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

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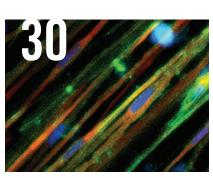
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PRESIDENT'S MESSAGE

Want real peer review? Publish in society journals

By Gerald Hart

eer Review Week, Sept. 16 - 20, is organized by a committee of 40 people from 29 scientific and publishing organizations worldwide. This year's theme is "Quality in Peer Review." The American Society for Biochemistry and Molecular Biology supports these efforts to highlight the importance of peer review by encouraging all ASBMB journal editors, associate editors and editorial board members to participate in events and activities that highlight the critical role peer review plays in the advancement of science.

Merriam-Webster defines peer review as "a process by which a scholarly work (such as a paper or a research proposal) is checked by a group of experts in the same field to make sure it meets the necessary standards before it is published or accepted." Careful review of manuscripts by qualified experts in the same area of science is essential to ensure that the published literature is kept to high standards of accuracy, rigor and reproducibility. Without rigorous peer-review processes, the scientific literature rapidly would be filled with "fake news." The ultimate purpose of peer review is to maintain the integrity of science by preventing the publication of invalid or poor-quality articles, including those that do not present novel findings.

Careful peer review by experts in your specific area of research is one of many reasons why we all should be reviewing for and publishing in nonprofit society-supported journals, such as those published by the ASBMB. Society journals do not have gatekeepers who are not practicing scientists; manuscripts are assigned to board members and reviewed by active scientists with research laboratories in the same areas as the submissions.

Society journals decide whether to publish a paper based on the quality of the science and its contribution to advancing a field. They do not base decisions to publish on whether a manuscript is newsworthy, a euphemism for "How will it affect our impact factor?"

In addition, any funds generated by a society journal go back directly to supporting science, as travel awards for young people to attend national meetings, education programs and advocacy for government funding of science. For-profit journals make money for their stockholders and do little to support the science community.

As we celebrate and extol the importance of peer review this month, remember this: If you want your articles to be reviewed by your peers, you should submit your papers to nonprofit society-supported journals.

Gerald Hart

(gerald.hart@uga.edu) is a professor and Georgia Research Alliance eminent scholar at the University of Georgia and president of the ASBMB.



Wellness, again

By Comfort Dorn

year ago, we requested submissions for our first wellness issue. We knew wellness was an important topic — whether for stressed-out grad students, overworked postdocs or PIs facing burnout — but we didn't know what kind of response we'd get.

The results surpassed our expectations: everything from deeply personal essays to step-by-step guidance and practical tools. Here's the end of my editor's note for that January 2019 issue:

"Have we covered all the bases? Absolutely not. But if you find this issue useful, thought-provoking or even inspiring, let us know. ... I'd be happy to do this again in January 2020."

January 2020 is right around the corner, and yes, we're going to do it again. We have more bases to cover. We invite you to pitch in.

What do you do for your body and/or mind? What should insti-

tutions and employers be doing to

promote wellness? What works? What doesn't — and why?

We did a lightning round in a recent staff meeting; here are some suggestions:

Your own program

What activities help you stay well? Have you gotten into yoga or tai chi? Do you have specific eating or sleeping rituals?

It's not just physical. How do you care for your mind and spirit? Do you make time for faith, family, pets or community service? What do your practices look and feel like? Why do they work for you?

Many scientists in the U.S. come from other countries, some with their own fraught politics, and face difficulties getting and staying here. If this describes you, how do you stay well? What role does your community play?

For many, pursuit of a Ph.D. is not all smooth sailing. Do you suffer PTSD from working in a toxic lab? How do you prevent yourself from carrying those feelings to another lab?

Workplace programs

The National Institutes of Health offers a menu of fitness and wellness programs from personal training to golf teams. Some employers offer gym membership discounts. Universities build gleaming fitness centers. What does your employer or institution do to encourage wellness? Is it a model for others? Could the program be improved? Institutional or employer policies also affect mental wellness — not just by providing crisis counseling

> (though we're interested in that) but also by establishing basic policies to support workers.

For instance, time off. Have you had to negotiate with an adviser or supervisor for a much-needed vacation? What was your strategy? Have you ever added a vacation to a conference trip? How did that work out?

Then there's child care. If you're a parent, what kind of support do you get? Does your

institution pay for child care when you go to conferences? What's the effect of such policies?

And we love to geek out, so we want to hear about wellness-related research. For instance, if you study the microbiome, what changes do you see when people adjust their daily habits? Or maybe you work on cannabidiol oil or acai berries or some other natural product. What's the biochemistry?

We have a million questions — and we're looking to you for answers. Not every submission has to be 100% serious. We're interested in failures and foibles too. (I, for one, will never do a yoga headstand.)

Deadline for submissions is Oct. 15. Go to asbmb.org/asbmbtoday/submit for details.

Comfort Dorn

(cdorn@asbmb.org) is the managing editor of ASBMB Today. Follow her on Twitter @cdorn56.



What do you do for your body and/or mind? What should institutions and employers be doing to promote wellness? What works? What doesn't — and why?

MEMBER UPDATE

Member update

By Erik Chaulk & ASBMB Staff

O'Handley honored as faculty mentor



Suzanne O'Handley has received the 2019 Council on Undergraduate Research–Goldwater Scholars Faculty Mentor Award.

O'Handley

This award is presented to distinguished faculty members who conduct their research in science, technology,

their resear

engineering and mathematics fields.

An associate professor in the school of chemistry and materials science at Rochester Institute of Technology, O'Handley was recognized for her distinguished achievements as a scholar, teacher and mentor.

In her 15 years serving as RIT's Goldwater campus representative, O'Handley has mentored six students who were named Goldwater scholars and has involved 65 undergraduates in her laboratory research. Under her leadership, RIT has had 28 Goldwater scholars and seven honorable mentions.

O'Handley received the award in April at the National Conference on Undergraduate Research at Kennesaw State University. The award includes \$5,000 to support the awardee's research program and/or undergraduate researchers.

Bissell receives two awards



Mina Bissell, a distinguished scientist with the Lawrence Berkeley National Laboratory, has received two awards for her contributions to breast cancer biology and medicine.

Bissell

The American Philosophical Society selected Bissell as the recipient of the Jon-

athan E. Rhoads Gold Medal for Distinguished Service to Medicine in recognition of her lifetime achievements. She will receive this award at the 2019 APS fall meeting in November.

The Weizmann Institute of Science has named Bissell as one of two recipients of the 2019 Weizmann Women and Science Award. Established in 1994, this award honors female scientists who have made significant contributions in their fields of research. It carries a \$25,000 research grant, and winners are invited to deliver lectures at the institute.

Among her accomplishments, Bissell illuminated the pivotal role of the extracellular matrix and the nucleus environment to gene expression in normal and malignant cells.

Taylor, Drain among new ACE fellows



Ann T.S. Taylor and Jerome Drain are among the 39 fellows newly elected to the American Council on Education.

Taylor chairs the division of natural sciences and mathematics and is the Haines associate professor of biochemistry at Wabash College in Indiana.



The first biochemist in the Wabash chemistry department, Taylor developed the courses and curriculum for the institution's biochemistry major program. She serves on numerous committees focusing on topics including policy, faculty devel-

rain

opment and philanthropy.

Jerome Drain is the dean of earth, life and natural sciences at Houston Community College. He began serving as HCC's interim associate vice chancellor of instruction earlier this year.

Prior to joining HCC in 2014, Drain held positions at Atlanta Metropolitan State College and Davenport University.

Established in 1965, the ACE Fellows Program promotes and strengthens higher education by identifying and preparing faculty members for senior positions.

Langer wins Dreyfus prize



Robert Langer, an institute professor at the Massachusetts Institute of Technology, has won the 2019 Dreyfus Prize in the Chemical Sciences.

The highest honor awarded by the Camille and Henry Dreyfus Foundation, this biennial prize, initiated in 2009, is

conferred in a specific area of chemistry each cycle. Langer is being honored for chemistry in support of public health for discoveries and inventions of materials for drug-

4 ASBMB TODAY

delivery systems and tissue engineering that have had a transformative impact.

Using biotechnology and materials chemistry, Langer's lab has developed polymers to deliver drugs continuously and at controlled rates for prolonged periods. These have been translated into commercial products to treat brain and prostate cancer, macular degeneration and mental health disorders such as schizophrenia and opioid addition. His work with Joseph Vacanti in tissue engineering led to the creation of new skin, cartilage, bone, corneas and blood vessels in humans.

Langer has written more than 1,400 articles. His many honors include both the National Medal of Science and the National Medal of Technology and Innovation. About 40 companies have been spun out of the Langer lab.

Langer will deliver a lecture at an awards ceremony at MIT in September. The Dreyfus prize includes a \$250,000 award.

Gairdner awardees include Springer, Stillman



2019 Canada Gairdner International Awards. Since 1959, the Gairdner Foundation has given the Canada Gairdner International Awards to scientists who have

Timothy A. Springer and Bruce

Stillman are among the recipients of the



made significant achievements in biomedical research. Laureates each receive a \$100,000 prize.

Springer, a professor at Harvard Medical School, is internationally renowned for his work in the fields of cell biology

Stillman

and immunology. The foundation is recognizing him "for discovery of the first immune system adhesion molecules, elucidation of their roles in antigen recognition and leukocyte homing, and translation of these discoveries into therapeutics for autoimmune diseases," according to a release from the foundation.

As president and CEO of Cold Spring Harbor Laboratory, Stillman is widely known for his discovery of the origin recognition complex and his research on the process and regulation of chromosome replication. The foundation is recognizing him for his "pioneering research on the eukaryotic DNA replication cycles including initiation, regulation and responses to DNA damage."

Springer and Stillman will be honored at the Canada Gairdner Awards Gala in October.

Chemistry society honors Kiessling, Butler



Laura Kiessling and Alison Butler have been recognized for their research by the Royal Society of Chemistry.

Kiessling, a professor of chemistry at the Massachusetts Institute of Technology



and a member of the Broad Institute, won one of the society's three 2019 Centenary Prizes recognizing "outstanding contributions to our understanding of the assembly, recognition and functions of carbohydrates." Kiessling is noted for her work on lectin-glycan interactions in cell-surface recognition, which can inform

pathogen recognition and stem cell fate.

Butler, a member of the chemistry faculty at the University of California, Santa Barbara, received the biennial Inorganic Mechanisms Award for studies leading to understanding of reaction mechanisms. Butler studies metallobiochemistry in marine microbes and algae, focusing currently on microbial iron acquisition through secreted chelators called siderophores. She also is known for earlier work on the mechanisms of haloperoxidase enzymes, which carry out halogenation of organic molecules.

Both Kiessling and Butler will receive medals and monetary awards, and each will complete a U.K. lecture tour.

Two named Dreyfus teacher-scholars



Sashita

Dipali Sashital and Timothy Wencewicz are among the 13 recipients of the 2019 Camille Dreyfus Teacher–Scholar Awards.

The awards, presented by the Camille and Henry Dreyfus Foundation, support the research and teaching careers of talented young faculty in the chemical sciences.



Wencewicz

Sashital is an associate professor of biochemistry at Iowa State University. Her lab combines biochemical, structural

Each award includes an unrestricted

and cellular tools to study the molecular mechanisms of nucleic acid-protein complexes involved in CRISPR-Cas systems.

research grant of \$100,000.

Wencewicz is an associate professor of chemistry at Washington University in St. Louis. His lab uses organic chemistry and enzymology to study the molecular mechanisms of antibiotic action, biosynthesis, resistance and delivery.

MEMBER UPDATE

14 student members named Goldwater scholars

Fourteen undergraduate members of the American Society for Biochemistry and Molecular Biology won awards from the Barry Goldwater Scholarship and Excellence in Education Foundation this spring. Trustees for the fund, which was established by Congress and named after the senator in 1986, selected 496 winners this year in partnership with the Department of Defense National Defense Education Program.

The ASBMB members who won scholarships are listed below along with their career goals:



Steven Fried, University of Arizona: "I will pursue a Ph.D. in chemistry with an emphasis in biophysics. I aspire to conduct biophysical research on protein dynamics as a university professor, and in so doing advance human health."

Fried



Zachary Fralish, Florida Southern College: "I plan to pursue a Ph.D. in biomedical engineering with a specialization in drug-delivery mechanisms."

Fralish



Liz Enyenihi, Emory University: "Ph.D. in biochemistry. I plan to conduct research in biomedical science and teach at the university level."



Dominique Mosley, Spelman College: "M.D.–Ph.D. in genetics. Conduct research on the development and application of cutting-edge genomic methods to precision medicine, teach, and advocate on behalf of vulnerable patient populations.

Mosley



Alexander Stewart, Western Kentucky University: "Ph.D. in virology. Research virus structure at a government research laboratory such as the (Centers for Disease Control and Prevention)."

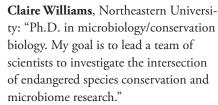
Stewart



Dillingham



Megan Dillingham, Western Kentucky University: "Ph.D. in systems biology. Conduct research in a government lab on mechanisms of cancer evolution and model the development of heterogeneity, metastasis and resistance to improve treatment and outcome."



Williams



Gina Duronio, Northeastern University: "My professional aspirations are to obtain an M.D.–Ph.D. in molecular biology and conduct basic and translational oncology research as a university professor or a faculty member at a research hospital."

Duronio



Caleb Carr, University of Massachusetts, Amherst: "I plan to earn a Ph.D. in computational biology and become a professor at a research university. I would head my own research lab and teach concepts integrating computer science and the life sciences."



Kwan Yoon, University of Massachusetts, Amherst: "Ph.D. in biomolecular engineering. Conduct research in biochemistry and eventually become a principal investigator."



Alicia Bostwick, Hope College: "Ph.D. in biochemistry. Conduct biomedical research focusing on causes of and treatments for human diseases such as asthma, allergies, or cancer."



Steenwinkel

Tessa Steenwinkel, Michigan Technological University: "I would like to obtain a Ph.D. in biochemistry and molecular biology with the goal to become a professor in the field of human health, with a focus on fertility and early human development."



Charlotte Mineo, Union College: "I will pursue a Ph.D. in biochemistry. I plan to teach as a college professor and research plant biochemistry to better understand host–pathogen interactions at the molecular level."

Mineo

JLR LECTURESHIP

Austin Lai, Emory University: "M.D.– Ph.D. in neurobiology. Teaching and researching neurobiology at the university level and clinically apply my research to treat patients."

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



DAVID EBENEZER

David Brindley of the University of Alberta gave the Journal of Lipid Research lecture at the FASEB Science Research Conference on lysophospholipid and related mediators in Lisbon, Portugal. His talk was about blocking the wound-healing enzyme autotaxin and the growth factor lysophosphatidate to improve breast cancer treatments.

MEMBER UPDATE





Columbia University emeritus professor of biochemistry and molecular biophysics Barbara Low died Jan. 10. She was 98.

Low was born March 23, 1920, in Lancaster, England. She received her undergraduate degree in chemistry in 1943 from Somerville College of Oxford University before obtaining master's and doctoral degrees in chemistry at Oxford in 1946 and 1948. She was as a doctoral student with Nobel laureate Dorothy Crowfoot Hodgkin.

After immigrating to the United States, Low worked

as a research assistant to Nobel laureate Linus Pauling at the California Institute of Technology and Edwin Cohn at Harvard University.

Low joined the faculty at Columbia as an associate professor in 1956 and was named professor in 1966. She was a pioneer in the field of X-ray crystallography in the early 1940s, and her research on snake venom neurotoxins led to a greater understanding of the acetylcholine receptor, a protein receptor that responds to the neurotransmitter targeted by snake venom.

She retired as a professor in 1990 but continued

VIRTUAL ISSUE Extracellular Vesicles

jbc.org/site/vi/extracellular_vesicles

JOURNAL OF BIOLOGICAL CHEMISTRY



ASBMBTODAY CALL FOR SUBMISSIONS

ASBMB Today is publishing two essay series in 2019 **DEADLINE: OCT. 10**



What I wish people understood about

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

Night shift

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

Email asbmbtoday@asbmb.org for more info, or submit at asbmb.org/asbmbtoday.

Upcoming ASBMB events and deadlines

Pain Awareness Month 3 Communication Course application site opens 10 Emerging Roles in Nucleolus registration deadline 12-15 Serine Proteases in Pericellular Proteolysis and Signaling 16-20 Postdoc appreciation week 16-20 Peer review week 1 Accreditation deadline 7 **Communications Fall Course begins** 6-11 **Mental Illness Awareness Week** 11 National Depression Screening Day 20-24 ASBMB-BSC Symposium on the Interplay Between Epigenetic Regulation and Genome Integrity 21-27 **Open Access Wee**k 24-27 **Emerging Roles in Nucleolus** Special symposia call for proposals for 2021 deadline 1 12 **U.S. Antibiotic Awareness Week** 13-16 Annual Biomedical Research Conference for Minority Students 14 Annual meeting abstract deadline 27 Annual meeting general travel awards deadline 25 Student Chapters renewal deadline

RETROSPECTIVE

J. Thomas August (1927 – 2019)

Tom August arrived at Johns Hopkins in 1976 as director of what was then called the department of pharmacology and experimental therapeutics. In 2006, he and a colleague founded Immunomic Therapeutics Inc., which nine years later entered a licensing agreement with a Japanese firm for its LAMP technology. At the time of August's death, the \$300 million upfront payment was the university's largest technology transfer.



Thomas August, an early member of the American Society for Biochemistry and Molecular Biology • who also served on the editorial board of the Journal of Biological Chemistry, an ASBMB journal, died Feb. 11 of cancer. He was 91.

A pioneer in immunology who worked to find vaccines for Zika, dengue, influenza and other viruses, August led the pharmacology department at the Johns Hopkins University School of Medicine for 23 years. Under his tenure, the department shifted its focus to molecular biology and virology.

In 1980, August changed the field of immunology with the discovery of lysosome-associated membrane proteins, or LAMPs, which help activate the immune system.

August was born in Whittier, California, in 1927, the youngest of six children. He served in the Army, stationed in Alaska, late in World War II. He graduated in 1954 from Stanford University School of Medicine and did additional training at the University of Edinburgh and Harvard Medical School.

Before moving to Hopkins in 1976, he held faculty positions at Stanford, New York University and Albert Einstein College of Medicine. He was a scientist and board member at Cold Spring Harbor Laboratory in the 1960s and worked with researchers at the California Institute of Technology, the Salk Institute, Oxford University, Uppsala University in Sweden, Perdana University in Malaysia and Johns Hopkins Singapore.

After August's death, the Perdana University School of Data Sciences named its inaugural symposium for postgraduates and young researchers in his memory.

Asif M. Khan, the school's dean, wrote in a letter to August's family that the school would not have existed without his foresight, guidance and support. "This is the least we can do to relive his memories and dedication to science, in particular his patience in nurturing early researchers," Khan wrote.

August held eight patents on vaccine-related technologies, published hundreds of scientific articles, and received many honors. In 2001, he was named a Hopkins university distinguished service professor.

James Stivers, interim director of pharmacology and molecular sciences at Hopkins, stated in a university press release announcing August's death, "It is hard to exaggerate the personal and scientific impact of Tom on our department. The example he set in terms of pursuing creative and innovative research with direct application to human health was inspiring, and his gracious demeanor and warmth will always be with us."

August was married for 67 years to Jean Nordstrom August, whom he met in high school. He is survived by his wife, three children, five grandchildren and three great-grandchildren.

-Comfort Dorn

These are edited excerpts from remembrances shared by several of Tom August's colleagues and from a memoir of childhood at the Cold Spring Harbor Laboratory written by his daughter, Christina. Read the full texts at asbmb.org/asbmbtoday.

Remembrance

met Tom August as a second-year medical student at the Johns Hopkins University ... (when he) offered me a training grant-funded place in his department as a graduate student in the late Mette Strand's laboratory, which was closely allied and in the same spaces as his own.

What strikes me in my memories of Tom is his unique combination of energy, enthusiasm, supreme powers of concentration and the joy he experienced in so many spheres of life. Tom was truly excited by everything he chose to do, whether in the laboratory or in his garden, and he tackled every task and difficulty as if it were a great adventure. By the time he arrived in the laboratory in the morning, he had already been up working in his garden from the early dawn.

In the laboratory, he was incisive and forthright. He could sit undisturbed and concentrate on a manuscript despite the roar of vacuum pumps, the chatter of graduate students and postdocs, and the incessant ringing of the telephone. And he brought the same concentration to bear on questions brought to him by his students.

Tom was accessible and open. He had a chairperson's-style office with a private bathroom and shower. At one point, somehow, a large white rabbit started living in the office, until he had to be re-homed because of a habit of chewing on the wiring.

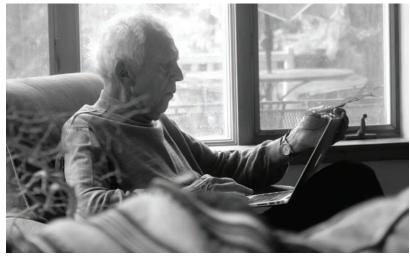
Around Christmastime, Tom would prepare a large punch bowl of eggnog, and everyone in the department stopped by to enjoy the holiday season with him.

> —**William S. Aronstein** Vice President, Medical Affairs CTI Clinical Trial & Consulting Services

first met Dr. J. Thomas August during my application to the graduate program in pharmacology and molecular sciences at the Johns Hopkins University School of Medicine. After I graduated, I joined Tom's laboratory to work on vaccines.

Tom had this great sense of wonder and enthusiasm for everything in life, but nothing could bring him more joy than to see new data and engage in a long scientific debate. His joy was infectious, and we all felt very motivated and energetic after those conversations.

As Tom's age advanced, he became more anxious and determined to see the final product of his life's work. His obsession, in his own words, was that he wanted to "make something useful" before he died. In his view, "useful" was something tangible, like a vaccine implemented in a national immunization program.



Tom August works at the family's Martha's Vineyard summer house in August 2018. August loved his garden there, on which he spent many hours every day. He also loved their holiday apartment in Lille, France, and was a great Francophile.

RETROSPECTIVE

A few weeks before he died, Tom was talking about his hope that he would be able to spend some weeks in Lille, France, and get back to Martha's Vineyard over the summer. He said: "I just love living." — Robert Stavis

At the end of each day, we would sit with Tom in his office to talk about what we had done, new experimental data or an article we had read. ... Tom would share a lot of fun stories, like driving an Alfa Romeo with music blaring and a goat wearing sunglasses sitting by his side, or the day during his medical residency at Stanford when he attended Marilyn Monroe with a pneumonia she got after performing a show in Korea wearing only what he described as "the famous mink bikini," or stories about a rabbit he had in his office that was trained to use the bathroom.

Thanks to Tom, Fiocruz–Pernambuco (a technical and scientific institute in Brazil) has the virology department that played an essential role during the outbreak of a new disease in northeast Brazil caused by the Zika virus. Although Tom did not see with his own eyes a vaccine using his technology implemented in an immunization program, he got pretty close to it. ... I am convinced that Tom will see from where he is a Zika vaccine using the LAMP technology and will be very proud of us.

-Ernesto T. A. Marques

Associate Professor, Department of Infectious Diseases and Microbiology, University of Pittsburgh Public Health Scientist, Fundação Oswaldo Cruz, Instituto Aggeu Magalhães, Pernambuco, Brazil

om's career was distinguished by major scientific and professional accomplishments, but the memories I treasure most are those of his irrepressible enthusiasm for just about everything, his insatiable curiosity — especially about science and the satisfaction that spilled over from time spent in his yard planting, splitting logs, spreading wood chip mulch, enjoying the pond and its critters, and sharing it all with neighbors and friends.

I still have rhubarb and a black turkey fig tree that Tom and Jean moved from their yard to ours over 30 years ago, and I will always remember the arms-full bouquets of flowers Tom brought in and distributed around the department from spring to fall each year.

–Wade Gibson

Professor Emeritus, Johns Hopkins Department of Pharmacology and Molecular Sciences



Tom August met his wife, Jean, when they were both in high school. They were married for 67 years.

Ve known Tom August for over 50 years — first as a summer student when I was in college and then as an M.D./Ph.D. student. (As a measure of his influence, I've always considered myself to be a Ph.D./M.D. and not the other way around.) He was my teacher, mentor, supporter, source of inspiration and dear, dear friend for my entire adult life. ... Seeing his career from a professional distance, what has always impressed me is that Tom didn't just know how to study a problem; he knew what to study.

Tom was an enthusiast ... about everything! When I was working as a summer student, he shared a book that he had found in the Cold Spring Harbor Laboratory Library called "The Behavior of the Lower Organisms" by H.S. Jennings, published in 1906. We had endless discussions around how the molecular biology of the behavior of an organism could be analyzed, and those discussions ultimately led to my thesis work on the phototactic response of the eukaryotic green algae Chlamydomonas.

Tom was equally enthusiastic off the academic grid. ... Whether it was swimming in Cold Spring Harbor at midnight in December or manning the bilge pump through the night on my family's sailboat (long story), Tom was in.

A few weeks before he died, Tom was talking about his hope that he would be able to spend some weeks in Lille, France, and get back to Martha's Vineyard over the summer. He said: "I just love living."

> **—Robert Stavis** Bryn Mawr, Pennsylvania

Cold Spring Harbor Laboratory, on the North Shore of Long Island, was, in the 1960s of my childhood, a rare bird. ... Its wildness, its flightiness, must have allowed for a certain kind of intellectual freedom and scientific risk-taking, the mood of which permeated every aspect of life there. We tried making maple syrup in a big kettle over an outdoor fire and foraged for a wild dinner when we dined on clams, eels, wild greens and roasted day lily tubers and drank homemade birch bark beer.

But there was also the rarified part of life at the lab. Being a middle-class child of the time, I knew them as "Dr. Hershey, Dr. McClintock, Dr. Luria" and "Dr. Crick, Dr. Watson, Dr. Delbrück." But I recognized them also as Al, Barbara, Salva, Francis, Jim, Max. I saw them in shorts and sandals, we ate together in the dining room, I watched them interact. I knew that lanky Dr. Watson and gentlemanly Dr. Crick had discovered something wonderful called a double helix, but I also knew that a dancing girl (as she was euphemistically explained to me by my father) had jumped out of Dr. Crick's 50th birthday cake. Dr. Delbrück was Toby and Ludina's dad, and I paddled with Dr. Hershey's son Peter in a little red rowboat named the Alfred.

My father worked in Jones Lab, the oldest of the labs on the grounds, having been built in 1893. Sometimes I would go to find him in the hip-roofed, high-ceilinged building by the seawall of the Inner Harbor. He would put me to work at a central worktable sorting fragile glass pipettes by size. I thought my father was so talented, the way he could use his mouth to suck a slender pipette full of some mysterious fluid, quickly slip his thumb pad over the top, and then with a delicate lifting of his thumb let it back out, single drop by single drop, into rows of petri dishes or glass test tubes upright in racks. I asked him (later) what he had been working on back then. The answer: RNA bacteriophages and, later, tumor viruses.

-Christina August Hecht



NEW MEMBERS

Subha Baniya, Wellesley College

Max Besser, Point Loma Nazarene University

Shivkumar Biradar, University of Pittsburgh

Breann Brown, Vanderbilt University

Ja'net Burdette, Western Illinois University

Michael Burgess, Broad Institute

David Cabrera, Van Andel Institute

Andres Caro, Hendrix College

Shelbi Christgen, St. Jude Children's Research Hospital

Alanna Condren, University of Illinois at Chicago

Markus Dagnell, Karolinska Institutet

Brian Dang, University of California, Davis

Kyle Davis, West Virginia University

Marc Delarue, National Reference Center/ Institut Pasteur

Tobias Eisenberg, University of Graz

Eliza Elliot, University of Delaware

Diego Fajardo, Universidad Complutense de Madrid **Geoffrey Fox,** Pennsylvania State University

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Philip Gordts, University of California, San Diego

Jeffrey Hasday, University of Maryland School of Medicine

Matthew Heath

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Qiu-Xing Jiang, University of Florida

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Zachary Van Roy, University of Nebraska Medical Center

Josephine Watson, University of Illinois at Urbana–Champaign

Keon Wimberly, University of Florida

Renae Wisz, Eastern Illinois University

Masahito Yamazaki, Shizuoka University

Xiaoyan Zheng, George Washington University

Alessandra Zimmermann, University of Maryland

Lipoprotein (a): Many strides made, yet there is a long road ahead

JLR VIRTUAL ISSUE • jlr.org/site/collections/lpa/

New ASBMB committee supports women in BMB

By Laurel Oldach

he American Society for Biochemistry and Molecular Biology has launched the Women in Biochemistry and Molecular Biology Committee, or WIBMB. The charge of this newest ASBMB committee is to advocate for women in these disciplines, both in academia and in industry.

Founding members Susan Baserga of Yale University, Kelly Ten Hagen of the National Institutes of Health and Karen Allen of Boston University said the inspiration for the committee arose from the widely reported dearth of women in senior roles in academia and from the community's enthusiasm for the Women Scientists' Mentoring and Networking event held at ASBMB annual meetings since 2008.

Baserga said working on the ASBMB's Public Affairs Advisory Committee was a further inspiration. The PAAC anti-harassment working group, chaired by Susan Forsburg of the University of Southern California, has been working for about a year to promote policies to address sexual harassment and gender discrimination in science. Members organized a congressional briefing in December 2018 to share findings by the National Academies of Sciences, Engineering and Medicine that such harassment is widespread, and they have continued to pursue solutions in conversation with science funding institutes and policymakers.

According to Baserga, the working group catalyzed a cadre of







Susan Baserga

Kelly Ten Hagen

Karen Allen

"mighty women" in the PAAC. "I was so motivated by their collective wisdom, their generosity and smarts, that I thought we could offer that to the wider ASBMB," she said, adding that past ASBMB president Natalie Ahn was a key champion of the proposal.

The formation of the women's committee was announced during this year's Women Scientists' Networking Dinner at the ASBMB annual meeting in Orlando. "I was so impressed with the energy in the room," Baserga said.

The committee plans to come together with the community annually at that dinner during the ASBMB meeting. The event will include talks on issues that uniquely challenge women scientists and will continue to serve as a forum for sharing experiences, challenges and solutions.

Beginning in 2020, two new awards recognizing individuals with a strong commitment to advancing the careers of women in biochemistry and molecular biology will be presented at the dinner: one for early-career faculty and one for more established scientists. Nominations for these awards will open in the fall.

"I am delighted that the ASBMB Council approved the creation of the Women in Biochemistry and Molecular Biology Committee ... to highlight the many important roles that women in biochemistry and molecular biology play in advancing our field," ASBMB president Gerald Hart said. "We hope that this committee will formally lead to increased involvement of women in the leadership of ASBMB as well as increase the numbers of outstanding women who are offered high-profile speaking opportunities at ASBMB-sponsored events."

Want to join?

If you are interested in joining the WIBMB, send your CV/résumé and a short letter of interest to ASBMB Executive Director Barbara Gordon (bgordon@asbmb.org).

Chasing the diagnostic potential of RNA editing

By Nathalie Gerassimov

icholas O. Davidson wears many hats: He is a practicing physician, he is the division chief of gastroenterology at Washington University in St. Louis, and he holds professorships in medicine, developmental biology, and pharmacology and molecular biology. On top of that, he is the co-editor-inchief of the Journal of Lipid Research and a principal investigator studying the genetic regulation of intestinal and hepatic lipid homeostasis, with authorship on more than 230 papers.

A recent paper by Davidson and colleagues, published in RNA Journal, deepens our understanding of tissue-specific regulation of programmed alteration of RNA, known as RNA editing, in the intestine and the liver.

"This paper identifies what we believe to be the complete machinery for a form of RNA editing," Davidson said. "The approaches and the tools from this study can be applied to gain a better understanding of the function of most, if not all, types of mammalian cells."

Davidson's professional journey and scientific outlook was captured in ASBMB Today in a 2012 interview. In brief, his interest in gastroenterology emerged during his medical training at Kings College Hospital Medical School in London under the mentorship of Roger Williams, one of the trailblazers of liver transplantation. He further built his expertise by working with the late Pete Ahrens Jr. at The Rockefeller University in New York and during

a gastroenterology fellowship at Columbia-Presbyterian Medical Center. His own lab started at the University of Chicago Medical Center before relocating to St. Louis. His research has helped shape the field of RNA editing over several decades.

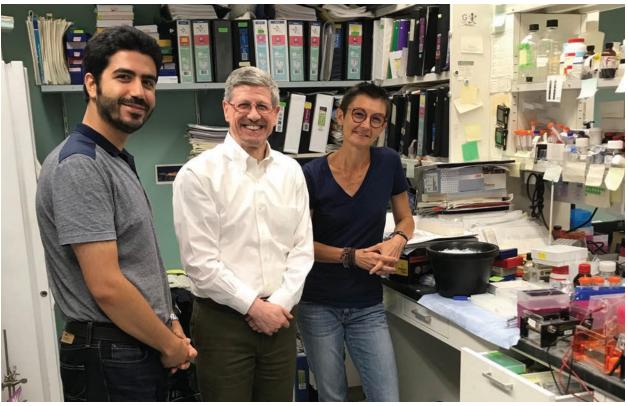
RNA editing can create heterogeneity in genetically identical cells by mediating amino acid substitutions, alternative isoform creation and modification of stop codons. Furthermore, RNA editing in the 3'-untranslated region has been shown to be the alteration that most frequently leads to changes in RNA stability, RNA localization and protein translation. Advances in high-throughput sequencing techniques have shown that RNA-editing events are more pervasive than





Apc min/+ Apobec-1 -/-

Apc^{min/+} is a mouse model for tumorigenesis. The top image shows a representative section of the intestine of an Apc^{min/+} mouse. Arrows denote some of the many polyps. Deletion of the RNA-editing enzyme Apobec-1 in this model drastically reduces the number of polyps in the intestine. The Davidson lab is exploring how loss of cytosine to uracil RNA editing protects against intestinal tumorigenesis.



The RNA editing team in the Davidson lab at Washington University in St. Louis include, from left, Saeed Soleymanjahi, Nick Davidson and Valerie Blanc.

originally thought, prompting the introduction of the concept of an epitranscriptomic code to parallel the epigenetic code.

In 1994, Davidson's team showed that one mechanism of RNA editing is the deamination of cytosine to uracil, which is catalyzed by the Apobec family, including Apobec-1. Other researchers later discovered that the Apobec-1 biochemical function requires a cofactor, and two different essential cofactors were discovered — Apobec-1 complementation factor, or A1cf, and RNA binding motif protein 47, or Rbm47.

Prior to this paper, the relative contribution of the two cofactors to physiological Apobec-1 function was not fully understood. Davidson's team looked at the global RNAediting landscape of mouse livers and intestines when either or both cofactors were deleted or were overexpressed as transgenes. Deletion of Rbm47, but not A1cf, caused a large, tissue-specific change in the RNA editing profile, with the intestines being most affected.

"The findings of this paper were somewhat surprising, since A1cf was discovered as necessary for the deaminase Apobec-1 to act on RNA, and it was originally thought to be the Apobec-1 cofactor," Davidson said. "However, our data using a conditional tissue-specific deletion of Rbm47 alone or with A1cf point to Rbm47 as the dominant Apobec-1 cofactor in adult mouse liver and intestine."

Davidson's lab now is using the genetic tools from this study to illuminate further the role of RNA editing during development, where it is implicated in regulation of growth.

RNA-editing alterations also have been reported in cancers and neurological disorders, and Davidson's lab is pursuing the profiling of DNA, RNA and protein levels in cancer tissues to substantiate further the diagnostic potential of RNA editing.

"This study fits into the emerging consensus in cancer biology that RNA editing can contribute to cancer susceptibility," he said, "and this is a big direction that we are focusing on." DOI: 10.1261/rna.068395.118

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What controls cholesterol biosynthesis?

By Laurel Oldach

omeostasis is an important biochemical principle. The pace of a biosynthetic pathway often is controlled by feedback from pathway products, adjusting the system to prevent excessive accumulation of its products.

Cholesterol biosynthesis is one example. Researchers know it is regulated by metabolic intermediates but until now have disagreed about which intermediates do the work. In the **Journal of Lipid Research**, Liang Chen and colleagues at Wuhan University and the Chinese Academy of Sciences report that several metabolites can affect the activity of two cholesterol biosynthesis enzymes. The study gives new insight into how cholesterol biosynthesis is regulated.

Researchers knew that an intermediate product of the biosynthetic pathway could inhibit each of two control points: HMG-CoA reductase, or HMGCR, which synthesizes a key cholesterol precursor called mevalonate, and sterol responsive element-binding protein, or SREBP, a transcription factor that affects many cholesterol synthesis enzymes.

Data suggested that lanosterol, the first intermediate in the pathway that is cyclic instead of linear, was the key regulator, but the researchers knew that a slightly modified version of lanosterol might be more important. The question is complicated because the cholesterol biosynthesis pathway bifurcates after lanosterol is formed.

In lanosterol or any of its down-

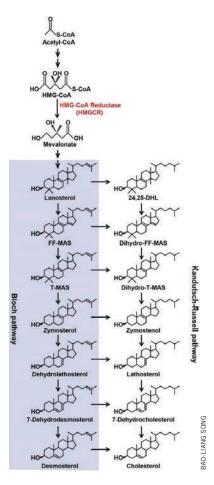
stream products, a double bond in the molecule's alkyl tail can be reduced, and the reduced molecules proceed through the same steps to be turned into cholesterol (see figure). So which intermediate cholesterol metabolite exerts the most control over the overall biosynthetic pathway?

That is a technically difficult problem. It is hard to induce accumulation of specific intermediates, because no effective enzyme inhibitors exist for specific steps in sterol synthesis and cells are unlikely to take up exogenously added pathway intermediates.

Chen and colleagues worked around these difficulties by generating a cell line better equipped to absorb mevalonate, a key intermediate produced by HMGCR. In these cells, intermediates can accumulate even if HMGCR activity is blocked. When these cells are provided with mevalonate, they scale up cholesterol production, triggering homeostatic degradation of HMGCR and blocks SREBP activation.

The team then systematically knocked out cholesterol biosynthesis enzymes using CRISPR, forcing traffic to back up immediately upstream of whichever conversion step had been blocked. Using lipidomic analysis of sterol extracts from each knockout cell line, they assessed the impact of loss of each enzyme and accumulation of its substrate, identifying key metabolites that impacted levels of HMGCR and SREBP.

The researchers showed that



A pathway diagram shows two parallel routes from mevalonate to cholesterol.

lanosterol down-regulated HMGCR but not SREBP, confirming that lanosterol and not its reduced relative is the key regulator. They also found that other sterol intermediates with reduced double bonds inhibited both HMGCR and SREBP. The authors say that molecules resembling these endogenous regulators could be a new way to control cholesterol levels. DOI: 10.1194/jlr.RA119000201

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Starving triple-negative breast cancer

By Jonathan Griffin

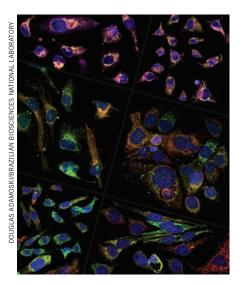
team of Brazilian researchers has developed a strategy that slows the growth of triple-negative breast cancer cells by cutting them off from two major food sources.

About 15% to 20% of all breast cancers are triple-negative, and the type is most common in African American women. These tumors lack estrogen and progesterone receptors and HER2 protein that are present in other breast cancers and permit certain targeted therapies. Every TNBC tumor has a different genetic makeup, so finding new markers to guide treatment has been difficult.

Sandra Martha Gomes Dias is a cancer researcher at the Brazilian Biosciences National Laboratory in Campinas, Brazil. "There is intense interest in finding new medications that can treat this kind of breast cancer," she said. "TNBC is considered to be more aggressive and have a poorer prognosis than other types of breast cancer, mainly because there are fewer targeted medicines that treat TNBC."

In a new study in the **Journal of Biological Chemistry**, Dias and colleagues demonstrate that in addition to glutamine, a well-known cancer food source, TNBC cells can use fatty acids to grow and survive. When inhibitors that block both glutamine and fatty acid metabolism were used in concert, Dias said, TNBC growth and migration slowed.

To maintain their ability to grow at a breakneck pace, cancer cells often consume nutrients at a higher rate



Heterogeneous presentation of glutaminase (red) and CPT1 (green) is shown across several TNBC cell lines. The cell line in the top right panel is resistant to the drug CB-839. A study by dos Reis et al. suggests that these cells survive treatment by increasing fatty acid (purple) consumption in their mitochondria (yellow).

than normal cells. Glutamine, the most abundant amino acid in plasma, is one of these nutrients. Some cancers become heavily reliant on this versatile molecule, Dias said, as it offers energy, carbon, nitrogen and antioxidant properties, all of which support tumor growth and survival.

The drug telaglenastat, also known as CB-839, prevents glutamine processing and is in clinical trials to treat TNBC and other tumor types. CB-839 deactivates the enzyme glutaminase, preventing cancer cells from breaking down and reaping the benefits of glutamine. However, recent research has shown that some TNBC cells can resist its effects.

To see if alterations in gene expression could explain how these cells survive, Dias said, her team exposed TNBC cells to CB-839 and then defined those that were resistant and those that were sensitive to the drug and sequenced their RNA.

In the resistant cells, molecular pathways related to the processing of lipids were altered, Dias said. In particular, levels of the enzymes CPT1 and CPT2, critical for fatty acid metabolism, were increased.

"CPT1 and 2 act as gateways for the entrance of fatty acids into mitochondria, where they will be used as fuel for energy production," Dias said. "Our hypothesis was that closing this gateway by inhibiting CPT1 in combination with glutaminase inhibition would decrease growth and migration of CB-839-resistant TNBC cells."

The double inhibition slowed proliferation and migration in resistant TNBC cells more than individual inhibition of either CPT1 or glutaminase. Dias said these results provide new genetic markers to better guide drug choice in patients with TNBC. DOI: 10.1074/jbc.RA119.008180

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On the trail of steroid aromatase: The work of Kenneth J. Ryan

By Martin J. Spiering

Ale and female animals typically display numerous differences. However, the two major hormone classes responsible for these differences, androgens and estrogens, differ only subtly in their chemical backbones: Androgens have a six-carbon nonaromatic ring — the A ring — in their steroid skeleton, whereas estrogens have an aromatic A ring.

A single protein, steroid aromatase (also called estrogen synthase), is the only known enzyme capable of aromatizing the A ring in androgens to produce estrogens.

Females and males require both sex hormones in a balance appropriate for each sex. Steroid aromatase maintains this balance during development and pregnancy and in reproductive systems and tissues. Researchers have long sought to better understand steroid aromatase activity in order to address complications during pregnancy, develop hormone-based contraceptives and manage estrogen-responsive cancers.

Three papers published in the **Journal of Biological Chemistry** authored by Kenneth J. Ryan and now recognized as classics laid the groundwork for understanding the role of steroid aromatase and other steroid-modifying enzymes in estrogen biosynthesis.

Before he embarked on his studies of placental steroid aromatase, Ryan, in one of these JBC papers, reported that microsomal fractions of adrenal glands from beef contain an enzyme activity that hydroxylates carbon 21 in the hormone progesterone and several of its steroid derivatives. This finding clarified the enzymatic nature of this pivotal step in steroid hormone production in adrenal tissues and helped establish an experimental system that Ryan then used to probe how estrogens are made from androgens.

In the 1950s, studies using extracts from animal tissues hinted at the enzymatic nature of the androgen-to-estrogen conversion. However, the amounts of enzyme activities in these preparations were insufficient for detailed investigations to improve understanding of the enzymes and mechanisms in these reactions. This prompted Ryan, then a clinician-researcher at Harvard Medical School, to try to boost estrogen production, extract these hormones more efficiently and begin to characterize the enzymes involved.

"He was one of the first people who did that sort of stuff," said Richard Auchus, a researcher at the University of Michigan with a long-standing interest in steroid production and modification.

Ryan was an obstetrician and had a ready supply of tissue ideal for investigating estrogen production human placentas obtained immediately after delivery.

Preparing and analyzing these biological materials was laborious. Ryan extracted the protein activities and products from kilograms of placental tissues, and even small glitches in the experimental protocols could result in loss of activity.

This effort bore fruit when Ryan confirmed in 1959 that the formation of the aromatic A ring is the result of enzymatic activity leading to aromatization. "He figured out that (the enzyme activity) was in the microsomal fraction and that it required NADPH (the reduced form of nicotinamide adenine dinucleotide phosphate), and he developed the chromatography to measure it," Auchus said.

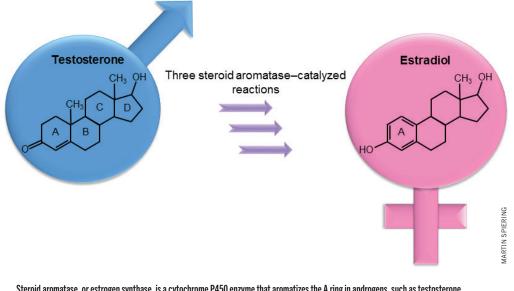
Ryan's findings suggested that the aromatization involved an enzyme system that used molecular oxygen to achieve A-ring aromatization, but with the tools available at the time, Ryan could not delineate the exact biochemical sequence of events.

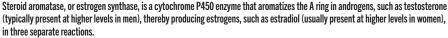
Initially, it wasn't clear whether the aromatization was performed by one enzyme or by several, because the reaction sequence required at least three oxidations, which yielded some, at the time, unusual products, Auchus said.

It "was fascinating that you got an aromatic A ring," Auchus said, but "this didn't really make a lot of sense to people back then. The reaction was weird because it involved both loss of a methyl group and formation of the aromatic A ring."

The reaction mechanisms remained black boxes, but Ryan's work had begun to pry the lids open, Auchus said. "Now people could start to look at the mechanism."

Numerous studies followed, elucidating the reaction mechanism,





structure and biological roles of steroid aromatase. In the 1980s, several researchers showed that the aromatizing activity is indeed performed by just one enzyme, a cytochrome P450 monooxygenase aptly named steroid aromatase.

Ryan next set his sights on establishing the biochemical origins of another important estrogen, estriol, now a standard biomarker in routine pregnancy care. Scientists knew estriol was produced by a classic pathway involving the hydroxylation of carbon 16 in the estrogens estradiol and estrone, but Ryan had found preliminary evidence for another pathway in which estriol also could be produced by aromatization of C-16 hydroxylated androgens.

Using his placental assay, Ryan confirmed his earlier finding, and he clarified that another estrogen, 16alpha-hydroxyestrone, is an intermediate in the classic estriol-producing pathway. These discoveries underscored the utility of Ryan's assay and represented key early steps in untangling the biochemical complexities in estrogen production. Born in 1926 in New York City, Ryan grew up during the Great Depression, working on farms in his teen years and, after graduation from high school, serving in the U.S. Navy during World War II. He enrolled at Northwestern University for his undergraduate studies and then attended Harvard Medical School, graduating magna cum laude in 1952.

During residencies at hospitals in the Boston area, Ryan landed a biochemistry fellowship shared with Nobel laureate Fritz Lipmann, enabling him to pursue his interest in the roles of estrogens in the biology of pregnancy.

In the 1960s, Ryan began taking on administrative duties, successively becoming chairman of several obstetrics and gynecology departments across the country. In the early 1970s, he returned to Harvard, where he helped build an academic OB-GYN department. In addition to his work in the clinic and research activities, Ryan trained and mentored many students and residents.

He also became active in medical

ethics. "He actually got involved with a lot of ethical issues, like fetal tissue research," Auchus said. "In his later years, he became a pretty prominent person in that field."

Ryan chaired the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. This commission produced the Belmont Report in 1978, whose guidelines for protecting the rights and dignity of human subjects in research continue to provide an ethical framework for research and health providers in the United States to this day. Ryan also was an early and strong proponent of reproductive choice.

He died in 2002 at the age of 75. This article originally appeared in the Journal of Biological Chemistry as a JBC Classic. It has been edited for ASBMB Today.

Martin J. Spiering (mspiering@asbmb.org) is the technical editor at the Journal of Biological Chemistry. Follow him on Twitter @spieringmj.



MCP special issue focuses on multiomics

A dive into systems biology propelled by new analytical approaches

By Laurel Oldach

hat can you learn from two omes that you can't tell from one?

You might determine how different bacterial strains in a water sample contribute specific functions to its overall microbiome. You might find that duplication of a section of a chromosome in cancer cells has wide-reaching effects on important proteins — or that it has a smaller effect than expected.

First, though, you need to find a way to wrangle gigabytes of data saved in numerous, perhaps incompatible formats. As high-throughput analytical tools improve, allowing researchers to collect ever more data, the challenge is how to interpret it all.

When transcriptomic, genomic, metabolomic and proteomic analyses are layered together, parsing out a signal can be a monumental task. Data are collected in different forms: RNA counts, genotypes, and mass spectra that might represent proteins, posttranslational modifications, complex carbohydrates or metabo-



this information into coherent, interpretable results the field needs new analytical strategies and new user-friendly software.

lites. To condense

Researchers surfing this multiomics wave report a plethora of new tools and approaches in a special issue of the journal **Molecu**lar & Cellular Proteomics. The issue, edited by Bernhard Kuster of the Technical University of Munich and Bing Zhang of the Baylor College of Medicine, includes 16 articles that explore ways to combine data from two or more omes.

First things first

For readers unfamiliar with multiomics, a review by Burcu Vitrinel and colleagues at New York University covers different ways that proteomics data and other types of data can be layered and the biological questions one might answer using these approaches.

An article by Vladislav Petyuk of Pacific Northwest National Laboratory and colleagues discusses the importance of data science solutions (such as publishing software and statistical approaches) for reproducibility in handling large datasets from multiomic studies.

Also in the issue:

Cancer proteogenomics

A robust section of the special issue includes combined genomic and proteomic approaches to understanding cancer. A number of these studies use a data set from the National Cancer Institute's Clinical Proteomic Tumor Analysis Consortium and The Cancer Genome Atlas, which make deep proteomic and genomic data from patients with defined cancer types available for bioinformatics analysis. Weiping Ma and colleagues across the United States and South Korea investigated how copy-number variations affect cellular phenotypes through protein and phosphoprotein abundance. They discovered new genome regions that affect the abundance of important cancer-associated proteins.

Xiaoyu Song and colleagues at Mount Sinai, the University of Chicago and the University of Colorado asked similar questions, integrating transcriptome, phosphoproteome and proteome information about advanced ovarian cancer to understand how copy-number variation or methylation at a given locus can reverberate through the cell.

Xiaohui Zhan of Shenzhen University and colleagues in China and the United States combined multiomics with clinical outcomes and images of breast cancer biopsies to yield markers, such as cell density or size, that might be prognostic — a boon for patients, since images of biopsies can be taken at many clinics, while omics approaches are less widely available.

Wenke Liu of New York University and colleagues used independent component analysis, a machine-learning approach, to find patterns in breast cancer proteogenomic data sets that might point to new cellular mechanisms.

Mei-Ju Chen and colleagues at MD Anderson Cancer Center introduce a new iteration of The Cancer Proteome Atlas, a repository

Zhang

IULIE NEWDOL

of protein array data from some 8,000 patients' tumor samples. The new platform, version 3.0, allows users to integrate the available protein array data with other omics data.

Osama Arshad and colleagues at Pacific Northwest National Laboratory combined protein and phosphopeptide abundance across tumor samples to identify new kinase substrates and match modifications altering kinase activity to the substrates they affect.

Ome-agnostic approaches

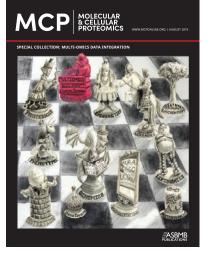
Gene set enrichment analysis, a staple of omics research, involves looking for patterns in the molecules that are altered across conditions.

Two research groups, Chen Meng of the Technical University of Munich and colleagues and Sara Savage and colleagues at Baylor report strategies for combining gene set enrichment analyses across different omic measurements of the same samples.

Metamultiomics: understanding the proteome of the microbiome

Combining multiple omes is challenging enough when working with a defined whole genome that determines the possible array of proteins. But that's not available for most organisms and even less so for complex microbial communities.

Sujun Li and Indiana University colleagues introduce an analysis program for metaproteomics that measures all of the proteins in a mi-



Combining multiple omes is challenging enough when working with a defined whole genome that determines the possible array of proteins. But that's not available for most organisms and even less so for complex microbial communities.

crobiome. The program uses metagenomics and metatranscriptomic data to assemble a custom metagenome specific to the experimental context — for example, ocean or wastewater samples — and then uses that to identify proteins.

Caleb Easterly of the University of Minnesota and colleagues present software that allows quantitative comparison between conditions in metaproteomic studies and also lets researchers ask how different bacterial groups contribute to functions of the microbial community.

Interactomics

Once the proteins in a sample are described, understanding how they interact gives a deeper insight into their function — and can generate some surprises.

Abel Sousa and other researchers at the European Molecular Biology Laboratory investigated how, in cancer with duplicated or deleted sections of genome, protein–protein interactions buffer the final quantity of these proteins encoded in these regions.

Joel Federspiel and colleagues at Princeton used proteomic and transcriptomic data sets to identify important proteins in the interactome of a Huntington's disease–associated protein.

Computational tools

Two articles are more specific to proteomics.

Steven Verbruggen and other researchers at Ghent University in Belgium introduce a new release of their popular PROTEOFORMER software, which uses ribosome profiling to identify new proteoforms and predict their fragmentation patterns.

Dain Brademan and colleagues at the University of Madison report on a web-based tool to visualize and annotate peptide tandem mass spectra no matter what techniques were used to generate them — and, if the user wishes, combine data from multiple experiments.

Find the full MCP special issue on multiomics at mcponline.org/content/ special-issues.

Laurel Oldach

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From the journals

By Jonathan Griffin, Kian Kamgar–Parsi & Tori Zirul

Picking cancerous mutations out of the crowd

Mutations that drive cancerous behavior may be candidates for targeted therapy, but differentiating them from the thousands of inconsequential mutations in cancer tissues has remained a challenge. Deepankar Chakroborty and an international team of researchers devised a new screening method to show cancerassociated mutations. They used the ability of Ba/F3 lymphoid cells to overcome their dependence on interleukin 3 with activated epidermal growth factor receptors, or EGFRs, which are perennially turned on in many cancers. By introducing random mutations into EGFRs and starving cells of IL-3, only those with EGFR-activating mutations survived. This technique, presented in the Journal of Biological Chemistry,

offers a simple means of identifying EGFR variants that potentially drive cancerous activity and merit further investigation.

DOI: 10.1074/jbc.RA118.006336

Fat in muscle linked to insulin resistance

Diets high in saturated fat are associated with metabolic diseases. Insulin resistance caused by fat depletion, known as lipodystrophy, is rare but has become a focus of research, including studies of associations between accumulation of fats stored in muscle, known as intramyocellular lipids, and insulin-resistant or insulin-sensitive states. The amount of intramyocellular lipid has been associated with both states (known as the athlete's paradox).

David B. Savage, Alison Sleigh and researchers from the U.K. and Switzerland write in the Journal of Lipid Research that they used magnetic resonance spectroscopy to compare the fatty acid composition in calf muscles of insulin-resistant lipodystorphic women with age- and gender-matched healthy controls and athletes. They hypothesized that differences in composition of the intramyocellular lipid pool might explain the athlete's paradox. They found that the intramyocellular lipid pool was more saturated in the lipodystrophic women compared with controls and athletes. Measures of the accumulation of saturated intramyocellular lipid were more strongly associated with measures of insulin sensitivity than the total amount of intramyocellular lipid.

A strong correlation in athletes and healthy controls between maximum oxygen used during exercise and relatively unsaturated intramyocellular pools suggests exercise and diet can help decrease the amount of saturated fat within muscles associated with insulin resistance. DOI: 10.1194/jlr.M091942

Potential drug target for Parkinson's

Research suggests that chemicals in the brain similar to the neurotoxin MPTP may induce or enhance the progression of Parkinson's disease. In 2013, a team of researchers from Vanderbilt University and the University of Pennsylvania found that the enzyme cytochrome P450 2D6, or CYP2D6, in the mitochondria metabolizes MPTP into a toxic form. The same team recently used dopamine neuron-mimicking cells and mice with the Cyp2d6 gene knocked out to show that the conversion of MPTP-mimicking chemicals produced in the brain by CYP2D6 induces neuronal degeneration. The results, published in the **Journal of Biological Chemistry**, suggest that CYP2D6 may be a promising target for treating Parkinson's disease. *DOI: 10.1074/jbc.RA119.008848*

How smoking triggers changes in Reinke's edema

Among the negative effects of smoking is Reinke's edema, or RE, where swelling of the vocal cords causes breathing and voice problems. Treatment involves surgical stripping of vocal cord layers in a section called the lamina propia, which often results in permanent damage. In the search for better treatment options, vocal fold fibroblasts, or VFFs, the main cellular component of the lamina propia, have become a focus of RE research. To better understand the effect of smoking on these cells, Markus Gugatschka and his colleagues at the Medical University of Graz exposed VFFs to cigarette smoke and monitored the subsequent protein changes.

In a paper published in the journal **Molecular & Cellular Proteomics**, the researchers write that they found increased levels of the inflammation-promoting polysaccharide hyaluronan and antioxidative stress proteins as well as lower levels of the

One step closer to fertilizer-free farming

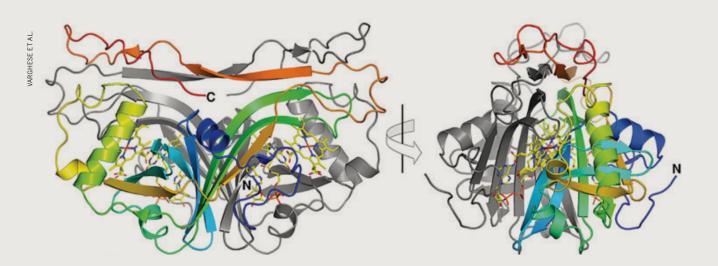
Farmers apply fertilizer to deliver ammonia and other essential nutrients to crops, but excess ammonia can wash away into fresh water, a hazard for wildlife and humans. To reduce agriculture's dependence on fertilizer, scientists seek to enhance the ability of plants to provide for themselves through nitrogen fixation, a process that converts nitrogen from the air into ammonia. One method is getting aerobic plants to express nitrogen-fixing enzymes, but oxygen deactivates these enzymes, known as nitrogenases. In a study in the **Journal of Biological Chemistry**, researchers in the U.K. biochemically and structurally characterized a protein that might protect nitrogenases from oxygen inactivation.

In nitrogen-fixing microorganisms, three types of nitrogenases have been identified; each relies on a different metal to function. The iron-only nitrogenase is the least understood of the three, but scientists view it as a promising candidate for expression in plants, as this enzyme requires fewer genes than the more common molybdenum nitrogenase. Other researchers previously had found that the purple bacterium Rhodobacter capsulatus requires expression of the protein Anf3 for its iron-only nitrogenase to work, but researchers didn't know why. To solve this mystery, Febin Varghese and colleagues at Imperial College London examined the structure and function of Anf3 in the model nitrogen-fixing bacterium Azotobacter vinelandii.

Using X-ray crystallography to view Anf3's structure at an atomic resolution, the team saw that it was similar to a family of oxygen-reducing enzymes. Electrochemical experiments showed that Anf3 converts oxygen to water, confirming its oxygen-reducing activity. These results indicate that Anf3 may protect iron-only nitrogenase from deactivation by consuming oxygen, which could be why the protein is needed for nitrogen fixation in R. capsulatus. The findings also might mean that Anf3 could do the same in aerobic plants, bringing nitrogen-fixing crops closer to reality.

DOI: 10.1074/jbc.RA118.007285

—Jonathan Griffin



In these orthogonal views of the dimeric, two-chain structure of Anf3, the A chain is shown in multiple colors, and the B chain is shown in gray.

rigid structural protein collagen. The researchers hypothesize that the loss of collagen, increase of hyaluronan and increased VFF cell death from oxidative stress could combine to facilitate the formation of edema, thus leading to RE. Future research to evaluate this hypothesis could provide potential targets for treatments to combat RE. *DOI: 10.1074/mcp.RA119.001272*

A hormonal link between diet and obesity

Previous studies in mice have implicated the hormone adropin in metabolic homeostasis, but its role in the metabolism of humans is unknown. To gain a better understanding of adropin activity, Andrew Butler and colleagues at multiple institutions in the U.S. used the transcriptome atlas of a nonhuman primate to profile the expression of the adropin-encoding gene ENHO. A second nonhuman primate model of high-sugar diet indicated that low circulating adropin is predictive of increased weight gain and prediabetes. The authors suggest that the data, published in the Journal of Biological Chemistry, warrant the investigation of adropin administration to promote metabolic health. DOI: 10.1074/jbc.RA119.007528

Brain over binge: Unlocking metabolic obesity-related gender disparities

Diet-induced obesity is a global problem. Hypothalamic regulation, responsible for metabolic processes, and its relationship to obesity have become a promising avenue for research. The endocannabinoid system, found in the hypothalamus, also plays a role in metabolic functions, working like locks and keys, where cannabinoid receptors are the locks and the endocannabinoid proteins behave as keys, creating a positive feedback loop regulating energy homeostasis.

In a paper in the Journal of Lipid Research, Cristina Miralpeix and a team of researchers in Spain write that they have found a link between specific endocannabinoids and diet-induced obesity in mice while noting disparities between genders. Groups of male and female mice were put on a high-fat diet and observed over time. Endocannabinoid levels of all the mice increased four to six times as compared with initial levels after short-term changes in diet. The increase of transient endocannabinoids affected metabolic functions such as body heat and weight gain. Furthermore, female mice became obese later than males, and their hypothalamic endocannabinoids showed higher levels, suggesting not only differences between sexes but also an inverse relationship between weight and endocannabinoid levels. The results also showed a striking rise in endocannabinoids after a short-term high-fat diet in all the mice that leveled off when a high-fat diet was maintained long-term.

This study could add insight into the relationship between hypothalamic regulation and obesity, and the results support claims of differences in male and female metabolic tendencies.

DOI: 10.1194/jlr.M092742

How disease and diet influence transcription

The Mediator complex is a multiprotein assembly and transcriptional coactivator that connects transcription factors to RNA polymerase II. Past research suggested that the Mediator complex can come in two sizes, but it has not been clear what determines the form of the assembly. Dou Yeon Youn and researchers from Albert Einstein College of Medicine and Rutgers Robert Wood Johnson Medical School found that the large complex exists in the livers of fasted mice and that, after feeding, nutrient activation of the mTORC1 pathway converts the complex into a smaller form. They also found that insulin-resistant mice in the fasted state exhibited increased expression of the small Mediator complex. Taken together, these findings, published in the Journal of Biological Chemistry, demonstrate the dynamic regulation of the Mediator complex under physiological and pathophysiological conditions.

DOI: 10.1074/jbc.RA119.007850

Boosting NAD+, an essential and versatile coenzyme

Recent work has indicated that increased concentrations of the coenzyme nicotinamide adenine dinucleotide, or NAD+, may provide an assortment of health benefits, including protection from liver disease and neurodegeneration. As such, there has been a surge of interest in agents that can raise NAD+ concentrations. Several NAD+ precursors have been identified, but high doses are required to obtain health benefits in animal models.

Yue Yang and colleagues at Weill Cornell Medical College investigated the ability of dihydronicotinamide riboside, or NRH, a likely NAD+ precursor, to enhance NAD+ concentrations. The researchers report in the **Journal of Biological Chemistry** that, compared with two wellstudied NAD+ precursors, NRH was more effective at raising NAD+ concentration in mammalian cells and in mice. *DOI: 10.1074/jbc.RA118.005772*

The role of LOXL2 in prostate cancer

An early step in the development of prostate cancer involves alteration of tissue-building cells called fibroblasts. Normal (healthy) prostate fibroblasts, or NPFs, respond to signals in the tumor to become cancer-associated fibroblasts, or CAFs. These CAFs produce proteins that stimulate production of the extracellular matrix, or ECM, which provides structural support and aids tumor growth. Despite the known importance of CAFs in prostate cancer, CAF– ECM interactions remain poorly understood. To understand these interactions better, Elizabeth V. Nguyen, Brooke A. Pereira and colleagues in Australia sought to characterize the protein differences between prostate CAFs and NPFs.

In their recent work, published in the journal **Molecular & Cellular Proteomics**, the researchers isolated CAFs and NPFs from four patients with prostate cancer and compared their respective protein profiles. They found that CAFs produced more proteins responsible for cell adhesion, specifically through affecting collagen (a major



structural element of the ECM). One of these proteins, LOXL2, has previously been shown to be more prevalent in prostate cancer, and the authors showed that this higher prevalence was associated with poorer prognosis. Further study on LOXL2 showed that this protein's overproduction by CAFs not only led to a more structured and robust ECM but also aided in the growth and enhanced the health of prostate tumor cells.

This is the first time scientists have shown directly that LOXL2 inhibition can perturb prostate tumor development. Previous research has shown that LOXL2 is amenable to therapeutic targeting, and drugs targeting LOXL2 already are being evaluated for use against breast and pancreatic cancer. LOXL2 shows significant promise as a target for more oncology therapies, and these researchers' work supports this approach.

DOI: 10.1074/mcp.RA119.001496

— Kian Kamgar–Parsi

Cancer-associated fibroblasts can alter cellular organization in prostate cancer (right) versus healthy tissue (left).

A model for the proteomics of plant defense

Just as animal bodies repair themselves after injuries, so too do plants. Previous research has identified the protein systemin as a key driver for plant defense and wound healing. Systemin exerts its effects by binding to receptors on plant cell membranes and signaling for initiation of a defensive response, but the specifics of this process are poorly understood. A new study by Fatima Haj Ahmad and colleagues at the University of Hohenheim, published in the journal **Molecular & Cellular Proteomics**, helps elucidate systemin's downstream effects.

Ahmad and her team treated tomato cells with systemin or an inactive systemin mutant and compared how the prevalence of phosphate groups in various proteins changed with time. By tracking these changes, the researchers identified over 50 kinases (phosphate adders) and phosphatases (phosphate removers) specifically affected by systemin signaling. This enabled them to create the most advanced model to date for the downstream effects of systemin and the defensive response in plants. This research provides a baseline for further elucidation of the systemin pathway and could provide crucial insights for botanists and farmers to help ensure plant health and defenses against damage and disease. DOI: 10.1074/mcp.RA119.001367

Connecting cholesterol regulation and Alzheimer's disease

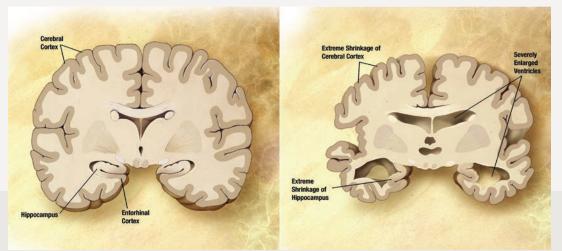
Alzheimer's disease, affecting more than 40 million people worldwide, destroys mental cognition as well as memory. Recent insight into maintenance of cholesterol homeostasis appears to offer answers to many of the questions posed by Alzheimer's. About 30% of a person's cholesterol is stored in the brain; when properly regulated, it plays an important role in neural activity through synaptogenesis and maintenance of plasticity and brain function. Not surprisingly, disruption of cholesterol homeostasis has been linked to neurodegenerative diseases such as Alzheimer's.

Cinzia Marchi at the University of Parma and colleagues in Italy investigated the link between dysfunctional chemical cues from the cerebrospinal fluid to neural synapsing and Alzheimer's disease. Their research was published in the **Journal of Lipid Research**. The team explored how the ability of cholesterol to be released from cells, known as cholesterol efflux, in cerebral spinal fluid was reduced in Alzheimer's disease. Cholesterol efflux levels of Alzheimer's patients were compared with healthy controls and people with dementia not caused by Alzheimer's disease. The team studied the ABCA1 and ABCG1 genes, which are responsible for cholesterol traffic from the cerebrospinal fluid and known to be risk factors for Alzheimer's when mutated.

To detect functioning of these genes, the researchers studied three biomarkers. In patients with Alzheimer's, significantly less of each biomarker was produced during efflux. However, these markers were not compromised in subjects with dementia unrelated to Alzheimer's. Furthermore, when apolipoprotein E, a known risk factor of Alzheimer's, and apolipoprotein A-1 levels were studied, the former was lower in non-Alzheimer's dementia, while the latter was comparable for all groups.

This investigation shows that the capacity to promote cell cholesterol efflux by ABCA1 and ABCG1 genes from cerebrospinal fluid is impaired in Alzheimer's. These findings could lead to development of new lipoprotein-based pharmaceuticals for treatment of the disease. *DOI: 10.1194/jlr.P091033*

—Tori Zirul



This illustration shows a cross section of a healthy brain, at left, and a brain affected by Alzheimer's disease, at right.

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For September: Manganese seldom travels alone

(BIO)CHEMICAL ELEMENTS

By Quira Zeidan

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YEAR

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www.e mark the 150th anniversary of Dimitri Mendeleev's periodic table of chemical elements this year by highlighting elements with fundamental roles in biochemistry and molecular biology. So far, we've covered hydrogen, iron, sodium, potassium, chlorine, copper, calcium, phosphorus, carbon, nitrogen and oxygen.

For September, we describe manganese, a transition metal with chemical symbol Mn and atomic number 25. Manganese is highly reactive, and it almost never is found as a free element in nature. Rather, it combines with other elements via its multiple oxidation states, which range from +7 to -3. It frequently is found in silicate, carbonate and oxide minerals, and in alloys — compounds containing metals — with iron. People used manganese-containing pigments that are naturally abundant in cave paintings dating back to the Stone Age.

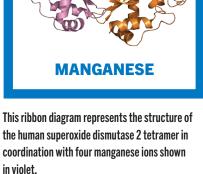
Nuclear reactions that occur in giant stars immediately before supernova explosions produce manganese. It has a short half-life of about 3.7 million years and decays into one of the four chromium isotopes — element variants with different numbers of neutrons. At 0.1%, manganese is the 12th most abundant element on the Earth's crust. A significant amount of manganese is present on the ocean floor in the form of manganese nodules — specific marine deposits composed by manganese hydroxide and iron.

In living systems, manganese chemistry is restricted to Mn⁺² and

Mn⁺³ ions that combine with biological molecules in the aqueous environment of the cell. Mn⁺² often overlaps and competes with magnesium and calcium ions as a structural component that stabilizes the net charge of molecules such as proteins and adenosine triphosphate. As a redox cofactor for a large variety of enzymes, manganese is at the catalytic center for cellular reactions that participate in aerobic metabolism.

Manganese is vital to microbial survival. Protein transporters in bacteria break down high-energy chemical bonds in adenosine triphosphate to drive the influx of manganese into the cell from the extracellular environment. Bacterial species of the normal flora of the human digestive and reproductive systems require manganese for survival and growth. The Lyme disease pathogen Borrelia burgdorferi can incorporate manganese in all of its metalloproteins, bypassing host defense by eliminating the need for iron. The diphtheria toxin secreted by the pathogen Corynebacterium contains manganese in its structure. Some bacteria use nonenzymatic Mn+2 ion complexes - generally in combination with polyphosphate ---- to scavenge reactive oxygen species that are byproducts of cellular metabolic reactions.

In yeast and other eukaryotes, the natural resistance-associated macrophage protein, or NRAMP, family of metal transporters uptake manganese using the driving force of proton gradients. Once inside cells, manganese



Plutonium

serves as a cofactor for a multitude of enzymes that include oxidoreductases, carbohydrate-binding proteins such as lectins, and extracellular matrix receptors such as integrins.

Superoxide dismutase, an important manganese-containing enzyme present in mitochondria — and in most bacteria — partitions harmful reactive superoxide ions into molecular oxygen or hydrogen peroxide, protecting cells from the toxicity associated with aerobic respiration. In plants and cyanobacteria, manganese is an essential component of the enzyme responsible for the terminal oxidation of water during the light reactions of photosynthesis.

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Oxygen



With the rollout of drugs that cost \$300,000 a year, what is the future of treating Duchenne muscular dystrophy?

By John Arnst

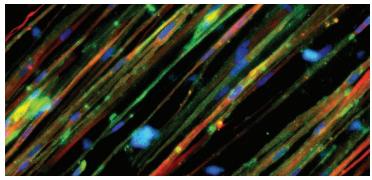
BELOW:

Dystrophin function (green) can be restored in DMD muscle cells derived from human induced pluripotent stem cells. Colin Rensch fell in love with the piano when he was 11 years old. Seven years later, he got the chance to take a piano lesson from jazz legend Herbie Hancock, thanks to the Make-A-Wish Foundation.

Rensch was a percussionist in concert band at his high school in Mattawan, Michigan and then studied music history at Hope College in Holland, Michigan. Now 25 years old, he is finishing a master's degree in history at Western Michigan University and applying to Ph.D. programs for musicology.

He also has Duchenne muscular dystrophy, the most common form of childhood-onset muscular dystrophy. When he was in high school, he began to lose strength in his arms and channeled his passion for music first into composing and then into studying the history of music.

"Knowing what I can and cannot do, that doesn't really faze me very much. But it's been a learning curve," said Rensch, who has a number of assistants, sometimes up to 10, who help him throughout the day. "I first started with my assistants when I was in college, (and) I've learned a lot since then. I



COURTNEY YOUNG, MELISSA SPENCER LAB, UNIVERSITY OF CALIFORNIA, LOS ANGELES

would say that coordinating with other people helping me is the most important thing."

Duchenne, or DMD, is one of nine forms of muscular dystrophy, inherited diseases in which muscle tissue wastes away. DMD almost exclusively affects babies assigned male at birth, at an incidence of 1 in 3,500. Among muscular dystrophies, it is the most severe. Despite advances in cardiac and respiratory care that have allowed people with DMD to survive into adulthood, nearly all succumb to heart failure by their mid-30s.

DMD was first observed in the mid-19th century but was untreatable until corticosteroids were developed in the 1950s. For decades, steroids were the primary treatment for patients with DMD, along with drugs for secondary conditions that affect patients' thyroid glands and lungs. That changed in 2016 with the rollout of Sarepta Therapeutics' Exondys 51, the brand name for eteplirsen, a drug that restores limited expression of the dystrophin protein by patching, or skipping, over the coding region of DNA called exon 51, which is missing in 13% of Duchenne patients. The drug, approved by the Food and Drug Administration in 2016, is estimated to cost \$300,000 per year.

But exon skipping is just one path forward for treating the disease. Each of the pharmaceutical companies Solid Biosciences, Pfizer and Sarepta has a drug candidate in clinical trials that delivers microdystrophin, a pared-down version of the massive gene that codes for dystrophin, to the muscles of people with DMD, where it is translated to make a mostly functional version of the dystrophin protein.

At the same time, studies in a handful of labs have shown promise in using the gene-editing machinery CRISPR–Cas9 to correct DMD-causing mutations in increasingly complex animal models. If researchers can find ways to subvert the human immune system's response to the viral vectors that deliver CRISPR–Cas9 and can produce enough of those vectors to meet the needs of patients with DMD and other monogenetic disorders, they may be able to restore functioning fibers to the muscles and hearts of more than 300,000 people worldwide.

Faulty fibers

Situated beneath the cell membranes of striated muscle fiber cells, dystrophin proteins support muscle strength. In their absence, the muscle fibers' actin and myosin contract and expand normally but the fibers are damaged more easily by routine activity.

Before children with DMD begin walking, their muscles generally don't undergo enough strain to show wear. This means diagnoses are usually made when a child is 2



Colin Rensch joined the board of the Patient Project Muscular Dystrophy in 2018. He is the first member of the board who has Duchenne muscular dystrophy.



In addition to investigating Duchenne muscular dystrophy, Jeff Chamberlain's laboratory at the University of Washington examines the molecular basis of limb-girdle muscular dystrophy type 21.

to 3 years old. Rensch said he was diagnosed when he was about 3.

During early childhood, however, the muscular stem cells that repair muscle by creating new tissue are extremely active and can compensate for and mask the damage being done, delaying a diagnosis until a child is age 7 or older.

Jeff Chamberlain is a neurologist at the University of Washington with expertise in muscular dystrophies.

"Early on in life, the boys do pretty well because there's all this ongoing muscle cell damage, but then it's repaired," Chamberlain said. "The problems start occurring around age 4 or 5. Patients start losing muscle mass, and what's thought to be happening is that this repair process just cannot keep up any longer."

As the repair process fails, macrophages that produce cytokines infiltrate inflamed muscle cells. This causes both the formation of excess fibrous tissue and the emergence of fat cells within the muscle tissue.

"There's a sort of competition between fibrotic cells and fat cells versus the actual "The problems start occurring around age 4 or 5. Patients start losing muscle mass, and what's thought to be happening is that this repair process just cannot keep up any longer."

-Jeff Chamberlain

FEATURE



UT SOUTHWESTERN



In addition to applying CRISPR–Cas9 to correct mutations for Duchenne muscular dystrophy, currently in animal models, Eric Olson's lab investigates potential regenerative approaches for cardiac and skeletal muscle and the role of epigenetics in regulating muscle development.

The dystrophin gene is on the X chromosome — if someone has two copies, the body generally can compensate for the faulty gene with a functional one.

muscle stem cells, and, so, eventually the muscle regeneration starts losing out with these other processes," Chamberlain said. "And the net result is over time patients lose muscle mass, and it's replaced by connective tissue and fat cells."

The loss of muscle mass is progressive. "I probably was ambulatory or ... semiambulatory until I was about 13," Rensch said. At that time, he started using a mobility scooter full time. He supplemented this with an elevating wheelchair when he started high school.

As the disorder progresses, patients also lose cardiomyocytes, a special subset of muscle cells that make up the heart.

DMD almost exclusively affects people with one copy of an X chromosome (see box: Different dystrophies). The dystrophin gene is on the X chromosome — if someone has two copies, the body generally can compensate for the faulty gene with a functional one. Given the location of the causative gene, DMD most often is inherited from mothers who have one affected chromosome. According to Eric Olson, a molecular biologist at the University of Texas Southwestern Medical Center who specializes in heart and muscle development, the unusually large size of the Duchenne gene makes routine prenatal screening largely impractical.

"It's not easy," Olson said. "If one does not know if there's a mutation or where it might reside in this massive gene, it's not trivial to screen for it."

About one-third of cases develop spontaneously during gestation and are therefore unlikely to be caught by prenatal screening: If neither parent is a known carrier, they wouldn't expect the disorder to develop during pregnancy.

It is, however, possible to screen for the disorder in newborns by measuring circulating levels of creatine kinase, a byproduct of muscular inflammation. "If it's elevated tenfold, that's diagnostic or highly indicative of Duchenne," said Olson.

To help identify the disorder as early as possible, the Muscular Dystrophy Association has urged the Department of Health and Human Services to add a screen for DMD to the Recommended Uniform Screening Panel, a list that most states adopt for their universal newborn screening programs.

Skipping gaps

The Duchenne gene is made up of 79 exons. These are spliced together when noncoding introns are removed from pre-mRNA to make mature mRNA, which is translated to create the amino acids that make up the dystrophin protein. Which of the exons or interspersed introns are missing varies from patient to patient.

Some exons, such as exon 74, can be deleted without affecting the reading frame of adjacent exons. In the absence of exon 74, translation of exons 73 and 75 proceed uninterrupted, giving rise to a shorter but mostly functional dystrophin protein.

This is the case with Becker muscular dystrophy, a less severe disorder related to DMD

DIFFERENT DYSTROPHIES

Duchenne muscular dystrophy primarily affects people with one X chromosome but occurs in people with two X chromosomes, most assigned at birth as girls, at an incidence of 1 in 50 million. When someone has two X chromosomes, only one is turned on at a time in a cell, and this activity can vary throughout the body. Depending on where the mutated genes are expressed, a person with one copy of a Duchenne allele, or a manifesting carrier, might experience mild symptoms of muscular dystrophy. These symptoms can be similar to Becker muscular dystrophy, which also primarily affects boys, and manifests when mutations to the dystrophin gene produce truncated, but functional, dystrophin proteins. However, most of the other seven major forms of muscular dystrophy listed below more equally affect men, women and nonbinary people.

Muscular dystrophy	Symptoms	Incidence	Typical age at onset
Myotonic	Myotonia, prolonged spasms or stiffness, in muscles after use.	8 in 100,000	Late childhood to middle age
Facioscapulohumeral	Weakness in the muscles that move the face, upper arm bone and shoulder blade. Can also affect speaking, walking, chewing and swallowing.	4 in 100,000	Young adulthood
Limb-Girdle	Weakness in the hips that moves to shoulders, arms and legs, with eventual loss of mobility.	2 in 100,000	Childhood to middle age, depending on type
Congenital	General muscle weakness.	1 in 100,000	Birth
Distal	Weakness in lower legs and arms, including hands, that may spread and progress to atrophy.	< 1 in 100,000	Middle to old age
Emery-Dreifuss	Weakness in muscles of shoulders, upper arms and calves, in addition to joint stiff- ness and heart	< 1 in 100,000	Childhood
Oculopharyngeal	Weakening of throat muscles, which pro- gresses to interfere with swallowing. Also weakens eyelid muscles.	< 1 in 100,000	Middle to old age

that occurs in about one in 18,000 births. The body of a person with BMD produces dystrophin proteins with reduced functionality, and they may retain enough muscle mass to continue walking into their 40s and 50s.

In DMD, however, deletion of an exon disrupts the reading frame of mature mRNA, prematurely terminating translation and creating a completely nonfunctional dystrophin protein. This is what happens with exon 51, which Exondys 51 encourages transcriptional machinery to skip during pre-mRNA spicing by using DNA fragments known as antisense oligonucleotides. The result is a restored reading frame and a mostly functional dystrophin protein. Whether a mutation on the dystrophin gene will give rise to DMD or BMD depends on which exons are affected by the mutation. However, sometimes mutations can present somewhere in the middle — as happened with Benjamin Dupree.

Dupree was 9 years old when doctors finally were able to explain that he had a hard time keeping up with other kids on the playground because he had a mild form of DMD; within six years, the condition progressed so that he was no longer able to walk on his own.

Rather than missing an exon, Dupree's dystrophin gene codes for the insertion of an extra intron. That intron, 47, codes for a stop codon, which ends translation of the





Benjamin Dupree, who is a patient advocate for Parent Project Muscular Dystrophy, was a percussionist when he was in band in high school.

dystrophin protein prematurely. According to Dupree, a small portion of his dystrophin proteins remain functional, meaning his symptoms present in a middle ground between DMD and BMD.

Normally, "it becomes hard to lift your arms around age 20 or so," said Dupree who is now 26. "That's been a little bit less severe for me. I still am able to put my arms above my head and lift a decent amount of weight."

Dupree has a bachelor's degree in biochemistry from Southern Methodist University, and volunteers for Texas Scottish Rite Hospital for Children. He is preparing for a graduate program in social work, after which he hopes to help guide other young people with DMD through the challenges he's faced. Since 2012, he has been a patient advocate for the advocacy group Parent Project Muscular Dystrophy, for which he first traveled to Washington, D.C., in 2014. He also has served on the FDA's advisory committee for Exondys 51, though it is not a treatment option for his form of the disease.

"I try to look at it from the position of 'If this drug was something that was applicable to every exon, in every case, how would I feel about that? What would my perspective be if this drug would work for me?" he said. Clinical trial data suggest that Exondys 51 works as intended, and at least half of the mutations that give rise to DMD could be amenable to exon skipping. Sarepta and other pharmaceutical companies have additional exon-skipping drugs in preclinical and clinical development for many of the missing exons that a faulty DMD gene may lack.

"I think that if there are enough (FDA approvals) for different exons or different drugs, it would build evidence for the approval of a mechanism rather than just individual drugs," Dupree said. "I think that's where they could eventually lead to something that would help me."

However, despite the FDA's approval of Exondys 51 in 2016 and recent clinical evidence that Exondys 51 slows patients' respiratory decline, a recent report published by the Institute for Clinical and Economic Review claimed that Sarepta had not collected sufficient evidence that the drug benefits patients.

These concerns played out in August when the FDA denied approval of Sarepta's second exon-skipping drug, Vyondys 53, designed for the exon 53 deletion that causes 8% of DMD cases.

All exon-skipping drugs must be administered continuously, which compounds their high price tag.

But re-administration may not be necessary if adeno-associated viral vectors, or AAVs, are used to smuggle smaller versions of an otherwise massive gene into patients' muscles.

Microdystrophin delivery

At 2.3 megabases, the dystrophin gene is the largest in the human genome; the median size of a human gene is 26 kilobases. The most commonly used vectors for gene therapies, AAVs have a capacity for carrying genetic material just shy of 5 kB, which can be upped to 9 kB by using dual-vector systems.

Overall size isn't a direct proxy for the size of a resultant protein or even the size of the mature mRNA generated once introns have been excised. For example, the gene that codes

All exon-skipping drugs must be administered continuously, which compounds their high price tag. for the largest human protein, the muscle spring protein titin, contains 365 exons but is only around 0.3 mB long. In the case of dystophin, massive introns make up more than 99% of the gene.

The relatively small size of the dystrophin gene's exons made it possible for Jeff Chamberlain and his colleagues at the University of Washington to develop microdystrophin, a compact version of the dystrophin gene around 4 kb long that codes for a smaller yet still functional version of the dystrophin protein. A similar, slightly larger iteration called minidystrophin subsequently was developed by a separate research group and is being evaluated in clinical trials conducted by Pfizer.

The AAV-based system delivers a copy of the microdystrophin gene flanked with promoter and enhancer sequences, which, respectively, help initiate transcription of a stretch of DNA and increase its odds of being transcribed. The promoter and enhancer sequences, which are specific to muscle cells, were developed by Chamberlain and his colleague Steve Hauschka.

"If you delivered the same proteins with a ubiquitous promoter that was active in many cells in the body, you could often get a very potent and sometimes lethal immune response," Chamberlain said. "So we've focused a little more on trying to restrict gene expression to muscle."

The muscle-specific promoters turned out to be a boon for drug development. The microdystrophin drugs developed by Pfizer, Sarepta and Solid Bioscience and now in early clinical trials all use muscle-specific enhancers developed by Chamberlain and Hauschka.

Dupree, whose symptoms fall between BMD and DMD and whose muscles contain truncated dystrophin proteins due to an intron insertion, said he is optimistic about the prospect of drugs that can induce the production of microdystrophin. Unlike exon-skipping therapies, a single microdystrophin drug would work for people with different



Luk Vandenberghe's lab produces a panoply of adenoassociated viral vectors, some of which his colleagues use in murine stem cells.

DMD-causing mutations.

"I think the microdystrophin is a really great option for us," he said. "I don't think that it's going to ever really be a complete solution. But I think it will be an improvement on what's currently here that'll hold people over until we have a more permanent or effective solution."

Despite the increase of expression in skeletal muscle, though, microdystrophin therapies still run into an obstacle many drugs face in the body — the liver.

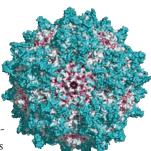
According to Luk Vandenberghe, a professor at Harvard's Grousbeck Gene Therapy Center specializing in AAV production, most AAVs that enter the body ultimately wind up in the liver rather than in the organ or tissue for which their genetic payload is intended.

"We believe that more than 90% of that dose ultimately gets trapped by the liver, which is a tissue that we don't need to target," Vandenberghe said.

Small virus, giant reactors

This problem of viral misdirection extends to treatments that might use CRISPR–Cas9, as that system also is delivered in AAVs.

CRISPR, which stands for clustered regularly interspersed short palindromic repeats,



ERIC ZINN/HARVARD UNIVERSITY

Adeno-associated viruses, which do not cause disease in humans, have no relation to the cold-causing adenoviruses. Their name comes from their discovery as a contaminant in preparations of adenovirus in the 1960s. first evolved as a bacterial defense mechanism that allows microorganisms to fight off hostile viruses by storing their genetic information alongside a set of enzymes known as CRISPR-associated proteins, or Cas, that are highly effective at snipping DNA. By turning the stored viral DNA into guide RNAs that complex with Cas, the bacteria cells can target and destroy a matching virus' DNA before it can replicate (see Sickled cells and CRISPR controversies on page 37).

Currently, there are no methods for removing genome-editing tools from the body once they've been introduced, a concern of Vandenberghe's.

"One needs to have a short-term intervention ... and then these genome-editing tools ideally need to leave the scene, because if they linger around for too long, they could have their own set of problems," such as off-target effects, Vandenberghe said.

Even if early clinical trials don't raise safety concerns, difficulty with large-scale production of AAVs remains a major obstacle.

"It's just hard to make," Vandenberghe said. "People are looking at generating 100,000-, 200,000-liter bioreactors, as large as you can think to get to the amount of virus needed."

By his estimates and those of his colleagues, the amount of AAVs needed to deliver a single dose of CRISPR–Cas9 into someone with DMD would cost hundreds of thousands of dollars.

To produce the many subtypes of AAVs used in basic and preclinical research involving CRISPR, manufacturers reprogram cells, such as the mammalian cell line HEK293 or the insect cell line Sf9, to act as small viral factories. Whatever the cell line, each cell can produce about 100,000 viral particles. By Vandenberghe's account, a single dose of AAVs is about 100 trillion viral particles for each kilogram the patient weighs. After factoring in weight, that comes to at least 10 orders of magnitude more than what a single cell can produce. "If you have to treat the global population of DMD patients or even just the population in the Western world, we are talking in scales that the industry hasn't seen," he said. "So we need innovation there. And that innovation is only slowly coming forward."

An early diagnosis of DMD could lower the cost of a CRISPR-based therapy significantly, because a smaller patient — an infant versus a child — would require a smaller dose. According to Olson at UT Southwestern, an infant also would be less likely to have prior exposure to AAVs; once an individual's immune system has encountered the common viruses, it will clear them out on subsequent encounters.

"There are efforts under way to have different (AAV) serotypes, so that maybe you've been exposed to one and you could come back a second time with an alternative serotype that would not have a preexisting immunity," he said. "There may be ways to combine that with immunosuppression or other approaches."

Mending fibers

Over the past five years, Olson's lab in Dallas has used CRISPR–Cas9 to repair the mutations underlying DMD in mice and in canines, which are a better proxy for the human form of the disease than mice.

At the same time, Charles A. Gersbach and colleagues at Duke University have been using a CRISPR–Cas9 system to edit the dystrophin gene in mouse models. In a paper published in 2016 in the journal Science, the researchers repaired a gene with induced DMD mutations, turning it to a variant that resembled BMD. Gersbach's paper appeared as one of a trio of articles in Science by teams at Duke, at Harvard University (led by the cell biologist Amy Wagers), and at UT Southwestern Medical Center (led by Olson) that described treating DMD in mice with CRISPR–Cas9.

Olson's papers on correcting DMD mutations in mice caught the eye of Debra Mill-

An early diagnosis of DMD could lower the cost of a CRISPRbased therapy significantly, because a smaller patient — an infant versus a child would require a smaller dose.

SICKLED CELLS AND CRISPR CONTROVERSIES

CRISPR–Cas9, which first was demonstrated as a potential gene-editing technique by Jennifer Doudna and Emmanuelle Charpentier in 2012, can be used to edit the genome in two distinct ways.

In somatic genome editing, researchers edit defective genes in an organism's affected tissues or in excised cells that are then reinserted. In germline editing, researchers aim to edit genes in embryos to prevent mutations from manifesting. Changes made during germline editing, including any potential errors introduced in the editing process, can be passed down to each successive generation.

In early 2017, the National Academy of Sciences and the National Academy of Medicine rolled out guidelines for how genome editing should proceed in humans. The academies essentially said researchers should proceed with extreme caution when editing the germline but could venture forth with somatic editing for diseases with well-understood monogenic causes.

"For something like sickle cell disease or Duchenne's muscular dystrophy, these are diseases where there's a single gene that is known to be mutated in patients that have the disorder," Doudna said. "And the genetics of that are well worked out. So we understand that by making a change to that causative gene, one could actually mitigate the disease."

Last November, Chinese scientist He Jiankui reported using CRISPR– Cas9 to remove from embryos the receptors to which HIV binds. His announcement at the Second International Summit on Human Genome Editing caused an international uproar.

In response to He's actions and a Russian scientist's recent declaration

of intent to use CRISPR on viable embryos, the NAS, the NAM and the U.K. Royal Society convened another summit on genome editing in August, with a new report and guidelines to come next summer.

Meanwhile, clinicians in the U.S. recently moved ahead with somatic editing for sickle cell disease.

Sickle cell disease is caused by a genetic defect in which blood cells carry insufficient oxygen and stick to the inside of blood vessels. The disease affects millions of people worldwide, almost all of African descent. It causes debilitating pain and reduces lifespans; many patients die in their 40s. There are few treatment options beyond bone marrow transplants.

In July, doctors at HCA Healthcare's TriStar Centennial Medical Center in Nashville administered to a patient with sickle cell disease bone marrow cells that had been edited to correct the defect that gives rise to faulty red blood cells. The clinical trial, conducted by the Boston-area companies Vertex Pharmaceuticals and CRISPR Therapeutics, will enroll



At the University of Michigan, Melissa Creary studies the social, cultural, ethical, political and historic tensions of sickle cell disease in both the United States and Brazil.



In 2012, Jennifer Doudna demonstrated with Emmanuelle Charpentier that CRISPR–Cas9 could be used as a gene-editing platform. Among her many current projects, she is working on understanding the biology of CRISPR systems in natural environments such as water and soil.

up to 45 patients between the ages of 18 and 35.

Melissa Creary, a professor at the University of Michigan specializing in the societal history and impact of sickle cell disease in Brazil and the U.S., is cautiously optimistic about the development.

"I think that, generally, CRISPR sounds like an exciting new technology. But our excitement about new technology should be tempered," Creary said.

"Who can afford it? How will people get access to it? What happens afterwards? What kind of support networks are in place? What are the unintended consequences? And how will people be supported around those unintended consequences if you're marginalized, much less if you're not? All of those questions, I think, need to be put in place much ahead of full implementation, while we're thinking about the feasibility of the tech."



THE ROLE OF CUREDUCHENNE

Over the past 16 years, CureDuchenne has provided seed funding to small biotech companies, helping secure more than \$1.3 billion from larger pharmaceutical companies and venture capital firms; nine of its funded projects, including antifibrotic agents, exon skippers and gene-correcting agents, have gone on to clinical trials. CureDuchenne provided early funding for the research that led to Exondys 51 as well as Pfizer's drug candidate using a minidystrophin.

Based in Newport Beach, California, CureDuchenne was co-founded in 2003 by Debra and Paul Miller less than a year after the couple found out that their son, Hawken, now 22, had Duchenne muscular dystrophy.

"We looked around, and there were a couple organizations, but they tended to be more support-type organizations and not focused on funding the cure," Debra Miller said. "We never knew (about) venture philanthropy until after we started investing. We did all the due diligence and found out that, yes, legally, we can do this as a nonprofit, as long as we're investing in our mission."

In late 2015, Miller and her board began to take note of news about DMD and CRISPR–Cas9, which led her to Eric Olson at the University of Texas Southwestern Medical Center at Dallas.

Early meetings went well, and Olson and CureDuchenne Ventures founded Exonics Therapeutics. The company launched with \$2 million in seed financing in February 2017 and recently was bought by the biopharmaceutical giant Vertex.

The acquisition, Olson said, "is going to greatly accelerate and enable our advancement of this technology in a way that would have been more challenging within a small startup biotechnology company."

Miller is also optimistic about the impact Vertex will have on the scientific team's research.

"They're a powerhouse," Miller said. "They know how to get drugs developed and approved. And I think if anybody can do this, Vertex will be the one to do it."



Hawken Miller, seated between his parents, Debra and Paul Miller, was diagnosed with Duchenne muscular dystrophy as a child. He recently graduated from the University of Southern California with a degree in journalism and is a multiplatform producer for the Washington Post.

er, CEO of the nonprofit CureDuchenne. Together, Miller and Olson founded Exonics Therapeutics, a biotechnology company with the express goal of using CRISPR–Cas9 technology licensed from Olson's lab to develop a platform for correcting DMD in humans (see box: The role of CureDuchenne).

Olson and his lab now are working out how to correct as many of the 3,000 mutations that can cause DMD as possible with a single CRISPR–Cas9 system.

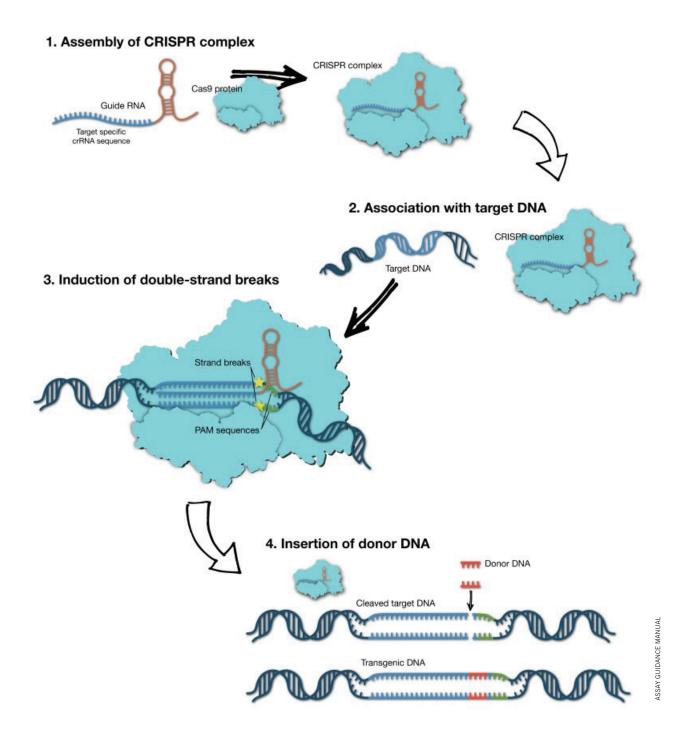
"That's a big challenge when it comes to CRISPR — how can you correct all these different mutations by gene editing?" Olson said. Many mutations that cause DMD cluster in specific regions of the genome and can be targeted en masse. One method that takes advantage of this phenomenon, single-cut CRISPR, was developed by Olson and his colleagues.

"We can make a single cut in the DNA in regions around these hot spots, and that allows for either skipping of an exon that's out of frame and restoring the reading frame or ... we can reframe the protein by insertion of a single nucleotide at the cut site," Olson said.

That process is conceptually similar to exon skipping: In the 6% of DMD patients

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HOW CRISPR WORKS



FEATURE





Amy Wagers' lab examines the mechanisms that regulate the functions of both hematopoietic stem cells and myogenic stem cells.

The treatment that works for each patient ultimately may come down to the mutation.

missing exon 44, exons 43 and 45 become spliced together during translation to mRNA, which creates a premature termination codon that disrupts the reading frame of that mRNA, ending translation of the protein.

By using CRISPR–Cas9 to insert a single missing nucleotide, or delete two, the triplet codons that code for amino acids, like the stop codon, can be reframed properly, restoring translation and function of the protein.

However, the composition of skeletal muscles complicates the repair of dystrophin proteins in muscle cells. While typical cells consist of a nucleus and organelles suspended in cytoplasm and wrapped in a cell wall, muscle cells are made of striated bands of proteins with several nuclei. This allows them to perform their essential flexing and contracting but means they don't divide. Instead, as muscle cells are damaged and die off, they are replaced by new cells, meaning any changes to them won't be permanent.

Enter stem cells.

When muscle cells die, the myogenic stem cells, or satellite cells, that sit beneath the lowest layer of skin are activated to create new muscle cells. By targeting this source of muscle fibers, Amy Wagers and colleagues at the Harvard Stem Cell Institute believe that genome-level repairs to the dystrophin gene could be made permanent and produce the full-length proteins that microdystrophin approximates.

"If you don't also modify the gene in satellite cells, in the sense that these cells seed replacement of the muscle fibers, there's the possibility that, over time, the modified genes that are therapeutic will get diluted in muscle by the fusion into the fibers of new, unmodified satellite cells," Wagers said.

In a paper published in the journal Cell Reports in June, Wagers and colleagues reported that when satellite cells in mice were targeted with a variety of muscle-specific adeno-associated viruses containing a gene that codes for the Cre protein, which is able to activate a simple fluorescent gene-editing reporter system by cutting at Lox sites, the fluorescent protein was expressed in more than 60% of the cells.

"We looked to see whether we were also getting modification in the precursors to muscle fibers in the muscle stem cells," Wagers said. "And we got evidence for that using two different genetic systems, that one could modify the DMD gene in satellite cells."

In addition to the need to validate the safety and efficacy of the CRISPR–Cas9 system, Wagers has concerns about the immune system's tendency to clear adeno-associated viruses from the body after its first encounter with them.

"Can you get enough efficiency with a single dose? Or can you somehow circumvent the immune response so that you can do multiple dosing?" she said. "Those are sort of related challenges."

Repair versus replace

The treatment that works for each patient ultimately may come down to their mutation.

"Every patient has a different mutation," Chamberlain said. "And, importantly, 70% of all patients have deletion mutations or duplication mutations ... they're missing large portions of the genes, which means they're missing large portions of the coding region. So, if you apply gene editing to those patients, you're going to make a minidystrophin or microdystrophin."

For point mutations, in which the reading frame that transcribed mRNA is shifted out of place, a repair might create a highly functional dystrophin that works more effectively than a microdystrophin, Chamberlain said. "But in other cases where there's a larger deletion or duplication, or the deletion removes a critical functional domain of dystrophin, then it's very likely that the microdystrophin would work better than that repaired copy."

According to Wagers, repairing and replacement treatments might end up being complementary.

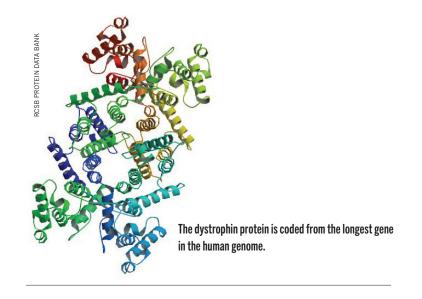
"I have seen people sort of spin this as a little bit as gene therapy versus gene editing ... and that's, I think, a false dichotomy," Wagers said. "The combination could be even more powerful because you have the immediate expression of the microdystrophin, which might stabilize fibers in which editing is going on, in order to ensure a higher rate of editing."

When muscle fibers are dystrophic, only a fraction of the nuclei inside of them can be edited. This carries the possibility that fibers die even though nuclei have been edited, because the gene product — a functional dystrophin — hasn't been expressed to rescue them yet.

"I think there's opportunity for combination type of approaches with gene complementation ... as a strategy for something that will give you both a transient and a long-term benefit," she said.

Multiple deletions, multiple paths

Colin Rensch, the musicology student from Michigan, is among the 50% of DMD patients with multiple deletions; he is missing



exons 46 through 52.

Since 2014, he, like Dupree, has been a patient advocate for Parent Project Muscular Dystrophy and has participated in federal advocacy efforts on Capitol Hill.

"I just think if you're trying to get the most people affected by it, the microdystrophin seems (of) much better use" than exon skipping, Rensch said. "It would be great if one of these other treatments could help until CRISPR could be an option."

As he makes plans to earn a doctoral degree in musicology, Rensch faces the possibility of moving away from the support system he and his family have in the Kalamazoo area. While assistants help him throughout the day, he lives independently in a house he and his family redesigned to be as accessible as possible.

"That's the one huge advantage that I'd have to give up to go away to a different school," he said. But his studies fall outside the graduate work offered by Western Michigan, so he'll likely have to relocate.

Rensch is resilient and determined to continue his academic career.

"I think that, for me, that's really an important thing — finding something meaningful in your life," he said. "I have the same kind of dreams that anyone else does ... I'm just going to keep living my life."



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

FEATURE

INTERNATIONAL COLLABORATIONS

Professor brings undergrad researchers from Iowa to India

By Laurel Oldach

n January of 2017, seven undergraduate students from Drake University in Iowa landed at Mumbai's international airport. They were 12 hours later than expected and had lost their luggage in transit.

The students hoped to bridge the gap until their clothes caught up with them by shopping in the city nearest to Pravara Institute of Medical Sciences, where they were to spend a month studying. But when they arrived, they learned that a prominent local politician had died; the city was in mourning, stores would be closed for at least the next three days and their hosts at the medical college, founded by the late politician, wanted them to attend the funeral.

Thanks to a quietly organized after-hours shopping trip, the students acquired appropriate clothes and were able to attend the ceremony and pay their respects. According to Pramod Mahajan, the Drake professor who organized the course, that year's students learned at least as much from that experience as from their research projects.

Mahajan was instrumental in starting the exchange program that took the students to India. He used skills honed during his business career (see "Mahajan's path to Drake" on page 44) to sell an interscholastic partnership that has been running eight years; since 2015, he has accompanied every class.

Putting together a program

Drake University prides itself on its study-abroad opportunities. But for years, it did not offer a health-related course in India. Despite efforts to connect with prominent Indian universities, Drake, a midsized, predominantly undergraduate institution, had trouble getting noticed.

Raylene Rospond, then dean of the school's College of Pharmacy and Health Sciences, spotted an opportunity in the announcement of the Obama–Singh 21st Century Knowledge Initiative, a grant designed by the two countries' then-leaders to develop collaborations between Indian and American schools.

To apply for the grant, the Drake faculty had to find a partner institution. And they needed to act fast; they began discussing the opportunity just a few months before the application deadline.

Mahajan knew of a likely candidate, a growing medical school near his wife's hometown in the state of Maharashtra. Pravara Institute of Medical Sciences is in Loni, a town of about 12,000 with a single movie theater, otherwise notable as the home of Asia's first cooperative sugar mill. The farmer who founded that mill in 1950 later turned to philanthropy, launching a medical trust. His son (whose funeral the Drake group attended ELROY SERRAO/WIKIMEDIA COMMONS



An exchange program run by Drake University and Pravara Institute of Medical Sciences brings students to rural Maharashtra (top photo) from rural Iowa (bottom photo). According to Pramod Mahajan, the Drake professor who helped start the program, the regions have more in common than one would think.

in 2017) founded the college in 2003.

Every time Mahajan and his family visited his in-laws, he said, he saw more new buildings going up in Loni. So when Drake's faculty met in the summer of 2011 to discuss applying for an Obama–Singh grant, partnering with PIMS seemed an obvious choice. Mahajan used his business acumen to develop an analysis of strengths, weaknesses, threats and opportunities of a possible partnership, which he presented to the meeting. It convinced his colleagues.

Though familiar with the college in Loni, Mahajan didn't have a single contact there. So he sent a cold email. "They could have said, 'Drake University? We don't know them.' It could have dissolved right there," he said in a recent interview. "But that didn't happen."

After a brief email correspondence and a hastily arranged visit, the two institutions struck up a collaboration and wrote the grant, all within just six weeks.

"Regretfully, that grant did not come through — but that did not stop us," Mahajan said.

The institutions decided to offer the course, funded by tuition, starting in 2012. With support from the administration, international programs staff and key faculty at both schools, the program has grown to include student exchange and collaborative research projects. To apply for the grant, the Drake faculty had to find a partner institution. And they needed to act fast.

FEATURE



MAHAJAN'S PATH TO DRAKE

Pramod Mahajan, a deliberate speaker with a salt-and-pepper mustache, can tell a lot of stories about adapting to and overcoming obstacles. His career has taken him from academia to industry and back.

After a Ph.D. in enzymology and a stint in a government lab in India, where he researched new manufacturing methods for antibiotic precursor molecules, Mahajan came to the U.S. as a postdoctoral researcher. He landed a faculty job at the University of Texas Medical Branch at Galveston, where he studied transcription mechanisms. But pay lines from the National Institutes of Health were low — the field didn't explode in popularity until the mid-1990s. Seeking greater stability, he moved into biotechnology, joining an agricultural company called Pioneer Hi-Bred.

"Their interest was in modifying plant genomes," Mahajan said. "I used to joke that the only thing I knew about plants was how to eat them."

He learned fast, securing more than 30 patents in 15 years for improvements in gene targeting-based methods for plant engineering.

"We succeeded in doing targeted modifications to the genome, even at the single-nucleotide level," Mahajan said. "But (the technique) was so low-efficiency that it just wasn't practical. It was one of those cases where the surgery was successful, but the patient did not survive."

In 2004, when agricultural giant DuPont bought and restructured Pioneer, Mahajan and many of his colleagues were laid off. With a family happily settled in Des Moines, Mahajan was glad to join the faculty at nearby Drake University as a professor in the pharmacy program.

The international experience

In late December 2018, this year's seven Drake students arrived at PIMS, ready to start four-week research projects at the college's Centre for Social Medicine.

In past years, students in the program have investigated cancer incidence, snakebites, burns and poisoning cases, using a mix of medical records and qualitative research methods. This year, they chose from three public health topics. One group of students looked retrospectively at postpartum hemorrhage, another team dug into a drop in HIV infection rates, and a pair of pharmacy students surveyed professors and practitioners of Ayurveda, a traditional medical discipline, to understand how they manage patients' pain.

Erin O'Keefe and Mikayla Soelter, who worked on the HIV project, got a chance to practice adapting their research question on the fly.

"Originally, (we were) going to investigate whether there was a change in HIV prevalence," said O'Keefe, a sophomore biochemistry major. "But the data that they gave us clearly told us that there was."

The students shifted their focus to a behavioral survey of high-risk groups, interviewing local sex workers under the guidance of PIMS public health students to understand what drove the decrease in infections. O'Keefe, who hopes to become a doctor, said the project challenged her to approach patients in a nonjudgmental way.

"If someone's going to a doctor, they clearly need help," she said. "You're not there to judge them; you're just there to give them the best care possible."

In addition to learning research methods, the students said, they learned a lot from the travel itself. "There's no way to describe what it's like to arrive on the other side of the world," sophomore Andrew Kosharek said.

For one thing, there were the crowds. Soelter, who hails from a small town in Minnesota, said, "I think 'rural' means (a town of) a couple thousand."

That's not the way it is in Maharashtra, where the population density more closely

resembles New England than the American heartland. Laughing, Soelter added, "Crossing the street the first time involved screaming."

According to Mahajan, despite the obvious differences, some core similarities link health care in Loni and Des Moines. While the hospital at PIMS offers superb medical care, some villages within its service area are up to 50 miles from the nearest clinic. "That is exactly how rural Iowa is," Mahajan said. He added that "some of the healthcare issues we're facing there," including chemical exposure and injuries from farm equipment, "are exactly the same."

The Drake students said they learned a lot from seeing how public health professionals at PIMS approached these challenges for example, with a mobile clinic program. Danielle McKay was one of the two pharmacy students studying Ayurveda. "What became a theme for us was that even though they might not have a perfect solution, they would go into the community ... and go for the solutions, even if they weren't perfect," she said.

"You kind of go in with the mindset that you know how to fix other people's problems," added Drake Reiter, who worked with McKay. "But when you actually go to that place, you realize ... they're the ones who know what problems they have, and they know what they want to do to solve them."

Mahajan doesn't expect all his students to take these insights into public health careers — although some have. But he finds giving students an introduction to public health research is its own reward.

In Texas, 20 years ago, "I was a faculty member entirely focused on getting that R01," Mahajan said. "After coming to Drake, I realized there's a lot to be done at the undergraduate level."



Laurel Oldach (loldach@asbmb.org) is a science writer for the ASBMB. Follow her on Twitter @LaurelOld.



The seven Drake students who visited PIMS in January are, in back, from left to right, Drake Reiter, Danielle McKay, Andy Kosharek and Erin O'Keefe, and, in front, Mikayla Soelter, Erin Steffenson and JaNiese Jensen.

Call for meeting proposals

The ASBMB symposia program aims to provide niche segments of the scientific community with opportunities to present unique, cutting-edge science and engage in active networking opportunities. Help advance your field by planning an ASBMB symposium.

Proposal deadline: Nov. 1

www.asbmb.org/SpecialSymposia/ Proposals/





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A letter from the 2020 annual meeting co-organizers

By Bob Haltiwanger & Carla Koehler

Bob: My first American Society for Biochemistry and Molecular Biology meeting was in 1982 when I was a second-year graduate student in Bob Hill's laboratory at Duke University. The society was called the American Society of Biological Chemists, or ASBC, back then, and the meeting was in New Orleans. It was my first scientific meeting and my first trip to the Crescent City.

The meeting was transformational for me as a young scientist. It opened my eyes to the breadth and depth of biochemistry and molecular biology and inspired me to get back in the lab and make my own dent in the field. I also enjoyed the food and history of New Orleans. Reflecting on my experience while walking around the French Quarter, eating lunch in K-Paul's and buying gifts for my family back home, I knew I had chosen the right career path. I've never regretted it.

Carla: My first ASBMB meeting was in 1988 when I was a graduate student in Don Beitz's laboratory at Iowa State University. It was my first large scientific conference, and I found the size of the poster hall overwhelming. As a junior faculty member, I co-organized a thematic session at a later meeting in San Diego. This provided a chance both to focus and to explore other areas of biochemistry.

With so many junior and senior researchers gathered in one place, important interactions typically happen while socializing. I've been amazed by the collaborations and insights that develop from this meeting.

**

The 2020 ASBMB annual meeting will be held April 4 to April 7 in sunny San Diego. It will feature outstanding award lectures from leaders in the field, daily thematic sessions geared toward core areas of biochemistry and molecular biology, Spotlight Sessions highlighting the work of younger scientists, poster sessions, workshops and more.

Six thematic sessions held over three mornings will highlight foundational areas of biochemistry and molecular biology. Read all about these sessions on pages 49 to 56 in this issue. World-class organizers and speakers will cover exciting recent discoveries in their fields. The wide range of topics focuses on molecular mechanisms of biology and disease.

Spotlight Sessions consist of related talks that highlight recent high-interest research selected from abstracts submitted by attendees. The criterion for selection is simple: Is the science exciting? These sessions, introduced in 2017, have been very popular, especially because younger scientists get a chance to present their work. We encourage anyone who has an idea for a Spotlight Session theme to contact us as soon as possible. We'll work with you to recruit relevant abstract submissions.

Poster sessions provide the greatest opportunity for individual scientists to discuss their recent work. Many students present their work publicly for the first time at poster sessions. To make these sessions more accessible and boost attendance, we've rescheduled them to avoid conflict with other events, and we're planning short flash talks to cap the thematic morning sessions and let presenters advertise their posters.

A spring meeting in California offers fabulous opportunities for dining, fun and networking. We look forward to seeing you in San Diego.

**

Read on to learn about all of this year's thematic sessions.

Bob Haltiwanger (rhalti@uga.edu) is a professor in the department of biochemistry and cell biology at the University of Georgia.



Carla Koehler (koehler@chem.ucla.edu) is a professor in the department of chemistry and biochemistry at the University of California, Los Angeles.



GLYCOSYLATION AND EXTRACELLULAR MATRIX IN DEVELOPMENT AND DISEASE

Outside-in biology and disease

Jamey David Marth & Joanne Murphy–Ullrich

or life to exist, cells need to be able to sense and respond to their environment. To do so, cells of multicellular organisms produce highly specialized networks of proteins and glycans that include the extracellular matrix, or ECM. Glycans and ECM both provide and recognize extracellular signals and translate them into biological information. In turn, cells alter their phenotype in this bidirectional life process, which combines intrinsic template-dependent biology (nucleic acids and proteins) with template-independent metabolism (glycans and lipids). Glycosylation and the ECM are critical features of this bidirectional control of cell biology and disease. Glycans, produced by the enzymatic process of glycosylation, are an abundant and diverse repertoire of glycosidic linkages. The ECM is a complex network of secreted glycoproteins, proteoglycans and glycosaminoglycans that interact with cell receptors, ECM molecules, growth factors and enzymes.

This session will explore the activities and mechanisms by which these cell-derived components govern health and disease, emphasizing emerging links with cancer, immunity, inflammation and metabolism and including infectious and neurological diseases.

Keywords: glycosylation, ECM, cancer, inflammation, development, fibrosis, immunity, infection, neurobiology

Who should attend: anyone who is interested in understanding how cells function and respond to the environment through componentry that includes glycans and the ECM in the regulation of development, metabolism, inflammation and immunity and in the pathogenesis of multiple diseases

Theme song: "Built to Last" by the Grateful Dead. *This session is powered by proteins and sugars.*

TALKS

- Role of O-linked fucose-glucose disaccharide modification of thrombospondin type I repeats during protein folding and embryo development — Bernadette Holdener, Stony Brook University
- Fibrillin-Notch interactions in development and disease Lynn Sakai, Oregon Health & Science University
- A genetic approach to glycomics in cancer Henrik Clausen, University of Copenhagen
- TGF-beta regulation by the matricellular protein thrombospondin 1 — Joanne Murphy–Ullrich, University of Alabama at Birmingham
- Quieting mast cells for treatment of allergies James Paulson, Scripps Research
- Decoding inflammatory signals from ECM glycans for the development of new immunotherapies — Kim Midwood, University of Oxford
- Glycosylation in a common pathogenic mechanism of colitis and sepsis — Jamey Marth, University of California, Santa Barbara and the SBP Discovery Discovery Institute, LaJolla
- Genomewide analysis of heparan sulfate assembly Jeffrey Esko, University of California, San Diego
- Protective roles of O-GlcNAc in neurodegenerative diseases
 David Vocadlo, Simon Frasier University
- The role of the O-GlcNAc transferase interactome in X-linked intellectual disability Lance Wells, *University of Georgia*
- Role of ECM in the brain-gut connection Fernando Gomez-Pinilla, University of California, Los Angeles
- The role of metabolism in modulating radiation fibrosis Fei-Fei Liu, Princess Margaret Cancer Centre, Toronto

Jamey David Marth (jmarth@sbpdiscovery.org) is director of the center for nanomedicine, Carbon professor of biochemistry and molecular biology, and Mellichamp professor of systems biology at the University of California, Santa Barbara and the Sanford Burnham Prebys Medical Discovery Institute in La Jolla.



Joanne Murphy–Ullrich (jmurphy@uabmc.edu) is a professor of pathology, ophthalmology, and cell developmental and integrative biology at the University of Alabama at Birmingham. Follow her on Twitter @tspcrt and @amsocmatbio with #ECMatrix.



MOLECULAR MOTORS — STRUCTURE AND FUNCTION

Understanding the inner workings of biological machines

Nathan Alder & Jochen Zimmer

Any biological macromolecules assemble into complexes to perform their physiological functions. These molecular machines range in complexity from relatively simple molecules to large macromolecular assemblies, and they are designed to perform specific tasks within the cell. This thematic session will cover exciting new advances in our understanding of the structure, function and engineering of molecular machines. The session will encompass the wide range of molecular assemblies that accomplish diverse and often essential tasks within a cell, including molecular motors responsible for protein processing and vesicle trafficking as well as supramolecular complexes mediating energy transduction, transport and protein synthesis.

Presentations in this session will cover a wide range of experimental and technical approaches, such as advances in structural biology (cryo-electron microscopy, X-ray crystallography and nuclear magnetic resonance spectroscopy), single molecule biophysics and super-resolution imaging. It also will cover novel conceptual advances, including new insights into the design of natural and synthetic molecular machines and how energy is transduced to power biological nanomachines at the molecular level.

Keywords: molecular motors, protein complexes, transporters, force generation and transduction, supramolecular assemblies.

Who should attend: those fascinated by structure– function relationships in biological systems, how macromolecules undergo modular assembly and what kinds of energetic input power the work of molecular machines.

Theme song: "Ghosts in My Machine" by Annie Lennox.

This session is powered by ATP and ion gradients.

Nathan Alder (nathan.alder@uconn.edu) is an associate professor in the department of molecular and cell biology at the University of Connecticut.



TALKS

- Single molecule biophysics Carlos Bustamante, University of California, Berkeley
- Myosin: Structure, function, regulation and disease Michelle Peckham, University of Leeds
- Watching a fine-tuned molecular machine at work: Structural and functional studies of the 26S proteasome — Andreas Martin, University of California, Berkeley
- Integrated 3D tomography and computational modeling to study forces in metaphase spindles — Stefanie Redemann, University of Virginia School of Medicine
- Functional assembly of the mitochondrial protein transport machinery Nathan Alder, University of Connecticut
- Nascent protein selection and triage at the ribosome exit site — Shu-ou Shan, California Institute of Technology
- Structure of the alternative complex III from Flavobacterium johnsoniae in a supercomplex with cytochrome c oxidase Robert Gennis, *University of Illinois*
- Special capabilities of the ribosomal machinery Roland Beckman, Ludwig-Maximilians-Universität München
- Sugary coats: Synthesis and secretion of extracellular polysaccharides Jochen Zimmer, University of Virginia
- Molecular assemblies of membrane remodeling and scission — James Hurley, *University of California, Berkeley*
- Hi-fi molecular transmission via crisscross cooperativity —
 William Shih, Harvard University
- Activation of the exocyst tethering complex for SNARE complex regulation and membrane fusion — Mary Munson, University of Massachusetts Medical School

Jochen Zimmer (jz3x@virginia.edu) is a professor in the department of molecular physiology and biological physics at the University of Virginia.



UNDERSTANDING THE MEANING OF LIFE

Decisions and fates: Insights into the rules of life

Suzanne Barbour

s it possible to build a functional cell from scratch? If so, what are the minimum components needed, and what molecular mechanisms are necessary to control their behavior and ensure they function in a coordinated manner?

How do cells make the decisions that determine their fate and the fate of the organisms they constitute?

These and other fundamental questions about the rules of life are the focus of this session. The answers to these questions have the potential to uncover the molecular rules that govern life as we know it. Although this is fascinating on its own, the answers to these questions also will provide insights into the molecular mechanisms underlying health and disease. It is only in the past two decades that we have had the molecular tools and instrumentation necessary to ask these questions.

The speakers in this session use computational, modeling and good old-fashioned biochemistry and molecular biology approaches to capture dynamic data, analyze changes over time and make predictions about responses and behaviors that would not be possible with experimental approaches alone.

Keywords: computation, modeling, cell fate, cell decision, signal transduction, synthetic cell.

Who should attend: biochemists, molecular biologists, computational biologists and cell biologists interested in the fundamental rules that govern life as we know it.

Theme song: "It's the End of the World as We Know It" by R.E.M.

This session is powered by interdisciplinary biochemical, molecular and computational approaches. (Sponsored by the ASBMB Minority Affairs Committee.)

TALKS

- Mechanical principles of nuclear shaping and positioning Tanmay Lele, University of Florida
- Longitudinal analysis of genetic networks as determinants of lifespan in C. elegans — Adriana San-Miguel, North Carolina State University
- Clocks, hourglasses and history-dependent clocks Arvind Murugan, University of Illinois, Chicago
- Synthetic NF-kB: A building approach to study complex signaling behaviors — Ping Wei, Center for Quantitative Biology, Peking University
- Computational approaches to predicting transcription factor binding and kinetics — Polly Fordyce, Stanford University
- Synthetic genetic circuits Domitilla Del Vecchio, Massachusetts Institute of Technology

Suzanne E. Barbour (sbarbour@uga.edu) is dean of the graduate school and professor of biochemistry and molecular biology at the University of Georgia. In September, she is transitioning to the University of North Carolina– Chapel Hill.



BIOCHEMISTRY OF LIPIDS AND MEMBRANES

These walls are worth the cost

Steve Claypool & Teresa Dunn–Giroux

A re you the type of person who feels comforted by being within the walls of your living space? Similar to us in our homes, cells are separated from each other by lipid membranes that also encapsulate the various collection of organelles therein. However, lipid membranes are much more than simple barriers. Different membrane-bound structures have distinct lipid compositions that confer identity, are dynamic and adaptable, communicate extensively with one another through physical contact sites, and provide an energy-rich storage depot available when times are rough. Further, like the doors and windows in your house, membrane proteins provide a means by which the two sides demarcated by a lipid bilayer can communicate.

An exciting emerging principle is that specific lipids are required for the activity of many membrane proteins. The goal of this session is to showcase the multitude of hats worn by lipids in both health and disease.

Keywords: lipids, membrane dynamics, homeostatic mechanisms, lipid metabolism, membrane proteins.

Who should attend: anyone who feels underappreciated, because that is exactly how lipids and their researchers have felt for decades; people unafraid of grease — and those who are, too.

Theme song: "Insane in the Membrane" by Cypress Hill.

This session is powered by Vaseline.

TALKS

- Lipid droplet proteome dynamics and lipotoxicity James Olzmann, University of California, Berkeley
- Mechanistic approaches towards understanding physicochemical membrane homeostasis in the endoplasmic reticulum — Robert Ernst, Saarland University
- The role of VPS13 and related proteins in glycerolipid transport at membrane contact sites Karin Reinisch, *Yale University School of Medicine*
- Cold-induced lipid dynamics in thermogenic fat Yu-Hua Tseng, Joslin Diabetes Center, Harvard Medical School
- Membrane proteins the lipid connection Carol Robinson, University of Oxford
- Structural basis of lipid scrambling and ion conduction by TMEM16 scramblases — Alessio Accardi, Weill Cornell Medical College
- Structural insights into TRPV channel gating Vera Moiseenkova-Bell, University of Pennsylvania
- Cardiolipin-dependent carriers Steven Claypool, Johns Hopkins University School of Medicine
- Seipin in lipid mobilization and lipodystrophy Weiqin Chen, Medical College of Georgia at Augusta University
- The role of organelle contact during Chlamydia developmental cycle — Isabelle Derré, University of Virginia
- Cardiolipin exerts tissue-specific control over systemic energy homeostasis — Zachary Gerhart-Hines, University of Copenhagen
- SPTLC1 mutations associated with early onset amyotrophic lateral sclerosis — Teresa Dunn, Uniformed Services University of the Health Sciences

Steven Claypool (sclaypo1@jhmi.edu) is an associate professor in the department of physiology at the Johns Hopkins University School of Medicine.



Teresa Dunn–Giroux (teresa.dunn-giroux@usuhs. edu) is professor and chair of the department of biochemistry and molecular biology at the Uniformed Services University of the Health Sciences.



REIMAGING STEM: WHO WE ARE AND WHAT WE DO

This ain't your grandfather's STEM

Daniel Dries & Nathan L. Vanderford

"If you are in a shipwreck and all the boats are gone, a piano top buoyant enough to keep you afloat may come along and make a fortuitous life preserver. ... I think we are clinging to a great many piano tops in accepting yesterday's fortuitous contrivings as constituting the only means for solving a given problem."

— R. Buckminster Fuller

ow do we ensure our students are designing life preservers and not piano tops? How do we move past asking them to tell us about density and buoyant forces and instead ask them to just build the darn life preserver? How do we cultivate creativity to move past the status quo? Whose creativity are we missing? Where have those voices gone, and why? How do we keep those voices in our conversations?

Join us in challenging our culture in the ways in which we teach, mentor and carry out our work. For, as Coretta Scott King said, "If you don't use your power for positive change, you are, indeed, part of the problem."

Keywords: inclusion, diversity, wellness, active learning, pedagogy, #MeToo, mentorship, discipline-based education research, interdisciplinarity

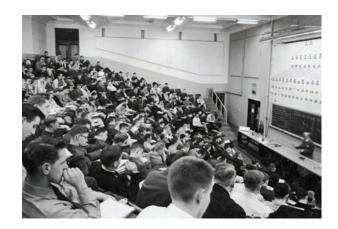
Who should attend: movers, shakers and those who want to learn how to move and/or shake

Theme song: "The Times They Are A-Changin" covered by Brandi Carlile

This session is powered by justice and equity. (Sponsored by the ASBMB Education and Professional Development Committee)

TALKS

- Preventing and overcoming harassment Alex Helman, National Academies of Sciences, Engineering and Medicine
- Promoting STEM identity: A vision for building tomorrow's STEM leaders — Sarah Rodriguez, *Iowa State University*
- Promoting mental well-being Nathan L. Vanderford, University of Kentucky
- Mentorship best practices Joanne Kamens, Addgene
- Best practices in discipline-based education research Kim Cortes, Kennesaw State University
- Teaching biochemistry in context Daniel Dries, Juniata College
- Using narrative in STEM education Reneta Lansiquot, New York City College of Technology
- Restructuring the classroom to promote student thriving, not just surviving — Shannon Jones, University of Richmond



Daniel Dries (dries@juniata.edu) is an associate professor of chemistry and biochemistry at Juniata College in central Pennsylvania.



Nathan L. Vanderford (nathan.vanderford@uky. edu) is an assistant professor of toxicology and cancer biology at the University of Kentucky. Follow him on Twitter @nlvanderford.



MOLECULAR MECHANISMS OF CELL SIGNALING

Breakthroughs in sending the message

Wendy Gordon & Adrian Salic

Some of the most fascinating biological processes, such as embryonic development, tissue regeneration and the physiological integration of body functions, rely on a network of cell–cell communication pathways. Although the molecular players in cell–cell communication have long been known from genetic studies in model systems, many of the underlying mechanisms only now are beginning to be deciphered. Within this area, cell-surface receptors function like air-traffic controllers, integrating inputs from the cell's exterior and interior to trigger signal transduction pathways, leading to specific cellular responses.

This session will focus on emerging mechanisms in cell-cell communication, particularly how cell-surface receptors interpret mechanical stimuli, how signaling molecules are controlled by less well understood post-translational modifications and how signaling polarizes cells and tissues. The session will showcase diverse modern approaches to understanding cell signaling, ranging from structural to organismal biology.

Keywords: mechanobiology, structural biology, post-translational modifications, signal transduction, receptors, ligands

Who should attend: cell biologists, biochemists, structural biologists and developmental biologists, and particularly grad students and postdocs interested in emerging themes and state-of-the-art methodology in cell–cell signaling research

Theme song: "Hotel California" by the Eagles. Once you come to our session, you will not want to leave. *This session is powered by communication.*

TALKS

- Piezo1 gains traction Medha Pathak, University of California, Irvine
- Mechanotransduction in vascular health and disease Martin Schwartz, Yale University
- Mechanical force and Notch signaling Wendy Gordon, University of Minnesota
- Mechanisms linking mechanotransduction and cell metabolism — Kristin DiMali, University of Iowa
- Getting hedgehogs where they need to go Stacey Ogden, St. Jude Children's Research Hospital
- Rhomboid proteins in cell signaling Matthew Freeman, University of Oxford
- Lipids and hedgehogs Adrian Salic, Harvard Medical School
- Role of Notch glycosylation in signaling Pamela Stanley, *Albert Einstein College of Medicine*
- Ligand engineering for probing receptor signaling mechanisms Chris Garcia, *Stanford University*
- Cellular communication via adhesion Demet Arac, University of Chicago
- Mechanisms of Wnt5a-Ror signaling in development and disease Henry Ho, *University of California, Davis*
- Wnt/planar cell polarity signaling in skeletal development Yingzi Yang, Harvard Dental School

Wendy Gordon (wrgordon@umn.edu) is an assistant professor of biochemistry at the University of Minnesota specializing in mechanobiology. Follow her on Twitter @WRGordonlab.



Adrian Salic (Adrian_Salic@hms.harvard.edu) is a professor of cell biology at Harvard Medical School focusing on the biochemistry and cell biology of cell-cell signaling. Follow him on Twitter @saliclab.



NEW DEVELOPMENTS IN METABOLISM

Mitochondria and metabolites in action

Marcia Haigis & Anne Murphy

itochondria are dynamic organelles important in mediating cell and tissue homeostasis. In this session, we will hear exciting new updates on the role of mitochondria beyond energy production in metabolism, ion homeostasis, and determination of the fate of cells and tissues by metabolites and their transporters.

Keywords: NAD, metabolite and ion transporters, sirtuins, mitochondria, metabolism

Who should attend: students, postdocs and anyone interested in mitochondria, metabolism, and health

Theme song: "Thunder" by Imagine Dragons *This session is powered by mitochondria.*

TALKS

- Modulating de novo NAD synthesis Johan Auwerx, École Polytech Fédérale de Lausanne
- NAD homeostasis and compartmentation Joseph A. Baur, University of Pennsylvania
- Chromatin regulation and genome maintenance by mammalian SIRT6 and SIRT7 — Katrin F. Chua, *Stanford University*
- Metabolic competition in the tumor microenvironment Marcia Haigis, Harvard Medical School
- Glutamine transporter as a target of mTOR signaling modulating longevity — John Sedivy, Brown University
- Neuroprotection through control of mitochondrial pyruvate transport — Anne Murphy, Cytokinetics Inc.
- Local and systemic actions of hepatic fatty acid oxidation Michael Wolfgang, Johns Hopkins Medicine
- Physiopathological roles of the mitochondrial calcium uniporter — Anna Raffaello, University of Padova
- Microbiome catabolites as novel modulators of cellular glucose and energy metabolism — Gary Williamson, Monash University
- Metabolic modulation of cardiac health: The role of glucose and amino acids — Rong Tian, University of Washington
- Control of macrophage activation by coenzyme A Ajit Divakaruni, *University of California, Los Angeles*
- Mechanisms of metabolite control over adipose tissue function — Edward Chouchani, Harvard University

Marcia Haigis (Marcia_Haigis@hms.harvard.edu) is a professor of cell biology at Harvard Medical School with a focus on mitochondria in health and disease.



Anne Murphy (anmurphy@ucsd.edu) is the vice president of biology at Cytokinetics Inc.



RNA AND DISEASE

Disease discoveries in three realms of the RNA world

Anita Hopper & Takahiro Ito

he RNA world is key to understanding gene expression in eukaryotes. This theme will include three sessions describing exciting discoveries in RNA and disease: small noncoding RNAs, RNA modifications and RNA binding proteins.

The session on small noncoding RNAs will focus on discoveries in model systems and humans regarding transfer RNAs, tRNA fragments and Piwi-interacting RNAs regarding their biogenesis, functions, and roles in development and disease.

After transcription, nearly every type of RNA becomes decorated with nucleoside modifications; the RNA modification session will describe novel roles these modifications play in decoding, RNA stability and RNA regulation and activities. It also will describe how these modifications function in normal and aberrant biological states.

RNA functions rely on interactions with RNA binding proteins; the session on RNA binding proteins will describe how RNA-protein interactions regulate chromatin structure, transcription and splicing and how the interactions are involved in development and disease.

Keywords: small noncoding RNAs, RNA modification, RNA binding proteins, tRNA, piRNA, miRNA, tRNA fragments, gene expression, stem cells, muscle cells, development, cancer

Who should attend: everyone who wants to learn how the RNA world impinges on gene expression in health and disease

Theme song: "Hello, Goodbye" by the Beatles, because the song reminds us of the life of RNAs in a cell.

This session is powered by different kinds of RNAs — obviously.

TALKS

- tRNA: Splicing and subcellular dynamics Anita Hopper, Ohio State University
- The role of 3'tsRNAs in gene regulation Mark Kay, Stanford University
- The Piwi-piRNA pathway: A new paradigm in gene regulation — Haifan Lin, Yale University
- piRNA biogenesis and function in Drosophila Mikiko Siomi, University of Tokyo
- RNA modification in cancer Jianjun Chen, Beckman Research Institute of City of Hope
- RNA modifications in health and disease Tsutomu Suzuki, University of Tokyo
- Acetylation of cytidine in messenger RNA regulates translation — Shalini Oberdoerffer, National Cancer Institute
- tRNA quality control: Mechanisms, evolution, and implications for human disease — Eric Phizicky, University of Rochester Medical Center
- RNA binding proteins in stem cells and cancer Takahiro Ito, University of Georgia
- The RNA exosome and genetic disease Anita Corbett, Emory University
- RNA, chromatin, and the coordinated control of gene expression Tracy Johnson, University of California, Los Angeles
- How mRNP composition determines mRNA fate Guramrit Singh, Ohio State University

Anita Hopper (hopper.64@osu.edu) is a professor of molecular genetics at Ohio State University.



Takahiro Ito (tkhrito@uga.edu) is an associate professor in the department of biochemistry and molecular biology at the University of Georgia. Follow him on Twitter @UGAltoLab.



What I wish people understood about transitioning away from a career at the bench

By Mohor B. Sengupta

came home from work one evening in late 2018 with the words of my supervisor ringing in my ears: "I am disappointed that scientific research is not your long-term interest."

Into the second year of my postdoctoral training, I was neck-deep in my research projects and volunteering as a writer for my institute's magazines on the side. My supervisor didn't like the second part. That evening was the first time I'd talked to him about transitioning into science writing.

I felt angry with myself for not having a good enough explanation. I felt guilty thinking of the resources I had used up only to decide that I wasn't up for long-term research. Most of all, I felt hurt because he made me feel irresponsible about my chosen future career path, which in his view should have been academia. After a few episodes of South Park followed by a good sleep, I woke up feeling glad — I finally saw my career goals clearly the day I decided science writing was my future profession.

Nine years of scientific research taught me many things, primarily resilience. By the second year of my postdoctoral fellowship, I was adept at troubleshooting, devising new experiment plans and pushing feelings of discontent with work under the carpet. Before I knew it, a whole new world of information and new networks opened up. My life at work was no longer an isolated struggle with an experiment.

I always enjoyed writing, but I started writing regularly as a breather activity, something that would help me wind down in my time away from the lab. I wrote about scientists and their work, about the latest research on topics far removed from my comfort zone, and about lectures by eminent scientists and clinicians who visited the National Institutes of Health, where I worked. Before I knew it, a whole new world of information and new networks opened up. My life at work was no longer an isolated struggle with an experiment. I was part of editing and science policy groups. I made friends with like-minded trainees. The variety of writing tasks helped me communicate science more easily. I edited manuscripts written by some of my lab members before they sent them to journals. The work was rewarding to me and useful to them, a win-win situation.

I realized that I enjoyed scien-

tific communication more than I enjoyed lab work. As a researcher, I had very little time outside the lab, and I craved that time. I knew it was hard to get a job in academia, but my concern wasn't about getting hired. It was about not fitting in as a researcher.

It didn't take much effort see that if I was unhappy, my performance and quality of life would suffer. It boiled down to a simple question: Does it feel better being an unhappy scientist in a big and renowned institute or a satisfied individual working on something that absorbs me? The choice didn't hit me until I'd dipped into activities outside scientific research. I took a long time to see that I'd be happier being a science communicator, but I'm glad I was able to see it.

When I told my supervisor and my parents that I intended to move away from academia, they expressed concern about my plans. My parents didn't have a clear idea about the rigors of a career in academics, and until then I hadn't been open with them about my dissatisfaction, so they wanted to know why I was leaving academia. Eventually, they supported me wholeheartedly, as they always have done. However, transitioning away from research didn't fit into my supervisor's view of an ideal scientific attitude. We are still not on the same page.

ESSAY

I grew up in a society that emphasized higher education and valued a handful of professions, scientist being high up in the pecking order. After years of being in a profession I didn't enjoy wholeheartedly, I felt that my social conditioning had failed me by not letting me explore my career interests at the outset. As a millennial, I had a pretty career-oriented upbringing. I grew up in a society that emphasized higher education and valued a handful of professions, scientist being high up in the pecking order. After years of being in a profession I didn't enjoy wholeheartedly, I felt that my social conditioning had failed me by not letting me explore my career interests at the outset.

In an orientation program with the career counseling office of my institute, a counselor told us that nearly a third of postdoctoral trainees leave academia. The office has a team of experts dedicated to offering guidance, advice and encouragement to transitioning fellows, because these postdocs find little support outside that office.

A friend and fellow science editor at my institute told me that many supervisors believe nonacademic activities outside the lab are a distraction and a waste of time. I know my boss is not alone in his misgivings; they are fairly common in the academic world of mentor-mentee relationships. As more people transition away from academia, trainee-oriented offices like the career counseling unit I mentioned are working to get senior scientists to acknowledge and be supportive of such moves.

I can safely say that I have had a very rewarding scientific career in terms of the work I did in clinical and basic neuroscience. If not for my joy in scientific findings, I never would have realized my greater passion to communicate that feeling with the world.

Mohor B. Sengupta

(mohorsengupta@gmail.com) has recently transitioned into a science writing position from being a postdoctoral researcher at the National Institutes of Health. She has been a writer and editor for several NIH publications.



She enjoys writing about scientific concepts, people in science and their achievements. Read her blogs at mohorsengupta.com and sciencepolicyforall.wordpress.com.

American Society for Biochemistry and Molecular Biology

ACCREDITATION PROGRAM

Application deadline Oct. 1



For more information, visit asbmb.org/accreditation.

Read this article online at asbmb. org/asbmbtodav for weblinks to all these event descriptions and more inspiration.

#ASBMBloves

Dear postdocs,

13 ways to thank postdocs

- Appreciation dinner (University of California, 1. Davis)
- Pet-a-dog happiness therapy and juice bar 2. (Stanford University)
- Postdoc research symposium and awards 3. (University of Wisconsin-Madison)
- **Yoga and Zumba** (University of Michigan) 4.
- **Cookout** (University of North Carolina) 5.
- Trivia (Van Andel Institute) 6.
- 7. Ice cream social (National Institutes of Health)
- Photo booth for professional headshots (NIH) 8.
- 9 **Donut social** (NIH)

10. Pizza party and networking (Queen's University Belfast)

National Postdoc Appreciation Week is Sept. 16–20 — a time to celebrate postdocs

Daily coffee breaks: Join us on Twitter (@ASBMB) at 1 p.m. for the chance

for your postdocs. We'll share it on Facebook, Twitter and Instagram!

Webinar on Sept. 17: Learn more at asbmb.org/webinars. • Twitter chat on Sept. 19 (use #ASBMBLovesPostdocs)

Thank you and happy National Postdoc Appreciation Week!

Have a great Postdoc Appreciation Week!

Thank-you shout-outs: Email asbmbtoday@asbmb.org with photos and a message

and their immeasurable contributions to the scientific community.

Here's what we have planned at the ASBMB:

Membership deals for new and existing early-career members

- 11. Barbecue and bake-off (University of Manchester)
- 12. Health screenings (Washington University in St. Louis)
- 13. Career counseling and professional development (American Association for Cancer Research)

Special thanks to all those who responded on Twitter for contributing to the list above.

– Allison Frick

With love from the ASBMB

BOOKS BY MEMBERS

PLEASED TO MEET ME: GENES, GERMS, AND THE CURIOUS FORCES THAT MAKE US WHO WE ARE

By Bill Sullivan, Showalter professor of pharmacology and toxicology, microbiology and immunology, Indiana University School of Medicine

Why are you attracted to a certain "type"? Why are you a morning person? Why do you vote the way you do? What makes you *you*. "Pleased to Meet Me" describes in everyday language how genetics, epigenetics,

ERIC SCHOCH



microbiology and psychology work together to influence personality and behavior. Mixing cutting-edge research with pop culture and humor, "Pleased to Meet Me" is filled with insights that shine a light on who we really are — and how we might become our best selves.



Published by National Geographic Books

Are you an ASBMB member who has published a book in 2019? If so, we'd like to feature your work in an upcoming issue of ASBMB Today. Please email a synopsis (<100 words), an image of the book cover and your headshot to **asbmbtoday@asbmb.org**.

ASBMB Art of Science Communication Course

Want to become a great science communicator? This online course will help. Course begins first week of October.



www.asbmb.org/Outreach/Training/

CLASSIFIEDS

USDA ARS GFHNRC Post-Doctoral Research Associate

USDA D25

A Post-Doctoral Research Associate position is available at the Grand Forks Human Nutrition Research Center, in Grand Forks, ND. The project involves developing mass spectrometry-based analytical methods and implementing these assays in human studies. These include: The quantitation of a panel of myokine, adipokine, cytokine species in human plasma, hair, saliva, and/or urine using targeted proteomic analysis; the quantitation of small molecule species such as endocannabinoids, corticosteroids, and similar species that relate to psychological processes including behavioral reinforcement and/or stress response (NMR, mass spectrometry) following chromatographic purification.

http://www.asbmb.org/Careers/Jobs/80988/

North Carolina State University Teaching Postdoctoral Scholar

Princeton University Assistant Professor in Cryo-EM



The Molecular Biology Department at Princeton University invites applications for a tenure-track faculty position at the Assistant Professor level. We are seeking a colleague who will build a world-class research program leveraging high resolution cryo-electron microscopy and/or cryo-electron tomography in the study of important biological questions. The successful candidate will join a highly collaborative faculty spanning a broad range of fields and will have access to superb resources including a state-of-the-art 300 kV Titan Krios TEM. We are especially interested in attracting colleagues who share our commitment to teaching, mentoring, and fostering a climate that embraces both excellence and diversity.

http://www.asbmb.org/Careers/Jobs/81037/

Eppendorf, Inc. Bioprocess Field Application Specialist



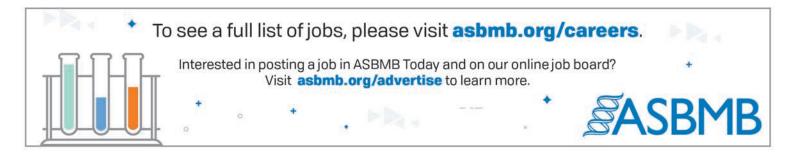
The Biotechnology Program (BIT) at North Carolina State University invites applications for a position as Teaching Postdoctoral Scholar in the area of molecular or chemical biology. Responsibilities will include teaching sections at the graduate and undergraduate levels of an existing course on the manipulation of recombinant DNA. Scholars will also develop and implement a new laboratory course in a cutting-edge area of molecular biotechnology in the scholar's area of expertise. Scholars will also have the opportunity to mentor undergraduate research students in independent research projects. The successful candidate must have strong interpersonal skills and teaching ability.

http://www.asbmb.org/Careers/Jobs/81039/

eppendorf

Eppendorf, Inc., HQ in Enfield, CT, seeks a Bioprocess Field Application Specialist to provide bioprocess fulfillment services including product demonstrations, installation, training, method development, application support and troubleshooting with regard to complex applications used by scientists in the life science laboratory setting. Position requires Master's Degree in biology or a related life science field including biochemistry or pharmaceutical sciences plus 2 years of life science applications experience. In the alternative, will accept a bachelor's degree plus 5 progressive years of life science applications experience. The experience must include 2 years of experience with upstream cell culture applications and 1 year of hands-on experience with bioreactors in an industrial setting. Will accept foreign educational equivalent. Experience could have been gained in any job title. Telecommuting home office and travel position. Position reports to Enfield, CT. Must reside in San Francisco Bay, CA metro area.

http://www.asbmb.org/Careers/Jobs/81040/



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