiners about what suffices as description.

Zytcer said of a recent patent office rejection, "Examiners and the legal folks at the patent office can't give a straight answer because (the law) is just open to too much interpretation."

Amgen's petition to the Supreme Court argued that the appeals court's ruling has "left innovators no way of predicting what disclosures will be sufficient" to secure patent protection for their inventions.

"I think that's somewhat exaggerated," Royzman said about Amgen's assertion. "For example, if you write a claim that's specific to your antibody, you can obviously get that claim. If you write a claim that says 'my antibody with sequence variation of 80 or 90 percent,' people are getting claims like that."

On the other hand, she said, "If you're going to say 'any antibody that binds to receptor X or protein Y, those are all mine,' then those claims are highly problematic."

Charles Craik, the UCSF professor, holds 16 patents. "I find it very disappointing that that's the direction antibody patents are going," he said. "It's slicing the salami so thin that you can't get a meal off of it."

For example, he said, his colleague Barry Selick, who is now vice chancellor for business development at UCSF, invented the humanized mouse antibody. "That's a spectacular patent, one of the most significant in biotechnology," Craik said. "If you're slicing things as thinly as the outcome of Amgen v. Sanofi, you couldn't get that patent."

Craik once wrote an application for a class of antibodies that was denied on the grounds that it claimed more than he possessed when he submitted the application. (He had hoped to claim antibodies that could bind to any protease and prevent conformational shifting from an active to an inactive form, but he secured a patent for antibodies against the active form of just one protease.) He worries that narrowing the scope of the average patent to protect specific epitope-binding sequences will harm the commercial possibilities of monoclonal antibodies.

According to Zytcer, if the appeals court's ruling holds, it may dampen universities' enthusiasm for patenting antibodies, especially for technology transfer offices with limited resources.

Lawyers writing patent applications that describe antibodies, he said, are "going to try to add a little more disclosure — but in reality, you're not going to get anything else from the clients. They have what they have at the time of development."

All the same, Royzman said, there's a strong argument to be made in Sanofi's favor — one she said the appeals court's ruling takes into account. "It is an important decision, because look: A lot of innovators develop their own antibodies, and it's a lot of work," Royzman said. "And those antibodies with their specific sequences are beneficial to patients and beneficial to us as a society — and it's problematic if somebody owns a target. That's at core what this case is about."

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

Meet Saddiq Zahari

The MCP editor of manuscript integrity ensures every paper complies with essential guidelines

By John Arnst

There's no denying that proteomics is a data-heavy field. Each study generates large data sets that enter public repositories and can be used as the foundation of future independent research. Over the last three years, Saddiq Zahari has helped shepherd more than 1,300 papers in the journal Molecular & Cellular Proteomics through the guidelines for proteomic identification, glycomics, clinical proteomics and targeted proteomics.

MCP is published by the American Society for Biochemistry and Molecular Biology, along with the Journal of Biological Chemistry and the Journal of Lipid Research. Since the journal was founded in 2002, its mission has been to foster the development and applications of proteomics in both basic and translational research.

Zahari earned his bachelor's degree in biotechnology from the University of Nottingham in 2008, followed by his master's degree in biotechnology from Columbia University in 2010 and his Ph.D. in biological chemistry from Johns Hopkins University in 2015. He did his postdoctoral work in the lab of MCP editor-in-chief Al Burlingame at the University of California, San Francisco, while simultaneously working as the manager

EMILY HUFF/ASBMB

Saddiq Zahari in his office at the American Society for Biochemistry and Molecular Biology. After completing his bachelor's degree at the University of Nottingham and while applying to graduate programs, Zahari worked as a barista in Kuala Lumpur, where he was raised and has many family members.

for compliance at MCP. He began working at the ASBMB's offices in Rockville, Maryland last winter.

Zahari spoke to ASBMB Today's science writer, John Arnst, about his work at MCP. The interview has been edited for length and clarity.

How did you become involved with MCP?

When I was about to finish my Ph.D., I knew that I did not want to do bench work for the rest of my life. I had published 10 papers, seven as first author, but I realized that academia wasn't for me, so I decided to explore other options in writing and editing. I saw that MCP, where I'd enjoyed publishing as a graduate student, was looking for someone to become the manager for compliance, who would make sure all the manuscripts comply to their guidelines.

At the time, the people at the ASBMB office in Rockville wanted me to be there, but Al and Robert Chalkley, our data management editor, wanted me to be with them in San Francisco at UCSF so I could learn more about the technical aspects of compliance. So I moved and joined Al's lab as a postdoc.

I was there for two years, and I learned a lot from Al and Robert about doing compliance checks and also how you evaluate all the data and how to make sure the manuscripts comply with MCP's guidelines.

What are the current guidelines and how long have they been in place?

Back in 2004, the editors got together with leaders in the field and came out with the first set of guidelines for the journal, the Paris guidelines. This was necessary because of the large data sets that proteomics studies entail.

Those guidelines ask authors to supply all the relevant information about how data analysis was performed, so that reviewers, and then readers, can assess the reliability and quality of the data and also so that, later on, people can reuse and reanalyze the data, which is available in public databases.

Over time, we added more guidelines. The second set were for clinical proteomics, which made sure that all data that came from humans and from human samples declared how many samples were used and what statistics were employed to analyze the data.

We then added the glycomics guidelines, which apply if you're looking at any glycan products. They ask for a clear definition of each glycan or glycoconjugate, how those relate to the biological question at hand and the details of how all of the findings were quantified.

Then just last year, we started the guidelines for targeted proteomics. This is a newer area in proteomics where instead of looking at everything in the sample, you just look at specific sets of proteins or peptides.

So we now have four sets of guidelines, and we're about to have a fifth one, which is currently being formulated, for data-independent acquisition, a newer way of analyzing and acquiring data for proteomics.

Talk about the work that you do as manager for compliance.

I think of myself as the gatekeeper. We get around 400 to 500 papers per year and I look at every paper. When a paper is submitted, I just do an initial quality control check to make sure that all the sections and relevant files are there. The guidelines come later.

If everything is there, then I forward the paper to the editors. If the editors decide to send the manuscript out to review, they'll send it to the reviewers, and it will also be sent back

"We need to make sure that when people find these proteins in the databases, they can be traced back to the paper, and people can look at the raw data and make sure that it is correct."

— SADDIQ ZAHARI

to me, so I'll be looking at the compliance in parallel with their review process. At that point, I make sure the manuscript conforms to all the guidelines that are relevant to it.

If the authors are missing items, such as database search parameters in the experimental procedures section or peptide and protein quantification in the results section or raw data in a publicly accessible repository, I note that, and it goes into the decision letter that the authors get, along with the scientific notes. When they resubmit the paper, they also need to address all the compliance issues that I've brought up.

My role is not to evaluate the quality; it's just making sure that all the compliance requirements have been met. I can delay a manuscript from being published, but I cannot decline a paper because they did not comply.

If the editors say, "OK, this paper can be published, but there are compliance issues," I will have to work with the authors until all those issues are resolved, and then it will get published.

After it's published, I look at the paper again to make sure that none of the details in the methods and results sections have been removed during copyediting. I would say every day I look at four or five papers, which is its own task, but I also need to go into the data that they've submitted with the manuscript as supplemental and the raw data that they've uploaded to public repositories.

Before I was hired, MCP didn't have someone doing compliance checking full time. It was one or two of our editors who were also doing their own research projects, had their own labs and were doing this in their free time. They needed someone who would streamline the process.

How have the guidelines affected the journal and the field as a whole?

The guidelines are especially important for raw data, because outside researchers later will use those as the groundwork for their own studies.

The data that are published in MCP are large-scale — the authors are not looking at two, three proteins; they're reporting thousands and thousands of protein identifications. We need to make sure that when people find these proteins in databases, they can be traced back to the paper, and people can look at the raw data and make sure that it is correct.

Some authors feel like the guidelines are a burden, some feel like they're important to comply with. I think compliance is important because it enables readers to make their own assessment about whether they believe the results that have been presented in the paper. It's my duty to make sure the data is there so that people can make those evaluations for themselves.

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

Uncovering a novel gene function in breast cancer

Villanova professor mentors undergrads, focuses on tumor viruses and oncogenes

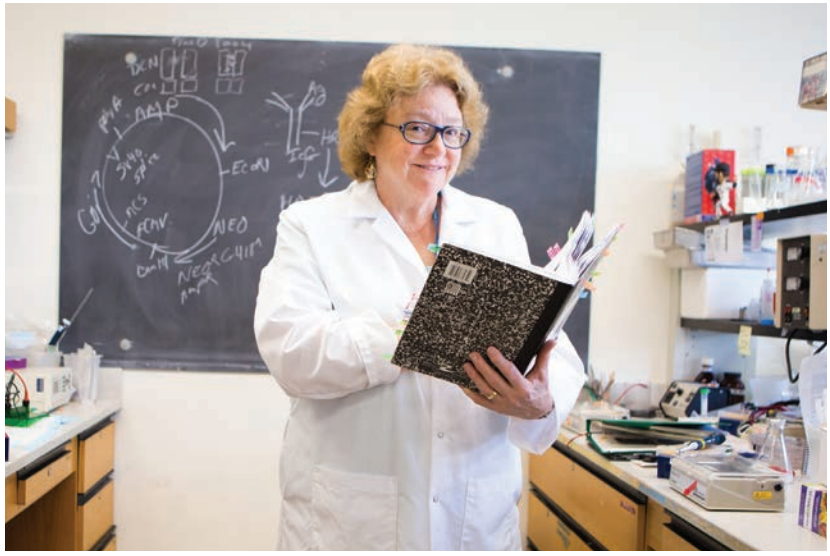
By Courtney Chandler

Janice Knepper landed on breast cancer research through her interest in virology. Her most recent publication focuses on the function of a nuclear body protein called Zc3h8, which her lab found can contribute to aggressive tumor behavior in models of breast cancer.

Now a professor and co-director of the program in biochemistry at Villanova University, where her lab focuses on mouse mammary tumor virus, Knepper didn't start out as a cancer biologist. She studied bacterial membrane proteins during her graduate work at Brown University, and her postdoctoral project at Johns Hopkins focused on cloning a human gene involved in purine biosynthesis. This unlikely project sparked her interest in virology and cancer.

"We used polyoma virus in one experiment, and I became interested in tumor viruses," Knepper said.

During her experiments, Knepper observed that polyoma virus was disrupting target genes by insertional mutagenesis and got the idea to use polyoma as a cloning tag to identify genes involved in cancer. She didn't get to follow this line of work during her postdoctoral project, but other researchers later showed that retroviruses do become oncogenic by this mechanism.



VILLANOVA UNIVERSITY

Janice Knepper in her lab at Villanova University, where in 1988 she started researching oncogenes identified in animal models of breast cancer induced by mouse mammary tumor virus.

She next worked under virologist Janet Butel at Baylor College of Medicine, where she became fascinated with mouse mammary tumor virus, or MMTV, a milk-transmitted retrovirus that causes mammary tumors in mice as a consequence of its infectious cycle. MMTV evades host immune responses and integrates into the genome of mammary epithelial and lymphoid cells during replication, thereby mutating the genes into which it is inserted. After insertion,

viral transcriptional regulation drives increased expression of adjacent genes.

Oncogenes can be identified in this system by looking for insertion sites that result in uncontrolled cell growth, which leads to tumor formation. Oncogenes identified in animal models of breast cancer induced by MMTV then can be investigated in human forms of the disease. This is exactly what Knepper began researching when she moved to Villanova in 1988.

"I became fascinated with MMTV activity in normal and tumor cells," she said. "At Villanova, I was excited to be able to use MMTV as a cloning tag to identify genes important in cancer in MMTV-infected mice."

VILLANOVA UNIVERSITY

Janice Knepper and Amber Shelton work in Knepper's lab at Villanova University, where Shelton earned a B.A. in 2017 and an M.S. in 2018.

Needle in a haystack

The many strains of MMTV can differ based on their insertion rates into various genes. Before Knepper began her research, several already-described insertion sites were associated with MMTV, so she first used a strain that has lower levels of insertion in these sites. This meant that an increased percentage of the insertions were at novel sites, which increased the potential for identifying new oncogenes. However, it also meant many targets to screen.

Luckily for Knepper, she was at a university with a large undergraduate base and good scientific resources. So she got creative and put her students to work. She had her undergraduate molecular biology laboratory class screen tumors by inverse polymerase chain reaction. Students cloned sequences from 20 tumor cell lines and then mapped them to the mouse genome.

Knepper manually culled the list of sequences for genes of potential interest based on her knowledge of the field and references in the literature. Although many of the sequences were not informative, one caught her eye: Zc3h8, originally called Fliz1. Although there were few references about Zc3h8, one mentioned a negative regulatory effect on GATA-3 in immune cells.

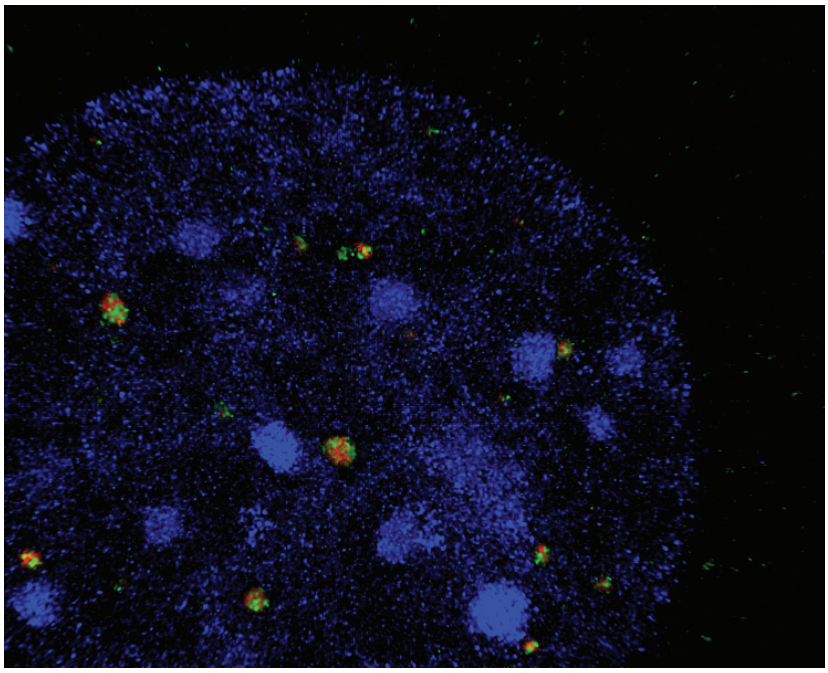
GATA-3 is a transcription factor that has roles in development of certain tissues, including mammary glands, and immune and inflammatory responses. It has been described as a clinically relevant marker of human cancers, particularly breast cancer.

Based on this, Knepper put together a plan for testing the role of Zc3h8 in mammary tumor cells.

Uncovering the story

The National Institutes of Health awarded Knepper an R15 grant in 2013 to identify the role of Zc3h8 in tumor cells, allowing her to recruit more researchers to her project. One of them was John Schmidt, who made this the focus of his postdoctoral research project in Knepper's lab. Previous publications about Zc3h8 didn't describe any specific role in cancer or mammary cell development.

"Because my interest was in mammary tumorigenesis, we focused on



COURTESY OF JANICE KNEPPER

Fliz1 (Zc3h8), in red, is co-localized with a nuclear body in a nucleus (stained blue with DAPI).

oncogenic behavior of cells with altered Zc3h8 levels," Knepper said.

Schmidt, who earned his Ph.D. from Cornell University, brought a background in cell biology and biochemistry to the project to explore the function of Zc3h8 thoroughly and broadly.

"My initial approach didn't produce anything that was scientifically interesting or insightful to the function of Fliz1," he said. "So we developed new hypotheses more focused on cell and molecular biology."

Zc3h8 is conserved among vertebrates, and their experiments demonstrated that cells with higher Zc3h8 levels grew faster and had more aggressive tumor phenotypes in cell culture and in mouse models.

Despite its tight control and obvious importance for cell phenotype, Zc3h8 appeared to have inconsistent effects on GATA-3. Knepper initially hypothesized that GATA-3 and Zc3h8 were linked and their effects on cells might be synergistic. However, attempts to knock out Zc3h8 were unsuccessful — cells with extremely low levels of Zc3h8 failed to proliferate, and the researchers were unable to generate knockouts with CRISPR/Cas9.

Furthermore, the link between GATA-3 and Zc3h8 was inconsistent. They observed effects on GATA-3 only in cells that expressed high, unstable levels of Zc3h8. In cells that had moderately changed levels of Zc3h8, they observed dramatically altered tumorigenesis phenotypes but no change in GATA-3 expression. Yet Knepper wasn't discouraged.

"Poorly understood genes may often generate these variable results," she said. "We have seen that Zc3h8 appears to be an essential gene whose expression is tightly controlled in cells, so unfamiliar is not the same as unimportant."

Schmidt's initially uninformative results served as the first step to describing Zc3h8 function, with Knepper's encouragement.

"Since the start of the project, Dr. Knepper encouraged me to always consider how to frame the results into a publication," he said. "She gave me the freedom to explore new scientific paths, all while remaining focused on the ultimate scientific goal — describing the function of Zc3h8."

Ultimately, they found that Zc3h8 regulates cell behaviors contributing to tumor growth and invasion through an unknown mechanism. The Zc3h8 protein is localized to the nucleus, where its phosphorylation state potentially could have an impact on transcription, DNA repair, apoptosis and viral defense.

They published their findings on Zc3h8 in July in BMC Cancer.

Combined impact

Knepper's ongoing research has improved understanding of cancer biology, specifically in regard to virally induced cancers. Her publication with Schmidt on Zc3h8 is only the most recent example. By characterizing this previously unknown gene,

their findings add to the growing body of research on genes that could be targeted in human cancers.

Beyond this, Knepper is proud of the impact the research has had on the students involved in the project. Villanova is a primarily undergraduate institution, she said, and this work allowed many undergraduates and master's students to develop their scientific acumen.

Jephne Wang was a junior at Villanova when she started working in Knepper's lab. She studied the localization of Zc3h8 in cells and tested its interaction with GATA-3, research that was included in the lab's recent publication.

"Dr. Knepper is both an inspiring scientist and an amazing mentor," Wang said. "She taught me how to ask interesting scientific questions, how to approach a research idea and how to patiently test the ideas."

Wang also looked to Knepper for career advice, and it was her experience in the Knepper lab that inspired her to continue doing cancer research in graduate school. She is now a graduate student at Washington University in St. Louis studying leukemia.

In addition to Wang, all four of the paper's other non-Ph.D. co-authors have used their experience in the lab as a springboard into research and medical careers. Knepper believes the impact of novel research on the greater scientific community and its impact on those who do the work are equally important.

"Investment of national research resources at Villanova and similar institutions provides critical training for future researchers," she said.

The R15 funding Knepper was awarded provided critical resources for her students to develop laboratory skills. Undergraduate research students at Villanova prepare their own research proposals on independent projects, which they eventually write and defend as a thesis. Knepper says this provides an aspect of intellectual development that is not always present at larger institutions.

COURTESY OF JANICE KNEPPER

Postdoctoral researcher John Schmidt, first author of the Zc3h8 paper, co-author Gerard Walker, Janice Knepper, and research student Jani Swiatek attend a Phi Beta Kappa induction ceremony for Walker and Swiatek.

"Mentoring undergraduates allows a researcher to inspire the next generation of scientists," she said. "Most scientists will not themselves make paradigm-shifting discoveries, but by training and mentoring students, they can have a major impact on the scientific future."

Knepper and Schmidt will continue to investigate Zc3h8. They are focused on manipulating Zc3h8 structure and identifying interacting molecules, she said. Undergraduate and master's students continue to be crucial members of the research team, and Knepper said she hopes their data will contribute to the fields of cancer and cell biology.

"We believe that our work will encourage others to explore potential Zc3h8 interactions to more fully describe how this unfamiliar gene can profoundly influence cell behavior."

Courtney Chandler (cochandl@umaryland.edu) is a Ph.D. candidate at the University of Maryland, Baltimore.

GIFT GUIDE

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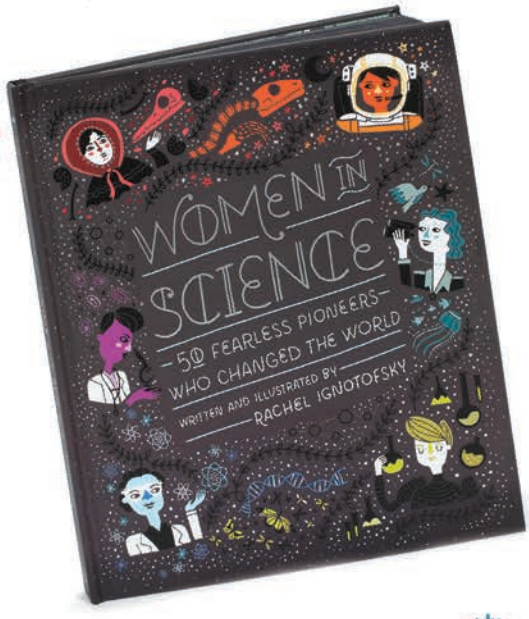

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These science-themed gift ideas might help you check a few loved ones off your holiday shopping list!

1. Tardigrade stuffed animal: $9.95 **2.** LEGO research institute set: $63.19 **3.** Canine breed detection DNA test: $84.99 **4.** Women in Science book: $11.45 **5.** Chemistry Fluxx game: $13.22 **6.** The Vast Wonder of the World book: $13.98 **7.** Explorer microbiome test: $89 **8.** Cocktail r-evolution molecular gastronomy kit: $49.95 **9.** Science socks: $10.20 **10.** Periodic table cutting board: $28

For details on where and how to buy these items, go to asbmb.org/asbmbtoday.

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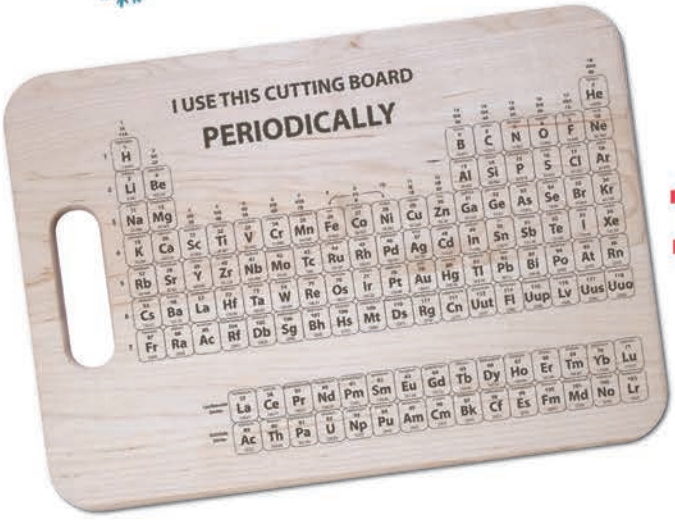


New this year: science in a flash

By Danielle Snowflack

Effective communication is critical to your success as a scientist. You often have only a few minutes, or a few sentences, to impress employers, influence grant-making agencies or provide a quote to a journalist.

So, what if you got one figure, four minutes and a microphone to describe your research — could you do it?

At the 2019 American Society for Biochemistry and Molecular Biology Annual Meeting, the Science Outreach and Communication Committee (formerly the Public Outreach Committee) will challenge graduate student and postdoctoral researcher travel awardees to push their science-communication skills to the limit at a flash talk competition.

Each flash talk will focus on the research described in the speaker's submitted abstract. For presenters, this is an ideal opportunity to think about their projects in different ways.

"Scientists often get caught up in the minutiae of their work, forgetting about the bigger picture," committee member Parmvir Bahia said. "This contest allows trainees to boil the research down to its essence. By considering how their work is relevant to a wider scientific audience, it might also help them appreciate the potential for collaborations outside of their narrow field of interest."

Before the annual meeting, committee members will provide online training to the travel awardees focused on the skills necessary to give a successful flash talk. Every second counts, so they'll share tips and tricks to ensure each speakers are using their time wisely. They'll discuss ways to organize the flash talks to have the greatest impact. And they'll talk about ways to describe science without using discipline-specific jargon. These strategies will help speakers connect with the audience, whether that audience consists of ASBMB members, scientists in different disciplines or even nonspecialists.

A panel of expert science communicators will score each flash talk using a rubric focused on the clarity and quality of the presentation. The panel will reward the presenter earning the highest score with some fun ASBMB swag. While the panel can choose only one winner, everyone wins at the end of this contest. All presenters will receive their scores, making this a great opportunity to get feedback on their science-communication skills.

What does this mean for you if you didn't receive a travel award?

The audience is the most important part. This competition is a fun way to hear some great science while relaxing and networking. Grab a snack, sit back and cheer on the presenters. At the end of the event, be sure to vote for the speaker you think should take home the audience choice award.

Could you give a great flash talk?

Here are a few tips:

- You only have four minutes and one slide, so you can't describe your entire project. Identify the goal of your presentation, and start there when drafting your talk.
- Write a draft of your talk and run it through a program like the De-Jargonizer (available at scienceandpublic.com). This software reads your text and identifies jargon in red. Be sure to address the jargon — either eliminate it or explain it.
- Practice, practice, practice. Use a stopwatch. You must be able to deliver your talk within the time limit, or you will be penalized. Make note of the places where you get caught up, and work to improve them.

An invitation from the chair

Ever had a colleague whose description of their research project/idea/data was so riveting you wanted to change fields? To find a way to collaborate? Or at the very least, to find a way to similarly sell your own science? ASBMB flash talks at Experimental Biology will showcase scientists sharing their ideas in ways that inform and invigorate. Join us and be impressed.

—Susanna Greer, chair of the Science Outreach and Communication Committee

Danielle Snowflack (dsnowflack@asbmb.org) is the ASBMB's director of education, professional development and outreach. Follow her on Twitter @drsnowflack.

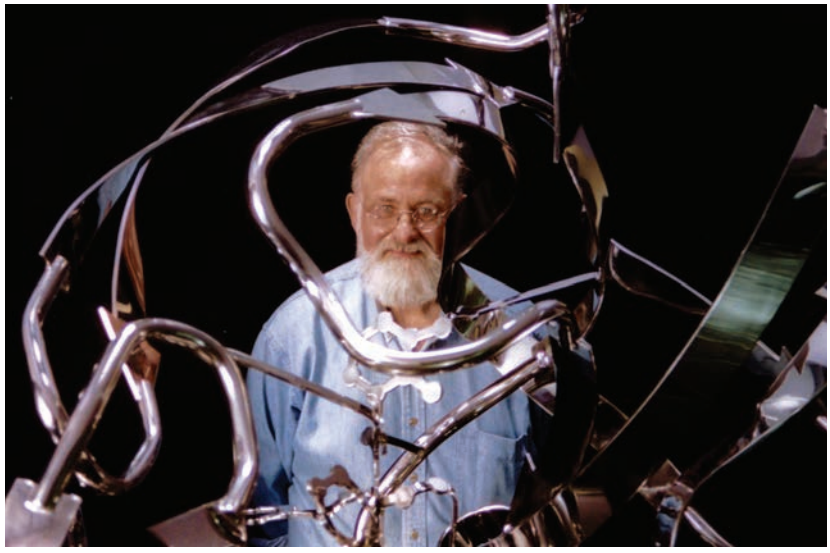
Up the creek without a sequence?

By Byron Rubin

My professional career began when I became a protein crystallographer, back when you could count the number of known protein structures on the fingers of one hand. Then, as now, my focus was not only to use structure to understand how enzymes work but also to develop ways to visualize these structures. Early on, I designed a popular tool for easily constructing 3D protein backbone models. This led to many commissions to create large-scale, metal molecular sculptures over the past 30 years.

Today, among the more than 100,000 known 3D structures, one shows me in atomic detail the likely origin of my prostate cancer. Specifically, a single nucleotide change in the codon for serine 863 in one allele of my CDK12 gene blocks the tyrosine-substituted protein from binding ATP. The result? Some DNA repair processes failed, mutations escalated and my cancer began growing at an accelerated rate.

The first hint of cancer was an elevated prostate-specific antigen last December, when I was 74. When my urologist, a renowned practitioner, ordered an MRI, I went to the library to learn how to interpret the resultant images. Surely I could master MRI interpretation by reading 15 or 20 articles and reviews. Days later, after an hour in the scanner, I went home with a DVD of my images. Several hours of inspection convinced me I was in the clear. But two days later my urologist phoned. He told me I had a sizeable tumor, aggressive prostate cancer, and immediate action was necessary. So much for my MRI home study course.



BLAIR HORNBUCKLE

Byron Rubin stands behind a stainless steel sculpture he created. The arrow and coil representation of HIV protease with the anti-AIDS drug, Viracept, bound to it was commissioned by Pfizer for its research facility in La Jolla, California.

While I waited for additional imaging and biopsy results, my new focus at the library was treatment, recurrence statistics and survival. To decide my best options, I read more than 100 papers. Should I undergo radiation, open or robotic prostatectomy, or do nothing? Which procedure, hospital, surgeon had the best outcomes? What were my survival statistics? Was I likely to live long enough to justify buying a new pair of shoes?

In effect, I'd become both a cancer patient and an aspiring oncologist. My years in science, I felt, should offer some benefit in making treatment choices. I had held research positions at the Fox Chase Center, Emory University, Eastman Kodak Company, Sterling Winthrop Pharmaceuticals and Harkness Pharmaceuticals, a drug-discovery company that I co-founded.

I met with two potential surgeons, a radiation oncologist, prostate cancer academic researchers, two prostate cancer support groups and a few friends who had worked through the same agonizing decisions. Oddly, doing all the research and reading both brought me closer to and distanced me from the increasing fear of my own mortality. My reading also made me realize that, should I survive cancer, life would not be the same.

DNA sequencing was just beginning to identify genes associated with prostate cancer. Could sequencing my DNA help guide my treatment

either now or in the future? After reading recent papers published by my own urologist and other specialists comparing treatments, recovery times, risks and benefits, and using a nomogram predictor of my five-year survival probability, my focus shifted to learning how to get my tumor's DNA sequenced.

I needed more than the linear DNA sequence of my tumor. I needed a detailed comparison of my cancerous and noncancerous DNA and the identification of every gene and intervening sequence that showed a difference. Fortunately, technology had brought down the price for a complete DNA sequence, but there was still the issue of interpretation.

Perhaps I could reconstruct my complete DNA sequence and that of my tumor from a bunch of FASTQ or BAM files that I could buy for one-tenth the cost of a complete commercial analysis. My scientist hubris had been shaken. I feared that my try at interpreting raw DNA sequence data would turn out no better than my efforts at interpreting my MRI.

Though it was costly and not likely to be covered by insurance, I chose to pay for complete DNA sequencing and interpretation. I also enrolled in a clinical study in which the same information likely would be obtained. Would the analysis and interpretation be the same? The biggest questions that remained were the following: What gene changes could be seen in my cancer? And would a precision-medicine-based treatment be available for me now or in the future?

Five months after robotic surgery in June, the answer came, and though I'd read articles identifying genes involved with prostate cancer, I wasn't ready for what my sequence analysis showed. Eighty-eight cancer-related genes were different from my germline sequence. Some genes were missing; others showed an increased copy number. Some showed single nucleotide changes. Others showed frame shifts. Of all of these variations, the changes in cyclin-dependent kinase 12, CDK12, stood out. Both alleles of this gene had mutated. One was the S861Y mutation I mentioned earlier, and the second was a frame-shift mutation at residue 1054. The two mutations each produced inactive enzymes. As a consequence, my tumor had impaired DNA repair.

ROBIN REDISH

Byron Rubin stands beside a stainless steel sculpture he created for Serono (now Serono MSD) for the lobby of their Rockland, Massachusetts, facility. The sculpture is a ribbon representation of the follicle stimulating hormone peptide backbone also showing the three carbohydrate moieties required for its activity.

The good news was that if my cancer recurred, which I had been told was very likely, there was a treatment, a treatment that would not have been considered had I not chosen to have my DNA sequenced.

My wife feels strongly that changing my eating style to a whole-food, plant-based, oil-free diet will prevent recurrence. Indeed, I've lost a lot of weight, and my 20 years of insulin dependence is now history. While yielding to my wife's well-researched and very thoughtful survival plan, however, I take comfort in knowing that my DNA sequencing gives me an alternative, should I need it. I might have had no alternative to traditional treatment had I not known about the potential value of DNA sequencing.

And, oh yes, I bought the shoes.

About this series

This is the final essay in our 2018 series, "When science meets sickness," written by scientists who have faced serious illnesses. Read more of the series at www.asbmb.org/asbmbtoday/collections/Sickness.

Byron Rubin (bhxray@aol.com) is an adjunct associate professor in the department of biochemistry and biophysics at the University of Rochester Medical School. He also creates metal molecular sculptures of biological macromolecules for museums, universities and pharmaceutical companies, which can be seen at www.molecularsculpture.com.

Biochem department chairs sponsor ASBMB memberships

By Bettie Sue Masters & Blake Hill

Richard Brennan, chair of the department of biochemistry at Duke University, made a surprise announcement immediately after an American Society for Biochemistry and Molecular Biology networking event in May: He volunteered that the department would pay the membership fee of any graduate student or postdoctoral fellow at Duke who wished to join the ASBMB.

Since that announcement, Brennan has added 39 members to the ASBMB rolls — 35 graduate students and four early-career investigators. And he is not alone. John Corbett, chair of biochemistry at the Medical College of Wisconsin, has a longstanding policy of paying ASBMB dues for graduate students and postdocs in his department and providing professional-development funds to his faculty that can be used for membership.

BRENNAN

When asked about his motivation, Brennan cited the multiple professional benefits of ASBMB membership and said the advantages gained by the trainees at Duke outweighed the minimal cost to the department, making it an easy decision.

"We knew that membership in the ASBMB would provide each trainee with superb career-development opportunities, including the ability to expand their professional networks through multiple mechanisms and to keep up with the latest scientific

The value of membership

Entering the world of science can be overwhelming. As a student, you are inundated with new knowledge and often placed in an environment where you have little exposure beyond undergraduate research opportunities. It's good to know you're not alone — support is available from an organized group of scientists with similar interests.

The American Society for Biochemistry and Molecular Biology publishes three highly regarded journals and hosts an annual meeting as well as specialized smaller meetings. Early-career scientists can benefit from these and many other services the society offers, including career development, support for minority scientists, advocacy (for grant funding and issues important to the science community), undergraduate chapters and biochemistry program accreditation, and science communication. These benefits have been developed to address your needs as you round out your career goals. The ASBMB leadership asks itself what would be useful to society members and then strives to provide it.

The Membership Committee, re-energized under Natalie Ahn's presidency, has been reaching out to the community of individuals who identify themselves as molecular life scientists. Over the past two years, we have met in person semiannually and by teleconference monthly to assess the society's services and offerings for potential members. Many of us have been ASBMB members throughout our professional lives, and the experience has connected us with colleagues and started lifelong friendships as well as paving the way to professional milestones.

With the long-range goal of organizing more regional activities supported by the ASBMB, the committee members have started hosting networking events. The first was held at Duke University in May. At this evening event, a new faculty member in the department of biochemistry, Kate Meyer, presented her research and then discussed her career pathway and what ASBMB membership meant to her. After a Q&A period, committee member Bettie Sue Masters presented a brief PowerPoint describing the benefits of joining the ASBMB. After this event, Richard Brennan, chair of Duke's department of biochemistry, announced that his department would sponsor ASBMB memberships for grad students and postdocs.

Interested in learning more about membership, networking events or sponsoring trainee memberships in your department? Contact membership@asbmb.org.

– Bettie Sue Masters & Blake Hill

developments and social trends in the field," he said.

Corbett said he sponsors ASBMB memberships for three reasons: "First, I deeply believe that scientific societies are central to our work as scientists. Second, I believe in society-based journals and think that the for-profit scientific publishing industry has a negative impact on the research enterprise. Third, the cost–benefit analysis makes sense to me. The cost of membership is not that great in the big picture, and the benefit of supporting the great work ASBMB does makes it an easy decision."


CORBETT

ASBMB membership provides trainees with access to the society's three journals, the Journal of Biological Chemistry, the Journal of Lipid Research, and Molecular & Cellular Proteomics, Brennan pointed out.

"Belonging to the ASBMB offers an important discount in publication costs, which unfortunately sometimes influence, inappropriately, the choice of journal in which someone submits her or his high-end science," he said. "If the work should be published in JBC, membership in the ASBMB can aid in this decision."

Corbett also stressed the importance of the ASBMB journals. "Practicing scientists that run labs run society-based journals," he said. "The for-profit scientific publishing industry places the emphasis on 'hot topics' instead of on doing solid, reproducible research … By supporting your favorite scientific society, you help run a journal for scientists by scientists."

Another benefit Brennan cited is the opportunity to obtain travel grants to the ASBMB annual meeting or one of the society's special symposia. "These meetings are key to the scientific and professional development of all our trainees," he said, "and their attendance will benefit each in multiple ways."

Corbett mentioned the work of the ASBMB Public Affairs Committee. "Membership gives individual scientists a collective voice to influence policy decisions in Washington," he said. "ASBMB gives us a seat at the table. A great example of this is the work they are currently doing to educate policy makers on the importance of investigator-initiated basic science research, which is essential for the translational discoveries we all want to see."

And finally, Corbett noted that the ASBMB has outstanding professional-development resources for early-stage scientists at each career level from undergraduate to tenured faculty member. "The importance of these resources cannot be overstated in today's competitive landscape," he said.

These two biochemistry department chairs, without knowing of each other's actions, have taken the initiative to support their students, postdocs and faculty by supporting their memberships in the ASBMB.

It is the authors' hope that others will be inspired by their actions to expand the benefits of ASBMB membership to their academic communities.


Bettie Sue Masters (Bettie.sue.masters@duke.edu) is an adjunct professor of biochemistry at the Duke University Medical Center and was president of the ASBMB from 2002 to 2004.


Blake Hill (rbhill@mcw.edu) is a professor of biochemistry at the Medical College of Wisconsin.

Accreditation — coast to coast

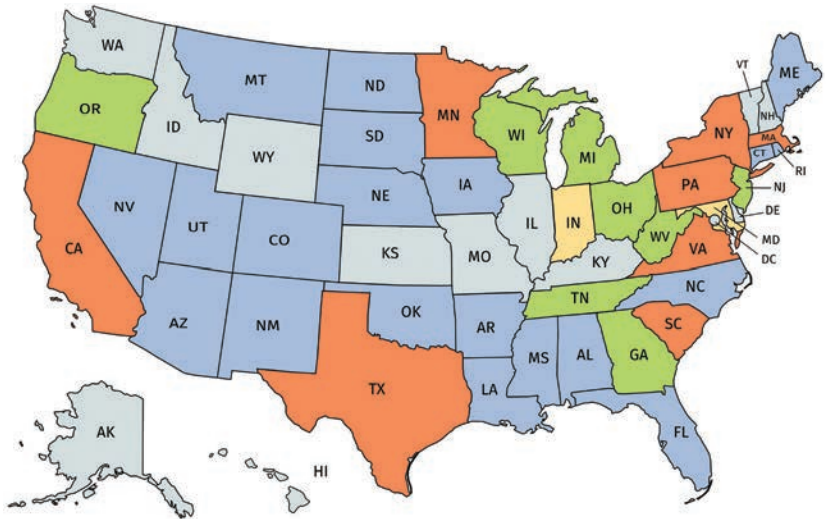
By Peter J. Kennelly

Now at the end of its fifth year, the American Society for Biochemistry and Molecular Biology's accreditation program for undergraduate degrees in biochemistry and molecular biology continues to grow at an average rate of 14 programs per year, with nearly 1,000 students taking the 2018 certification exam.

Accredited programs are now in 38 states, spanning the continental U.S. Among the 85 accredited institutions are 20 R1 universities, led by four from the Big Ten — Minnesota, Nebraska, Penn State and Purdue — along with three each from the ACC and Southwest conferences. At the other end of the spectrum are primarily undergraduate institutions with enrollments of 1,500 or fewer, such as Earlham, Hampden Sydney, Hendrix and Huntingdon colleges.

Over the past year, we aimed to improve the quality and visibility of our growing program. In 2017, ASBMB volunteers conducted a survey of current and prospective accreditation stakeholders; the results were recently published in the journal Biochemistry & Molecular Biology Education. In response to the feedback, we have streamlined and clarified the accreditation application and introduced updated sample examination questions on the accreditation website.

ASBMB volunteers hosted in-person and remote question-writing workshops that have given us more, and more consistent, questions in the certification exam. In April, 994 students took the annual exam. Of these, 417 (42 percent) earned ASBMB certification, of which 122 (12.3 percent) were certified with distinction. This was somewhat lower than the record high certification rate of 53.3 percent and 18.1 percent, respectively, for the 2017 exam. The 2018 version contained an identical number of questions and employed the same scoring criteria as the year prior.



PETER KENNELLY/MAPCHART.NET

This map shows the geographic distribution of accredited programs. States highlighted in orange are home to 4 to 7 accredited programs. Yellow, green and blue states have three, two and one accredited programs, respectively. Gray indicates no accredited programs.

The expansion and improvement of the accreditation program and its associated certification exam is a tribute to the commitment and skill of scores of volunteers supported by a handful of full-time ASBMB staff. These volunteers, whose efforts are acknowledged by their designation as ASBMB education fellows, report that their participation offers valuable experience in honing their skills as educators and evaluators, opportunities for stimulating discussions with peers from across the country, and a sense of ownership of a much-needed resource for biochemistry and molecular biology scientist–educators.

Why do I mention this? Because this is a program for the biochemistry and molecular biology education community run by scientist-educators from this community. Ownership comes with responsibilities, and we want more of our stakeholders to join with us in providing the ideas, perspective and plain old elbow grease needed to sustain the growth and development of the accreditation program.

If you'd like to learn more, contact Quira Zeidan (qzeidan@asbmborg), Adele Wolfson (awolfson@wellesley.edu) or myself (pjkennel@vt.edu).

Newly accredited

The ASBMB accredited programs at 15 colleges and universities in the last year. See the full list at asbmb.org/asbmbtoday.

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

CLASSIFIEDS

Pfizer Inc.: Senior Principal Scientist

The Pfizer Oncology Research & Development group in La Jolla is seeking a full-time employee to support the small molecule drug discovery efforts through a leading role in our high-throughput screening (HTS) and sample logistics laboratories. The candidate will work with a high degree of independence for HTS assay development, data analysis, hit-identification with internal and external resources while actively engaging in the project science to participate in constructive decision-making to advance the drug discovery process. The candidate will also oversee the Sample Logistics (compound management) team to inform them of oncology portfolio priorities to balance the lab workload in addition to facilitating communication between chemists and assay scientists for creation of compound libraries and atypical compound delivery workflows, respectively.
pfizer.dejobs.org

Marymount Manhattan College: Assistant Professor of Biology

The primary instructional responsibilities of the successful candidate will be to teach lectures and labs for Anatomy, Human Physiology and Animal Physiology. Since many of the students taking Anatomy and Physiology are dance majors, expertise with dance and movement pedagogy or equivalent is required. Specialization in neuroscience or neuroanatomy is strongly preferred. The ideal candidate will establish a research program involving undergraduate students in the biological sciences, coordinate the Body Science and Motion concentration with the Dance department, and contribute to the behavioral neuroscience major.
Applicants should submit a curriculum vitae, a short statement of teaching experience, research objectives, and identify at least three individuals as references. All materials should be sent to
biofacsearch@mmm.edu

Genentech, Inc.: Scientist Biochemical and Cellular Pharmacology

We are seeking a talented Scientist to join the Biochemical and Cellular Pharmacology Department at Genentech. The successful candidate will be part of a dynamic and highly motivated team driving the characterization of large molecule drug candidates that are being developed in diverse therapeutic areas, including oncology, immunology, ocular diseases and neuroscience. The successful applicant will be responsible for the development, optimization and execution of new biochemical and cell-based assays to support our protein therapeutic discovery programs for the selection and advancement of lead molecules. This position requires working with multidisciplinary teams, including biology team members from Discovery Research, as well as with Antibody Engineering, Pharmacokinetics and Safety Assessment. The candidate is expected to contribute at the bench as well as at strategic levels.
gene.com/careers/detail/201810-122930/Scientist-Biochemical-and-Cellular-Pharmacology

Indiana University: Lecturer, Visiting Lecturer, Chemistry

The Department of Chemistry at Indiana University invites applications for two non-tenure track lecturer positions in biochemistry, chemical biology or organic chemistry starting in Fall 2019. These appointments will be considered at the level of Lecturer or Visiting Lecturer. The Visiting Lecturer position will be for a 2-year period. Successful candidates will teach lower-level undergraduate courses in general chemistry and upper-level undergraduate courses in their areas of expertise. Candidates must hold a Ph.D. in chemistry, biochemistry, or a related field, and applications from candidates with prior teaching experience are especially encouraged. Salary will be competitive and commensurate with experience. Applications completed by December 15, 2018 will receive full consideration, but the review will continue until the positions are filled.
indiana.peopleadmin.com/postings/7064

EB ORLANDO

EXPOSURE EMERGES BEYOND

When you present your research at the ASBMB annual meeting at EB 2019, you receive deserved recognition and critical feedback that will help you advance your work. Submit your abstract to be considered for inclusion in this year's poster presentations.

All who attend will have a chance to discuss their work with influencers in their area of specialty, connect with peers in the life sciences community and gain inspiration to take back to the lab. Sign up by the early registration deadline to save 30 percent.

KEY DEADLINES:
Jan. 30, 2019: Late-breaking abstract | Feb. 5, 2019: Early registration

Visit ASBMB.org/meeting2019 to view abstract topics and register.

ASBMB '19
ANNUAL MEETING
ORLANDO | APRIL 6-9

Held in conjunction with Experimental Biology