ASBMB today

Vol. 12 No. 11 December 2013

"A good ambassador"

Hudson Freeze

2013 GOLDEN GOOSE AWARD WINNER

American Society for Biochemistry and Molecular Biology

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Submit to ASBMB Today's next series, "Open Letters"!

We welcome letters of all sorts:

- Letters to people, places and things, both real or imagined*
- Letters so funny that we'll choke on our coffee while reading them
- Letters of such sincerity that we'll want to call a loved one or forgive an enemy
- Letters that got you, or didn't get you, what you wanted
- Letters that you wish you could have sent without getting into trouble
- Letters that just plain need to be read by others

Still don't get it?

Well, then take a look at Pages 8 and 9 of this issue for a couple of examples (sort of on the sappy side).

To have your open letter considered for publication, do the following:

- Send it in a Word document or in the body of your email. Letters with fewer than 1,000 words are preferred, but longer letters won't be rejected outright.
- Include a brief author biography of 100 words or fewer.
- Attach (do not embed, if you're using a Mac) a high-resolution photograph of yourself to go with your letter.
- Send your letter to asbmbtoday@asbmb.org by Dec. 31, 2013.

** You might be wondering what we mean by this. It's not as crazy as it might sound. An imagined person, for example, could be "that person who always (add your own description here)." Letters like this are cathartic. Trust us.*

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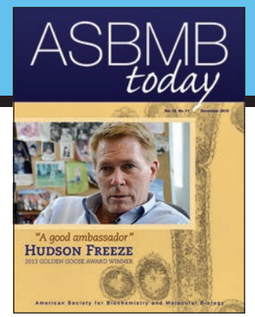

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IMAGE CREDIT: UNIVERSITY OF WISCONSIN-MADISON.

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The reliability of scientific research

BY JEREMY BERG

When I was going through our mail, the cover of the Oct. 19 issue of The Economist jumped out at me: "HOW SCIENCE GOES WRONG." I thought "This is not good" and scanned the story (1), which highlights two studies that indicated that, when scientists from the pharmaceutical industry tried to replicate results from important papers in preclinical cancer research, only 10 percent to 25 percent of the key findings could be reproduced. The article proposes several explanations for the lack of replicability. The author's hypotheses include the impact of the publish-or-perish culture (favoring rapid publication of new results with few incentives for replication or validation studies) and the incentives for cherry-picking data and exaggeration.

The issue also contains a second article, "Unreliable research: Trouble in the lab" (2). The briefing refers to a study published in 2005 by Stanford epidemiologist John Ioannidis, "Why most published findings are false" (3). Rather than looking for cultural issues that may encourage publication of unreliable results, these articles instead examine the research process from a statistical point of view. More specifically, they use so-called Bayesian analysis to examine the problem.

To understand Bayesian analysis, consider the following. Suppose you have a diagnostic test for a disease. If the disease is present, the test is positive 95 percent of the time, meaning that it is quite sensitive. If the disease is absent, the test is negative 90 percent of the time, meaning that it is fairly specific. Given these parameters, it seems like a fairly reliable test. Suppose that 1 percent of the population has the disease. What is the likelihood that someone who tests positive for the disease actually has it?

Consider a population of 2,000. One percent, or 20 individuals, has the disease. For these people, 95 percent, or 19 out of 20, are expected to test positive, and 1 is expected to test negative. The remaining 1,980 do not have the disease. Of these, 90 percent, or 1,782, are expected to test negative and 10 percent, or 198, are expected to test positive. Taken together, these data mean that 217 (19 + 198) individuals are expected to test positive, but only 19 actually have the disease. Thus, the likelihood that a person with a positive test actually has the disease is 19/217, or 8.7 percent, a surprisingly low number.

Suppose the prevalence of the disease is much higher, say 30 percent. If you repeat the analysis above, the likelihood that a person with a positive test actually has the disease rises to 80 percent.

How can Bayesian analysis be applied to scientific results? The article in The Economist (2) assumes that scientific hypotheses have a false positive rate of 5 percent (based on the widespread use of a p value of 0.05 when testing statistical significance) and a false negative rate of 20 percent. To complete the analysis, the authors have to assume a value for the equivalent of the prevalence of the disease. This is referred to as the "prior probability" in the general case. The authors assume a value of 10 percent, meaning that 10 percent of the hypotheses deemed interesting enough to investigate are, in fact, correct. Based on these parameters, in a sample of 1,000 studies, the number of hypotheses that are true and that are found to be true is expected to be 80, while the number of hypotheses that are false but appear to be true will be 45. Thus, the percentage of hypotheses that appear to be true but are not will be 45/(80 + 45), or 36 percent. If one accepts all of the assumptions, this analysis provides an explanation for why a significant fraction of published papers cannot be replicated.

Given both the empirical data and this statistical analysis that suggests that the phenomenon of important studies that cannot be replicated is real, what should the scientific community do? First, we must take ownership of the issue. Denying that the lack of replicability is not an issue or that it does not affect any particular field in the absence of compelling data supporting this conclusion is not an effective strategy and is likely to involve a substantial amount of wishful thinking or self-delusion.

Second, each researcher has a responsibility to ensure that his or her own published work is as reliable as possible within the limits imposed by resources and other constraints. In the Bayesian context, this will increase both sensitivity and specificity. Some of the published analyses include anecdotes in which investigators, when confronted with the lack of replicability of one of their published works, made comments indicating that the experiment "worked" only one out of 10 times but that successful result is the result that they published. In addition, each researcher should make sure that the experimental sections of his or her papers are as complete as possible and highlight those details that are particularly important for obtaining the results described. The responsibility also falls on the reviewers and editors of manuscripts, who must do their parts to make sure that manuscripts do not contain clear flaws and include adequate information to allow experimental replication. The fact that most journals are now largely or wholly online facilitates the inclusion of adequate experimental details.

Third, the community should find effective mechanisms for sharing the results of replication experiments, both successful and unsuccessful. Some small-scale projects in this area already are underway, particularly in the area of post-publication review. For example, the new electronic journal eLife (4) includes a comment section for each article, where, in principle, researchers can ask questions about procedures or describe their own experiences. The National Institutes of Health, through the National Center for Biotechnology Information, is experimenting with PubMed Commons (5), a vehicle to allow members of the scientific community to comment on papers within PubMed. PubMed Commons is in an invitation-only pilot phase now but will expand if the pilot is deemed a success.

In addition to these mechanisms, journals and funding agencies should consider carefully their policies with regard to the performance and publication of successful and unsuccessful replication experiments. Replication studies never will be as sexy as novel findings, but they are important for the scientific enterprise, and addressing some of the disincentives for performing or sharing these results could provide considerable benefit.

The imperative for taking on these issues is highlighted in articles that have appeared since The Economist articles. For example, the Los Angeles Times published an article titled "Science has lost its way, at a big cost to humanity" (6). It highlights some of the data discussed above as well as some of the potential responses. While we must be careful not to overreact and set up unwise or overly burdensome policies or waste valuable resources, we must keep in mind that the credibility of scientific results and the scientific process is one of the most valuable assets that we, as members of the scientific community, have. This is essential for our role as a largely publicly funded enterprise and, most importantly, for our ability to contribute to the solutions of important problems.

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Year in review

BY BENJAMIN CORB

Jazz composer Duke Ellington once said, "A problem is a chance for you to do your best." In 2013, thanks to questionable decisions by lawmakers in Washington, members of the the American Society for Biochemistry and Molecular Biology and the Public Affairs Advisory Committee were presented with massive problems and several opportunities to do our best.

In August, the ASBMB issued the report "Unlimited potential, vanishing opportunity," which for the first time provided lawmakers with data and anecdotes together telling of the difficulties scientists are having and witnessing as federal investments in science continue to get squeezed (1).

The report was a watershed moment for the ASBMB's advocacy efforts and garnered national and international attention. The report generated hundreds of news stories, and leaders such as National Institutes of Health Director Francis S. Collins and President Obama took to their Twitter accounts to share the findings with their followers.

The ASBMB became a leading voice on the impact of sequester on the scientific community, taking part in meetings with congressional leadership and presenting its findings to senior White House officials.

In November, the ASBMB authored the science chapter of a comprehensive report on the nationwide impact of sequester coordinated by the group NDD United titled "Faces of austerity: how budget cuts have made us sicker, poorer, and less secure" (2). ASBMB members participated in composing both reports, responding to surveys for the ASBMB report and serving as the focus of a vignette published in the science chapter of the NDD United report.

In addition, ASBMB members from 26 states took science advocacy into their own hands and participated in the second year of the 100 Meeting Challenge. In 2012, the first year the ASBMB encouraged its membership to meet with elected representatives in home districts, members conducted 44 meetings. In 2013, members more than doubled their first-year participation, orchestrating 105 meetings.

Another 200 members took to the Internet and authored letters to the editors of their local newspapers, delivering a message that highlighted the valuable research they are doing and the importance of robust federal investment in science research.

In October, as the government shut down operations for the first time in 17 years, the public affairs office turned its blog (3), the ASBMB Policy Blotter, into a real-time news source on the government shutdown and science-funding agencies' responses and procedures.

Readership of the blog sky-rocketed, with more than 3,000 daily visitors seeking the latest information on, for example, the status of research projects on the NIH campus during the government shutdown and how the National Science Foundation was dealing with the shutdown. And when the shutdown ended, we provided information on the rescheduling of grant reviews as quickly as information became available from NIH.

The public affairs office and PAAC will be working harder in 2014 to capture the voice of the ASBMB membership and to educate lawmakers on the impact their decisions have on the scientific enterprise.

In March, we will hold our next Capitol Hill visit day, bringing scientists from across the nation to Washington to meet with lawmakers and discuss policies that would benefit the biomedical research community.

At the ASBMB annual meeting in April in San Diego, the PAAC will present its vision on how to build a sustainable biomedical research enterprise, an effort that will continue to be refined throughout 2014.

And the public affairs staff will continue to strive to engage members across the country in advocacy efforts through training webinars, teleconferences with leaders in the administration, and new and creative ways to communicate with elected leaders at the local level.

As 2013 ends and we look ahead to 2014, I'll leave you with a quote from the immortal Oprah Winfrey: "Cheers to a new year and another chance for us to get it right!"

Benjamin Corb (bcorb@asbmb.org) is director of public affairs at ASBMB.

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Hood wins Research!America award

BY KAUSIK DATTA

HOOD

An innovator and pioneer in many biomedical fields, Leroy Hood has been honored for his life's work with the 2014 Geoffrey Beene Builders of Science Award instituted by Research!America, a nonprofit education and advocacy alliance based in Alexandria, Va. This accolade is the latest to recognize Hood's seminal contribution to genomics research, including the mapping of the human genome.

A visionary physician-scientist, Hood fostered the evolution of automation in wide-scale studies of genes and proteins, developing instruments (including the DNA sequencer) to bring ease and efficiency of performance as well as precision in genomics and proteomics research, thereby revolutionizing these fields of science, which regularly generate and parse immense amounts of information.

For these accomplishments, Hood earlier received the 2002 Kyoto Prize, the National Academy of Engineering's 2011 Fritz J. and Dolores H. Russ Prize (considered the pinnacle of bioengineering honors) and the 2011 National Medal of Science.

Hood also has advanced humanity's knowledge of the genetics and structure of antibodies, which earned him the 1987 Lasker Award, and made significant contributions to neurobiology. In addition, he developed the field of systems biology, bringing computational approaches to biomedicine and visualizing human health as a sum total of various networks, which was recognized by the 2006 Heinz Award.

Choudhary named EMBO young investigator

CHOUDHARY

Chunaram Choudhary of the University of Copenhagen was one of 23 young researchers honored this year by the European Molecular Biology Organization. The program supports researchers under 40 years old who established their first labs within the past four years. As an EMBO young investigator, Choudhary will receive 15,000 euros annually for three years. The program also includes lab-management and other professional-development training, access to core facilities at the European Molecular Biology Laboratory, and funding for meeting attendance and travel.

Hirschberg wins 2013 Rosalind Kornfeld Award

HIRSCHBERG

Carlos Hirschberg, a professor and the founding chairman of the Boston University Goldman School of Dental Medicine's molecular and cell biology department, has been honored by the Society for Glycobiology with the 2013 Rosalind Kornfeld Award. The award is issued to researchers who have made significant contributions to the field over their lifetimes. In a statement, the society said that Hirschberg's "work is so well established and so much part of the standard description of glycosylation processes that some take it for granted. No textbook figure or review article diagram of glycosylation in the secretory pathway can be drawn without showing the essential roles of the transporters Hirschberg and his group identified." In short, Hirschberg's team is credited with determining how nucleotide sugars cross biological membranes; discovering novel transporters in the membranes of the Golgi apparatus and the endoplasmic reticulum; and purifying, cloning and elucidating the mechanisms of several multi-transmembrane spanning proteins. Also, his group purified, cloned and functionally expressed, for the first time, the heparan sulfate N-sulfotransferase and demonstrated that is has N-deacetylase activity.

Six members elected to Institute of Medicine

- Phyllis A. Dennery, University of Pennsylvania and The Children's Hospital of Philadelphia
- Eric R. Fearon, University of Michigan, Ann Arbor
- Richard D. Kolodner, Ludwig Institute for Cancer Research
- Danny Reinberg, Howard Hughes Medical Institute and New York University School of Medicine
- J. Evan Sadler, Washington University School of Medicine, St. Louis
- Christopher A. Walsh, Howard Hughes Medical Institute, Boston Children's Hospital and Harvard Medical School

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

ENTROPY HAPPENS

BY THOMAS E. SCHINDLER

After 11 years in biomedical research, I tried teaching. I enrolled in an accelerated alternative-certification program in Connecticut. In my first job, I taught biology at Farmington High School. A few months into my new career, my 4-year-old daughter was diagnosed with cancer.

In November 1993, I took Hannah to the pediatrician because of a trivial complaint. During the routine exam, her doctor felt a mass in Hannah's abdomen. The subsequent X-ray looked suspicious, so he recommended that Hannah have a sonogram at the university medical center.

The next day at school I got the call: a large abdominal tumor, either Wilm's or neuroblastoma. Two days later, Hannah was hospitalized for the surgical biopsy. During the pre-op exam, they noticed a swelling at the base of her neck — the left supraclavicular lymph node was swollen — suggesting that the cancer had spread. The next day, Nov. 30 and my wife Susanna's 40th birthday, we learned that Hannah had stage IV neuroblastoma and a 12.5 percent chance of survival. My wife choked, "Do you mean Hannah is going to die?" Many times during the next year, I also feared the worst.

So began Hannah's ordeal of inpatient chemotherapy followed by the subsequent toxic effects: hair loss, fatigue, vomiting, fevers, transfusions and 10 days in isolation with shingles. Hannah also had her bone marrow "harvested," purified (of tumor cells) and stored for a future bone-marrow transplant.

During the hospitalizations, my wife and I spent hours in the medical library researching neuroblastoma. One oncologist who kept coming up in our literature searches was Audrey Evans at the Children's Hospital of Philadelphia. We had no idea that she would become the critical connection that saved Hannah's life.

In April 1994, we took Hannah to Children's Hospital in Los Angeles to have tumor surgery. We stayed for free at the deluxe Ronald McDonald House in Hollywood. The surgery, however, was unsuccessful. Because the tumor was wrapped around her aorta and kidney, it could not be completely removed without damaging the kidney.

Despondent, we returned home. A few weeks later came the miraculous connection. We were just sitting down to dinner when we got a call from Audrey Evans. She had heard about Hannah from Ed Rensi, then a vice president of McDonald's. Rensi, while serving on the board of directors of Snap-On Tools, met my mother at the 1994 annual meeting. My mother told Rensi that Hannah had just returned from staying at the Los Angeles Ronald McDonald House. Rensi immediately called Evans.

Twenty-two years earlier, Rensi and Evans had worked closely together to launch the very first Ronald McDonald House. What a surreal experience to get that call from Evans, then considered the grand dame of neuroblastoma! She spoke warmly about the one surgeon who could remove Hannah's tumor, Michael LaQuaglia. Evans said she wished that she could hire him away from Memorial Sloan-Kettering Cancer Center because he was such a good surgeon and a stellar human being.

Hannah had three more rounds of chemo that summer to further shrink the tumor. In early September, LaQuaglia's team successfully removed all of her tumor during an 11 ½-hour surgery. LaQuaglia was surprisingly humble, a rarity among cancer doctors. He almost shrugged, saying, "It's just what we do. We're cancer gnomes."

Even though the tumor had been removed from Hannah's abdomen, there was still the possibility that cancer cells could be lurking elsewhere in her body. She needed a bone-marrow transplant to prevent a recurrence.

Thomas E. Schindler with his daughter, Hannah.

Hannah had bravely suffered the grueling surgery and months of poisonous chemotherapy, but the bone-marrow transplant was by far the worst ordeal. We arranged to have the transplant at Children's Hospital in Cincinnati, because it had an excellent reputation and the people there were very interested in Hannah's case. At the time, most children who received allogeneic transplants died, but Hannah's doctors predicted much better results with an autologous transplant.

The term "bone marrow transplant" belies the horror of this cruel but effective treatment. First the patient is given a lethal dose of chemotherapy that obliterates her bone-marrow cells as well as her intestinal epithelia and mucous membranes. Then comes the "rescue," so named because without the transplanted bone-marrow cells the patient dies. Thus, we spent another Thanksgiving week at a hospital. But this time we could actually give thanks, because Hannah truly was recovering.

Although her growth was delayed by the year of traumatic treatments, Hannah thrived. She returned to school and normal life, though scarred and wizened by her suffering. Hannah has been cancer-free for nearly 20 years now. She graduated from Bard's College at Simon's Rock in 2010, married her high-school sweetheart, Adam, in 2012, and is now expecting her first child, due in April.

A teacher's schedule is better suited to raising a family than any other. We enjoyed many coincident vacations, especially in the summers. Teaching at the local high school meant that I eventually had both of my children as students in my chemistry class. We all successfully navigated this potentially loaded experience in our own ways: I fretted in anticipation, my son figured out how to hardly ever address me directly and Hannah naturally just kept calling me "Dad."

I chose to tell each of my classes about Hannah and her cancer, and I am glad that I did. Often students would want to talk to me privately about a parent or relative who had cancer. Our culture celebrates individualism and devalues the community of sufferers. That community has enriched our lives in many ways. What redeems our suffering is the empathy that connects us to each other when we share our hurts.

Thomas E. Schindler (tschindler.phd@gmail.com) earned a Ph.D. in immunology from the University of Illinois Medical Center in 1981. After a postdoctoral stint at Memorial Sloan-Kettering Cancer Center, he joined Xytronyx, a small biotech company in San Diego started by his graduate adviser, Peter Baram. He took a year off in 1992 to move back east and become a high-school science teacher. Since early retirement from full-time teaching in 2007, he has taught biology and microbiology in nearby community colleges. Now he is pursuing a new career: science writing. His first pieces have dealt with fascinating topics that he enjoyed relating to his students: buckyballs, prions, BEC and Archaea.

An open letter to our contributors

Dear ASBMB Today Writers,

"Publishing your work is important. Even if you are giving a piece to some smaller publication for free, you will learn something about your writing. The editor will say something, friends will mention it. You will learn." – Tim Cahill, founding editor of Outside Magazine, in an interview with travel writer Rolf Potts (1)

Those of us in the writing world talk (and write) a lot about why we should or should not give away our work for free. We will get clips, exposure and training. We will devalue an already undervalued field.

As editor of ASBMB Today, a nonprofit publication, I rely almost entirely on you, dear volunteer contributors. Some of you are seeking publications to beef up your CVs. Some of you are seeking experience so that you can move away from the bench. Increasingly, some of you are seeking a public forum in which to share personal stories seasoned by science.

No matter why you do it, I want to thank you. Thank you, on behalf of myself, our organization and our readers, for putting yourself through the terrifying and sometimes humiliating process of writing.

I know that what you do is not easy, and I know that your time is valuable. I also know that seeing your name and stories in print has its intrinsic rewards, but those don't put gas in your car. My hope, though, is that writing for ASBMB Today will pay off for you one day.

You deserve to be congratulated by your peers, colleagues and supervisors. For you have done what most don't have the guts to do: You've informed, entertained and comforted strangers at the risk of exposing yourself as imperfect and vulnerable, which of course we all are.

Sincerely,
Angela Hopp

Angela Hopp (ahopp@asbmb.org) is editor of ASBMB Today. Follow her on Twitter at www.twitter.com/angelahopp.

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An open letter to a professor who once comforted me

Dear Faculty Member of Johns Hopkins University,

You probably don't remember speaking to me that night. But you did, right by the cascade of shopping carts outside the grocery store in Baltimore.

I was a mess: unshowered, filthy hair pulled into an attempt at a ponytail and glasses because I couldn't fit contact lenses into my puffy eyes.

I had spent the past two days crying in my studio apartment. Forty-eight hours before, I had been handed my first and (since then) only academic failure. I had received a conditional pass for my Ph.D. qualifying exams.

I acknowledge that my exam evaluation had the word "pass" in it. But with the "conditional" thrown in, it might as well have been a "fail." To quote the TV show "Glee," it was the "Asian F."

Until that point, I had never fallen short of my efforts. The conditional pass scared me: Was I about to wind up as a cautionary tale about someone who thought she was better than she really was and ended up flunking out of grad school?

Crying requires energy, and I finally had reached the point when I needed more food to continue. So there I was, feeling so lost I couldn't decide if I wanted the shopping cart on the left or the right. I was blocking you. By now, the news of my conditional pass had swept through the basic sciences establishment. I may have been a student in the largest graduate training program at Hopkins, encompassing more than 90 laboratories, but gossip has a way of making a behemoth function like a small group of fishermen's wives.

All you said to get my attention was, "I heard, and I am sorry."

I turned around, surprised anyone would speak to me in my state, let alone offer sympathy. You stood there, kindness in your eyes. I tried to say something, but much to my alarm, the tears welled up again. You saw the tears and, still looking steadfastly at me with those blue eyes, said, "You'll get through this."

Oh, the power of words. I needed to hear that. I needed to hear that I would be fine from someone on the outside. My parents, friends, lab mates and thesis adviser all had rallied around me, but the cynical me felt they were vested in my success. You didn't have a stake in my future, but you seemed to think I'd bounce back. All I could do in response to your words was nod.

The next day, I returned to the lab. I was shaken and uncertain what was going to happen in the long run. But your words had the immediate effect of making me latch onto the task at hand. A month later, I aced the makeup test and qualified for a Ph.D. thesis.

The tailspin triggered by the conditional pass continued for a while as I grappled with what the sense of failure meant. I forced myself to reassess my life goals, skills and priorities over a year or two and eventually turned my trajectory and charted a different course. After all, you did say I'd get through it. And I did.

Thank you for taking those few minutes on that freezing February night to speak to me.

Sincerely,
Raj Mukhopadhyay

Rajendrani Mukhopadhyay (rmukhopadhyay@asbmb.org) is the senior science writer and blogger for ASBMB. Follow her on Twitter at www.twitter.com/rajmukhop.

"A good ambassador"

Hudson Freeze

BY RAJENDRANI MUKHOPADHYAY

A RECIPIENT OF THIS YEAR'S GOLDEN GOOSE AWARD FOR HIS DISCOVERY OF A SPECIAL BACTERIUM AND A WORLD EXPERT IN GLYCOSYLATION DISORDERS, HE IS SAID TO GO "BEYOND JUST SCIENCE."

Hudson Freeze almost didn't return the phone call he received to tell him he was one of the recipients of the 2013 Golden Goose award. "I got it as a recorded message from one of the people involved," he says. "I was thinking, 'Oh Lord, this is the prize patrol. I'll have to sign up for 15 different journals for two years, and they are going to give me some sort of prize for doing that,'" he says, laughing. "But I decided to call them back."

The Golden Goose award is given to scientists and engineers who have done federally funded research projects that appeared to be odd or insignificant at first but went on to have sizeable impacts on science and society. Freeze won the award along with his undergraduate research adviser at Indiana University, Thomas Brock, for a discovery that has changed how molecular biology research is done.

Freeze and Brock were the first to isolate Thermus aquaticus, which they recovered in samples they collected at Yellowstone National Park's hot springs during the summer of 1966. Thermostable Taq polymerase, on which the polymerase chain reaction is based, was later isolated from this bacterium.

The undergraduate project was a sign of Freeze's ability to do science that makes an impact. Over the course of his career, Freeze, now based at the Sanford-Burnham Medical Research Institute in La Jolla, Calif., has focused on glycosylation. "He's the world leader in the study of congenital diseases of glycosylation," says Gerald Hart of Johns Hopkins University. "What's really unique about Freeze's work is he's a hardcore basic scientist, but he applies his work to human diseases and actually treats children" with those diseases. Freeze's laboratory now does whole exome sequencing to identify as many genes as possible in patients with congenital glycosylation disorders. (Freeze says that, at his last count, there were 99 distinct congenital glycosylation diseases.)

So how does a person go from isolating a thermophilic bacterium to studying glycosylation disorders? It seems it starts with a curiosity about extreme and odd life forms.

"LIT A FIRE UNDER ME"

Freeze grew up in Garrett, Ind., with his parents and younger sister, Jackie. "Dad had graduated from high school probably near the bottom of his class, and Mom never graduated from high school," says Freeze. "But they were both bright, and they understood the importance of education."

Freeze's father worked as a brakeman and conductor on the Baltimore & Ohio railroad system, which was founded by John. W. Garrett, after whom their town was named. His mother stayed home to take care of Jackie, who is mentally disabled.

The high school Freeze attended had only 500 students. It was there that Freeze caught the science bug from Jack Bateman, who taught chemistry and biology. "He just lit a fire under me," says Freeze. "I remember the first day of biology class. He said, 'People, I'm going to take you on a very exciting trip. We are going to learn things, and believe me, you're going to work hard. But we are going to learn things that you will not even believe. You will not believe how interesting biology is.'"

Under Bateman's guidance, Freeze got hooked on astrobiology and won a science fair with his project about possible life forms on Mars. The interest carried him to major in microbiology at Indiana University. After his sophomore year of college, Freeze went to see Brock about a research assistant position. Brock asked him if he would like to accompany him to Yellowstone National Park to look for microorganisms in the hot springs. Freeze

was thrilled to be asked. His high-school interest in astrobiology in high school was still there, and the hot springs represented an extreme environment that promised to have interesting critters.

On that trip in August 1966, Freeze and Brock collected water samples from various hot springs over several days. Brock's cabin at the national park had a room turned into a laboratory where they prepped the collected samples and got them ready to be taken back to Indiana University. During the fall semester of his junior year, Freeze got down to the business of growing, isolating and characterizing the bacteria.

Initially, Freeze almost gave up on Taq. The first tubes of it he tried to grow had a dilute medium. Over a few days, there wasn't much turbidity, a sign of multiplying bacteria, in the tubes. At last, he spotted something at the bottom of one test tube: They were salt crystals. Freeze was disappointed, but he continued to let the tubes incubate in the hot bath. "A day or two later, I picked up another tube and looked at that. I said, 'Oh, more crystals.'"

But this time, Freeze decided to stick a few crystals under a microscope. "As soon as I got it under the microscope, there were these long strings of bacteria. It was the absolute thrill of discovery at that point because" — here, his voice drops to a stage whisper — "I was the first person in the world to see these things!"

I missed science...I thought, 'I can do something better than this.'

Freeze isolated Taq, put it in another medium, and experimented with its growth conditions. The description of Taq was his first scientific publication, which he coauthored with Brock.

GOING OFF SCRIPT

The fun with Taq spurred Freeze to continue on to graduate school at University of California, San Diego, in 1969. When he got there, Freeze fell in love with another peculiar organism called Dictyostelium discoideum. Its lifecycle captured his imagination. Known in everyday parlance as slime mold, the organism transforms from a collection of unicellular amoebae into a multicellular slug.

Under William Loomis' guidance, Freeze decided, for his Ph.D. thesis, to figure out how the surface sheath around the slime mold slug formed. He says, "It turned out that there were carbohydrates in there. I didn't know anything about carbohydrates."

Fortunately, another graduate student was knowledgeable about sugar analysis by gas chromatography, so Freeze teamed up with him. As Freeze's research progressed, he says, "What became important is that there were a number of different kinds of mutants that you could isolate in Dictyostelium."

Some of the mutants didn't make the surface sheath. Curious, Freeze began to investigate the enzymes involved in putting together the sheath. He eventually tracked down some mutations in lysosomal enzymes. Freeze says it wasn't clear how those mutations would affect a structure like the surface sheath, but he did note that there were abnormalities in some glycoproteins.

As Freeze was untangling how the slime mold put its sheath together for his Ph.D. thesis, he was also moving around in the Los Angeles entertainment business. "Clearly I wasn't a star and ended up as a scientist instead," he says self-deprecatingly.

Freeze had acted in high school plays and had decided to join a small acting group that did dramatic readings at independent coffeehouses. "This is in the early 1970s. Tom Waits was one time with us. This is when Tom Waits was completely unknown," says Freeze. "He was this weird guy who sat over by the piano, all hunched over."

Freeze caught the attention of a director looking to cast someone in the role of Brick, the lead male role in Tennessee Williams' "Cat on a Hot Tin Roof." Freeze balked at first, thinking he wasn't good enough. But then he agreed. As the show ran, the director introduced Freeze to a Los Angeles acting coach named Sal Dano. Dano told Freeze he saw potential in him as a mainstream actor, provided that he lost some weight and got himself an agent. Dano then invited Freeze to join the master acting classes he taught once a week in San Diego. Freeze was bowled over by Dano's confidence in him. "I was thinking, 'Get an agent! Oh my god! This guy is talking some serious stuff!'" recalls Freeze. "I got this boost that I never thought was possible. So, yeah, I joined Sal's class. I got pictures taken. I got an agent."

Freeze won a national acting talent search launched by Paramount Studios. He did commercials for JC Penney and the Chevrolet Corvette and modeled clothes. From those gigs, "I was making as much money from acting as I was in graduate school. But of course, that was only $2,000 a year at that time, not a big thing," he says. Freeze landed the lead role in an independent industrial film called "Forests for the People," which, when Freeze last checked, can be found only in the Maureen and Mike Mansfield Library at the University of Montana. "I'm sure it's protected by armed guards day and night," he quips.

But he soon had to make a decision on what to pursue, and the decision was relatively easy to make. "I missed science," he says. "I realized how stupid a lot of this stuff was that was going on in the [acting] business. I thought, 'I can do something better than this.'"

Hudson Freeze and his sister, Jackie.

FROM SLIME MOLD TO SICK KIDS

As Freeze continued on at UCSD as a postdoctoral fellow between 1976 and 1979, he kept at the problem of the mutated glycoproteins in the slime mold surface sheath. He eventually worked out that the glycoproteins were missing mannose-6-phosphate. Mannose-6-phosphate gave Freeze his first insight into clinical research.

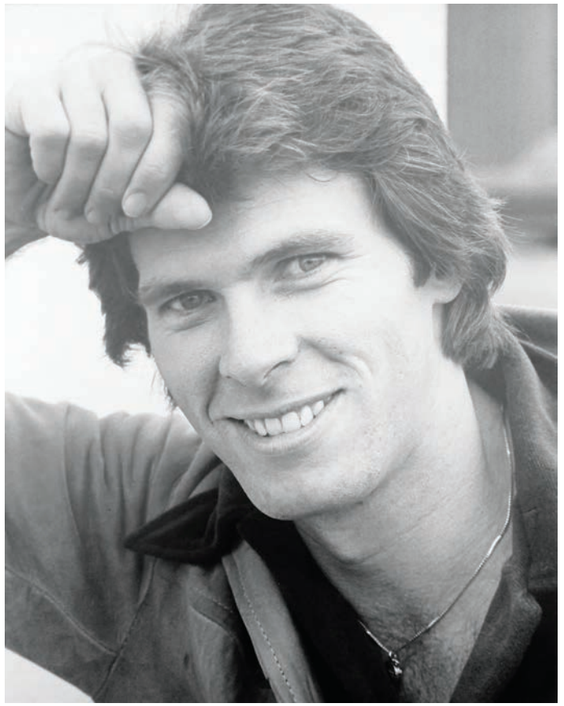
There is a human disorder called inclusion-cell disease, "which was mysterious back in the late 1970s," says Freeze. Around the time Freeze discovered that slime mold had mistakes in mannose-6-phosphate processing on some lysosomal enzymes, I-cell researchers also realized that the enzymes they were working with involved mannose-6-phosphate. Freeze spent a year at Washington University in St. Louis in the laboratory of Stuart Kornfeld, which focused on I-cell disease. "The environment at Wash U and in his lab was just mind-boggling. This lab worked around the clock. You had people on the day shift and on the night shift," says Freeze. "It was so exciting there. They were getting at some of the first biosyntheses of carbohydrates that were defective because of gene mutations."

Freeze made an impression in the Kornfeld laboratory. "Hud is a Midwestern boy," says Ajit Varki at University of California, San Diego, who had introduced Freeze to Kornfeld. "The day he was supposed to arrive in St. Louis, there was a blinding snowstorm. Everything was shut down. But he came driving through from San Diego in a Honda Civic, all by himself, without any trouble. We were so surprised to see him show up on that day!"

As Freeze worked in the Kornfeld laboratory, it became clearer that the work he was doing in slime mold could improve our understanding of human diseases. And the realization spurred a conundrum: Should he go to medical school to be better equipped to do clinical work or continue doing fundamental research? When he returned to San Diego, he decided to apply for both medical school and a grant from the National Institutes of Health. "Believe it or not, both of those things came through in the same week," says Freeze, still sounding surprised after all these years. But after some soul-searching, Freeze decided to stay in research, because he felt it would keep him challenged in the long run. Nonetheless, as he continued to work with slime mold glyco-

sylation, he kept his eye out for any human disorders that could benefit from his work.

The link between research in an amoeba and human disorders came in the mid-1990s. Varki had received some cells from a clinician. These cells had been taken from children who appeared to have glycosylation disorders. Freeze, collaborating with Varki, began to analyze the cells. "I did the same experiments on those cells that I would have done on my slime mold cells in terms of labeling sugar chains with radioactive mannose," says Freeze. "When I did that, I saw some of the human cells actually displaying the same kind of abnormalities that I saw in the slime mold. I said, 'Oh my God, this is the right kind of connection. There is something worthwhile here.'"



A young Hudson Freeze in the early 1970s.

Human glycosylation defects were largely unexplored territory at the time, and, because of that, Freeze found himself in an interesting position: "In the mid-1990s, there wasn't very much knowledge of glycobiology. You'd have to walk the country far and wide to find a glycobiologist. Physicians would say, 'Based on these little tests, I can see my patient has some glycosylation disorder, but none of my doctor friends knows anything about this. Where do I go?' They were forced to engage with basic scientists like me because of the vacuum that was there."

Over the past 17 years that Freeze has worked with congenital glycosylation disorders, he has met many patients. His office and laboratory walls are plastered with photos of children with these diseases. Freeze says growing up with his disabled sister has made him very comfortable around disabled children.

THE BOY IN GRAY LEDERHOSEN

There is one little boy who stands out the most in Freeze's mind. In the mid-1990s, Freeze had a couple of German medical students do fellowships in his laboratory. Their supervisor in Germany, Thorsten Marquardt, noticed a paper in which Freeze's group had demonstrated that they could correct a particular glycosylation defect in cells by simply adding mannose to the cell culture medium. Marquardt called Freeze to tell him that he was caring for a 6-year-old boy who had an unknown glycosylation defect, but the defect probably was different from those in the cells Freeze's group had studied. The boy was in an intensive-care unit in Munich with unstoppable gastrointestinal bleeding. He was close to dying.

'"We will do anything. Do you have any idea how much mannose you might give him?'" Freeze remembers Marquardt asking him.

Just two days before, Freeze and his colleagues had finished the calculations on some data. Freeze had received permission from the U.S. Food and Drug Administration to test mannose as a potential drug. He and several of his lab members spent two weekends holed up in the conference room, drinking solutions of mannose and then measuring its concentration in their blood over the course of the day to understand its pharmacokinetics. Based on the numbers they had crunched, Freeze was able to tell Marquardt how much mannose solution to give to the child over a period of time. But he told Marquardt he had no idea if the treatment would work, wished him luck and hung up the phone.

Over the next eight months, as the boy's doctor gave him solutions of mannose based on Freeze's calculations, the boy got better. The gastrointestinal bleeding stopped within the first few weeks, and his chronic diarrhea came to an end. Freeze was incredulous when he heard the news. He was certain that the mannose was a red herring and something else had reversed the boy's symptoms.

On his next trip to Europe, Freeze stopped off in Munich to meet the boy's doctor as well as the boy and his mother. "This kid shows up in gray lederhosen. He was the cutest thing you ever saw," says Freeze. "The doc was very protective of him, and he showed me the improvement of clinical symptoms after the boy was on mannose. We said, 'Yeah, that is improvement!'"

But they still didn't know why the mannose treatment was working. The null experiment would be to stop giving the child mannose and see what happened, but that experiment would be unethical. "We went down to the beer garden, and the doc said, 'Look, I'm keeping him on mannose. You do whatever you need to do, but we're keeping him on mannose,'" says Freeze. Then Freeze, Marquardt and the two German students who had spent a stint in Freeze's laboratory began to muse over beers what could be happening in the boy.

Freeze had received some of the boy's cells months earlier so that his team could analyze them. Before he had left on his trip, they had noticed that the boy's cells incorporated more radioactive mannose on the glycoproteins than the control cells when the cells were fed radioactive mannose by cell culture. That was an important clue.

Normally, mannose-6-phosphate is derived from glucose through a series of steps. One of these steps is the action of phosphomannose isomerase on fructose-6-phosphate to make mannose-6-phosphate. (The enzyme can work in reverse and convert mannose-6-phosphate into fructose-6-phosphate.) Mannose-6-phosphate eventually winds up in glycoproteins.

In the beer garden, Freeze wondered out loud if the boy had a mutation in phosphomannose isomerase that meant his body couldn't make mannose-6-phosphate from fructose-6-phosphate.

"Well, I was on vacation," says Freeze. The two medical students who already had returned to Germany from their stint in Freeze's lab stayed up day and night running assays on the boy's cells. When he returned to San Diego, "they called me at the equivalent of midnight their time. They said, 'We got it. You were right. It was phosphomannose isomerase.'"

The boy had a mutation that made phosphomannose isomerase work inefficiently. "Now it all made sense," says Freeze. The mannose treatment was overcoming the inability of phosphomannose isomerase to make mannose-6-phosphate. The mannose fed to the boy was being converted into mannose-6-phosphate by other enzymes and allowing the N-glycosylation of necessary proteins to proceed. The boy's particular disorder is now known as congenital glycosylation disorder Ib, or CDG-Ib for short. The boy has since grown into a young man.

Varki notes this success story has a dark underlining. "Unfortunately that kind of work was taken advantage of (by) charlatans who sell large quantities of sugars on the web, saying that healthy people need seven essential sugars and all that nonsense," he says. "Hud and Ron Schnaar, who was president of the Society for Glycobiology, actually took the trouble to go on ABC News' '20/20' once and talk about this problem. It is really damaging our field."

Varki says that Freeze has done all he can to shut down those fraudulent outfits, who are armed to the teeth with lawyers. He adds the fact that Freeze takes the trouble to try to rein in unwelcome consequences of his work shows "he has a sense of commitment that goes beyond just science." Varki also points out that outreach and advocacy for science are important to Freeze; he is the vice president-elect for science policy at the Federation of American Societies for Experimental Biology (the American Society for Biochemistry and Molecular Biology is a member organization). "He's the perfect person for it, because he's very articulate and thoughtful," says Varki. "He's a good ambassador for science."

Freeze says he still uses what he learned from his acting days to give scientific lectures and engage audiences when doing science outreach. Varki and Hart report that Freeze is known to pull out a guitar and perform rock songs at conferences. When he's not traveling, Freeze spends an evening every week as a tenor in a black gospel choir ("I'm the white pixel in the choir picture," he notes). He loves gospel because "it has so much heart and soul." He pauses briefly and then says, "Because you want to give, emotionally, everything you can."

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Meet Eric Fearon

A new associate editor for the Journal of Biological Chemistry

BY RAJENDRANI MUKHOPADHYAY

In January 2013, Eric Fearon at the University of Michigan Medical School joined the ranks of the associate editors at the Journal of Biological Chemistry. Fearon has a longstanding interest in the molecular mechanisms underlying colorectal cancer progression. American Society for Biochemistry and Molecular Biology science writer Rajendrani Mukhopadhyay spoke with Fearon to learn more about his research, career path and hobbies. The interview has been edited for length and clarity.

Could you briefly explain what your research group works on?

My group works on trying to understand the molecular pathogenesis of colon and rectal cancers. We use a variety of approaches, predominantly now mouse models and some cell-culture-based work. The strategy is to understand what some of the genes that are recurrently mutated in human colorectal cancers do in terms of altering cell phenotypes of the epithelial cells. We study some of the common genes that are mutated, such as the adenomatous polyposis coli tumor suppressor, k-RAS, p53, PIK3CA and so forth. We're trying to understand what the genes do individually and what they do when there are the kinds of combinations of mutations that one sees in primary human colon cancers. It takes us a little bit into the Wnt pathway, the PIK3CA pathway and the MAP kinase pathway and how these pathways talk to one another collectively in cells.

How did you become interested in this topic?

I've had a longstanding interest in the genetics of cancer from the time I was a graduate student at Johns Hopkins University in Bert Vogelstein's lab. I worked on a variety of topics during my time there but spent a lot of time trying to understand how stepwise or accumulated genetic alterations might contribute to the initiation of colon adenomas and their progression to carcinoma.

What happened in your life that made you choose science as a career?

I don't know exactly if there is one event in anyone's life that crystallizes the decision. But I was an undergraduate at Johns Hopkins in the biophysics department and thinking I might be interested in pursuing research. My undergraduate adviser, Skip Hunt, who was a neurobiologist in that department, encouraged me to do research. I chose Warner Love's crystallography lab, which turned out to be a fabulous place to pursue research as an undergraduate. I found that I really enjoyed the technical aspects, working with my hands in the lab and thinking and reading about science. But I didn't have the skill set to become a crystallographer at that point, even though I thought structural biology was really an amazing area of science! I continued to dabble a little bit during the day and on the weekends in that laboratory but also started doing some molecular genetics work with Haig Kazazian down at the medical school. I was working on a large deletion of the beta-globin locus in a family with a severe form of thalassemia. It was due to a deletion of not only the adult beta-globin gene and the delta-globin gene but also the fetal globin genes. That really got me excited about the potential power of molecular biology. When I searched around for laboratories to continue working in, I thought I could try to apply recombinant DNA techniques to understand some of the genetic lesions that might be present in human cancer cells. That steered me to the Vogelstein lab. So my interest in science originated pretty early on in my sophomore year of college. I thought science was really amazing thing – you could get an opportunity to pursue these fundamental questions of biology and maybe even earn a living at it!

Did you grow up in Baltimore?

No, I grew up in what, by most standards, would be viewed as a small town. I grew up in a town in Maine called Farmington, which is about 45 miles or so from the New Hampshire border and about 65 miles from the Quebec border. It was a great place to grow up, because you got to experience, as people in Maine say, all four seasons!

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

I find it a great privilege and an honor to be invited. The people who've served on the editorial board at the JBC and continue to serve are among, from my point of view, some of the most outstanding people in biological science. It was a great honor to be an editorial board member for five years or so. When I was invited to be an associate editor, I readily accepted, because I thought it would be another way to think about science and try to contribute to the field. I find it fun because it is an opportunity to read papers pretty much from any area of biology. I really like reading about how other people are doing science, because it informs how I think about my own science.

Do you have any hobbies?

I'm really excited about coming into work every day, but I'm one of these people who like to have other hobbies outside the lab. I still cycle some. I don't tend to ride to work. I tend to ride out on the road, sometimes early in the morning or on the weekends. I probably ride a little over 120 miles a week. Compared to most cyclists who cycle seriously, that's only a middling interest. It's a good chance to think about problems while you are out riding on your own. I play a little bit of golf, but I'm not very good at it. I have some dogs, which take up a lot of my time. I have two big rescue Weimaraners who are good guys. One is 9 ½ and the other is about 2 ½, so they are busy guys, as most Weimaraners are.

What advice would you give to younger scientists?

The one piece of advice that I got, and I still think it's really true, is to read as many papers and to read as broadly as you can. It's a way always to have potentially new insights into challenges you may be facing. It gives you a sense of how other people have come before you and how other people now are thinking about scientific problems – how they pursue them, write about them, synthesize the data and present it. That's what's fun about being a journal editor, because you get to do that pretty much every day.

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Meet Henrik Dohlman

A new associate editor for the Journal of Biological Chemistry

Henrik Dohlman, a professor at the University of North Carolina at Chapel Hill, recently became an associate editor for the Journal of Biological Chemistry. This is a partial transcript of a podcast in which John Kyriakis, a longtime associate editor of the JBC, interviewed Dohlman about his research, role at the journal and predictions for the field of biochemistry. The interview has been edited for length and clarity.

You've been studying yeast for a while. What is the work that you're currently doing?

The process that we're interested in, desensitization, is characteristic of signaling pathways that respond to hormones, neurotransmitters, drugs — including drugs of abuse — and environmental signals like odors and light. These are all mediated by G-protein–coupled receptors, or GPCRs.

You started out in (2012 Nobel laureate Robert J.) Lefkowitz's lab many years ago.

I was a grad student at Duke (University) in the Lefkowitz Lab in the '80s. I actually started off as a chemistry major, and I decided to switch to biochemistry for grad school. I sort of came to the realization in college that most of the great discoveries in chemistry were made before I was born, and while this was in the early days of molecular biology, I figured that's where the action was going to be in the future. So I switched to biochemistry. I went to grad school at Duke. I ended up in the lab of Bob Lefkowitz, who was and remains one of the leading figures in the GPCR field.

In those days, there was a big effort in the lab to purify and clone the β2-adrenergic receptor. That's the receptor for epinephrine or adrenaline, and that was one of the first GPCRs to be cloned, and it was the early days of molecular pharmacology. People for the first time had a sense of what these things look like, and you could study them in isolation … (I)t was a very exciting time to be in that laboratory. It was actually in that lab that I got interested in this question of feedback regulation … I got interested in looking at this, taking a genetic approach, and that's actually how I ended up working with yeast, which is a great system for doing genetics.

Now, where did you do your postdoc?

So I got interested in yeast, and so I was looking around for a yeast lab, and I ended up working at (the University of California, Berkeley) with Jeremy Thorner. I picked Jeremy's lab because, of course, it was a leading yeast lab, and Jeremy's background was actually in biochemistry …

I was interested in identifying genes that might be involved in desensitization of the GPCRs in yeast. This was in the days before knockout mice. (It) didn't ever occur to me to do this in an animal cell, but I got interested in trying to find desensitization factors in yeast, looking at them genetically and then integrating that with some biochemistry.

I know often people come on these career choices after some sort of revelation or something happens where suddenly something clicks or it's sort of a slow kind of a realization. What was the situation for you?

I would say that being a scientist is in my genes. My father and my grandfather were both academic researchers … My grandfather had done some pioneering work with the Nobel laureate Robert Bárány in Sweden in the 1920s. They were looking at the connection between the inner ear and balance, and he continued to do bench work well into his 70s and 80s. My father is 91, and he continues to have an active research program … And even my brother had done some influential work in the field of immunology, so I was just sort of surrounded by it growing up, and these were my role models. And actually, come to think of it, my other grandfather, he grew up upstairs from his father's brewery back in Sweden, and so I guess you could say that working with yeast is also in my genes.

The other great use for yeast. So how has the experience (as a JBC associate editor) been so far?

It's actually been very interesting to … peek behind the curtains and see how the journal operates. And so far, it's been very seamless. The JBC has a great support staff, as you know, and they have been very patient with me as I learn the system. It's been a very interesting process.

So you're happy that you were picked to do this? Did you think it would be a fun time or – ?

Absolutely. The JBC is the flagship journal of the society … I've long been a big fan of the journal. I like the fact that it's run by a scientific society. It's a democratic operation. It's a journal of the people, by the people, for the people. It exists to serve the research community, and that's very appealing to me. The other thing I like about JBC is it has a great history. It's been around for more than a century, and yet it's been the real innovator in Web-based submissions and reviewing and digital publishing and digital archiving. I imagine that was a pretty risky move for the journal, and maybe it wouldn't have happened if it was a for-profit operation, but these are innovations ... they've accelerated the time to review and to publish articles, and so that speeds up the dissemination of knowledge.

Where do you think the field of biochemistry is going?

The sequencing of the human genome, more than a decade ago, in many ways that was a relatively easy task scientifically, technically, compared to where we are now, where we're trying to figure out what all of those genes encode and how those proteins encoded by the genome are alternatively spliced, and then when the proteins are made, how they're modified and how they figure out where to go in the cell and whom to associate with in the cell.

All these questions of protein expression and localization, modification and regulation, sorting out their functions, and how they are dynamically

regulated — these are the challenges that are going to keep us occupied for the next century. I think this is a very exciting time to be a biochemist.

Yeast becomes a way … to bridge between the single molecule, in-depth, insightful work and the overwhelming mountains of genomic or structural data that are coming down the line. So that's what you're seeing now, or that's where your vision for your particular field is?

So the yeast community is getting access to these databases and these new technologies ahead of most other systems … And, of course, the technology, if it can be worked out in a simple system like yeast … will guide how more complex systems are analyzed. For example, the Yeast Genome Sequencing Project: That was done in the mid-'90s. (T)hat's a situation where there are very few introns, and it's very easy to figure out where they are. But even then, it was a huge task to annotate the information that was emerging from that effort and then all of the other things that were related to that — all these microarray studies and these proteomic studies.

The yeast community has been really proactive in developing bioinformatics tools that have made my life as a researcher much easier, and they have guided similar efforts in other systems, in other model organisms, everything from flies and nematodes to mice and humans.

We also have lives outside the lab. Is there anything that you do for fun?

I really like my job, and it's sort of what I think about when I go home. I'm embarrassed to say that I live a pretty, pretty narrow existence. I jog every morning, and I like to travel and go on hikes. I'm close to my family, and I feel like I have a great life, but science is a big part of it. So I would say science is not only my job, but it's my hobby, and if that sounds really geeky, that's –

No, it doesn't. I think, actually, in this day and age, it's got to be both, given the difficulties that the community is facing. If you're going to be doing it in the academic world, it's got to be 24/7. You have to really love it because, you know, with all the walls that they're putting up, if that becomes more of a burden than actually doing the science, then what's the point?

There are a lot of challenges to being a scientist today. There's no doubt about it, and funding is a big one. But to be successful as a scientist, my experiments will fail; my papers will get rejected; my grants will get turned down. And all you do is come in the next day, and you have this hope that the experiment will work and the paper will get resubmitted and accepted and your grant will get funded.

You hear a lot of complaining in labs. People are whining that their experiment didn't work or something didn't happen, but I think scientists are the most optimistic people to just come back, as you say … And it's just sort of a tremendous privilege to be able to do this.

If I had to pick one word to describe my existence, it's "privileged." I feel so lucky to have this job and to be able to do what I do and to look forward to coming into the lab in the morning. There are a lot of people who cannot say that about their jobs, and I feel really lucky that I'm one of the people that can. And I wish for nothing less for my students and my children.

I'm at the point in my career now where I learn as much from my students as they learn from me, and that contributes a lot to my enjoyment of this job.

THE JOURNAL OF LIPID RESEARCH

New biomarker for diagnosing patients with degenerative eye disease

BY MARY L. CHANG

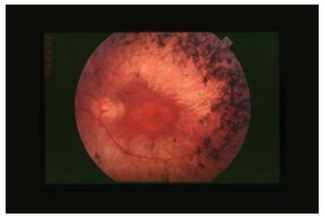

IMAGE CREDIT: CHRISTIAN HAMEL, CREATIVE COMMONS COORDINATOR

Fundus of patient with midstage retinitis pigmentosa.

Retinitis pigmentosa is an inherited eye disease that causes progressive loss of vision, sometimes leading to blindness. In a study published in the December issue of the Journal of Lipid Research, Rong Wen, Byron L. Lam and Ziquiang Guan of the Bascom Palmer Eye Institute at the University of Miami report that patients with retinitis pigmentosa have increased levels of the compound dolichol-18, compared with healthy individuals. Their study suggests that dolichol profiling could be adapted for use in tests to diagnose patients with the disease as well as to identify carriers of the causative gene.

Dolichols are long-chain alcohols containing multiple isoprene units. While the functions of free dolichols are unknown, the enzyme dehydrodolichol diphosphophate synthase, or DHDDS, is known to have paramount importance in the early stages of dolichol synthesis.

The researchers previously discovered a single nucleotide mutation in the gene that encodes DHDDS; this mutation leads to an amino acid change that has been established as the cause of autosomal recessive retinitis pigmentosa in the Ashkenazi Jewish population. The mutation results in abnormal dolichol metabolism.

In this study, urine and plasma samples from retinitis pigmentosa patients and carriers of the gene were analyzed with liquid chromatography-mass spectrometry. In patients, dolichol-18 was found to be the dominant dolichol species, whereas in healthy individuals, the normal dominant dolichol species was dolichol-19.

The researchers assert that their method of examining the ratios of dolichol-18 to dolichol-19 is a more useful measure than traditional genotyping, because it enables the clinician also to observe whether dolichol metabolism has been affected. Abnormal dolichol metabolism is suggested to be related to other neurodegenerative disorders, such as Alzheimer's disease, so Wen et al.'s finding that dolichol profiling could be useful in evaluating the efficacy of treatments designed to correct such abnormal metabolism shows promising clinical potential.

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jbc THE JOURNAL OF BIOLOGICAL CHEMISTRY

Harry F. Noller's 'Reflections'

One, two, three dimensions of ribosome function

BY SOO HEE LEE

Harry F. Noller reflects in the Journal of Biological Chemistry on his lifelong pursuit of cracking the functionality of the ribosome, via its structure, culminating in the aha moment when a "chubby L-shaped density appeared in exactly the position that we had predicted for the A site."

Noller's story starts more than half a century earlier, during his childhood in East Bay, Calif., in the era of the atomic bomb, the science fiction of Robert Heinlein and Arthur C. Clarke, and local newspaper headlines touting revelations on "the secret of life" in the test-tube reconstitution of the tobacco mosaic virus. Musings on these and other elements of science, both fantastic and real, marked Noller's youth. It is not surprising, then, that as a high-school student Noller decided one day to drive up to the University of California at Berkeley, where he told a receptionist he wanted "to find out about biochemistry." He was welcomed to the office of professor Donald McDonald, who spent an hour kindly satisfying his curiosity, thereby influencing his decision to major in biochemistry at Berkeley.

Noller graduated in 1960 and worked as a lab technician for a year before attending graduate school at the University of Oregon, where he trained as a protein chemist. After receiving his Ph.D. in 1965, Noller started a postdoc at the Medical Research Council Laboratory of Molecular Biology in Cambridge, U.K., determining the amino-acid sequence of glyceraldehyde-3-phosphate dehydrogenase. A year later he was doing a postdoc at the University of Geneva,

Left: Harry Noller in his laboratory at UCSC as an assistant professor in 1970.
Right: Noller on sabbatical in Cambridge in April 1976, holding the autoradiogram of his first successful DNA sequencing gel.

working with Alfred Tissières on ribosomes. Noller's new line of inquiry was fueled by a chance encounter with Sydney Brenner, also then at the MRC, at a tweed-and-sherry party. Brenner was part of the team in 1961 that genetically demonstrated the triplet nature of the translational code. At the party, Brenner said to Noller, "If you're a protein chemist, why don't you work on something interesting, like ribosomes?" Noller writes in his "Reflections" article that he realized "you can spend your life and career working on something boring or something exciting." So he read up on ribosomes. In Tissières' lab, Noller confirmed that the numerous bands isolated from the 30S and 50S ribosomal subunits were indeed different proteins; outside of the lab, Noller could be found playing jazz saxophone across Europe.

Noller became a faculty member at the University of California, Santa Cruz, in 1968, a time when the ribosome was known as a multienzyme protein complex, and the notion that RNA is enzymatic was downright preposterous.

At UCSC, "there were not a lot of 'experts' around to discourage you from going in unusual directions," Noller writes. His lab tested modification reagents to knock out ribosome activity. Successful inactivation with Rose Bengal, which targets histidine in proteins and guanine in RNA, led Noller's team to test a guanine-specific reagent, kethoxal, which left the ribosomal proteins active but the ribosome inactive. Additionally, the lab showed protection from kethoxal inactivation with prior tRNA binding. The lab quickly identified the kethoxal-modified guanines and spent the next decade identifying the tRNA-protected sites.

During this time, finding more than half of the published sequences incorrect, Noller came to terms with having to sequence rRNA. Multiple events influenced his approach. In 1975, Noller went on a three-part sabbatical to three different institutions. During the second leg, at the University of Geneva, he serendipitously ran into Joel Kirschbaum, who happened to have a λ transducing phage containing the entire rrnB operon and who taught Noller how to grow the virus and extract the DNA. During the third leg of his sabbatical, in Fred Sanger's lab at the MRC in Cambridge, Noller learned DNA sequencing from Bart Barrell. Moreover, Wayne Barnes in the lab taught him to clone his DNA into ColE1 plasmid using restriction enzymes.

He recalls, "I had the eerie sensation that everything was falling into place guided by a mysterious force." The final event was a "crucial conversation with Jürgen Brosius at a sidewalk café in Geneva." As a result, Brosius came to do postdoctoral research with Noller and set up a system of running 16 sequencing gels a day. Noller's team thus finished the 16S rRNA sequence, the sequence of the 23S rRNA and then all of the rrnB operon.

The team next determined rRNA secondary structure by sequencing several phylogenetically distinct 16S and 23S rRNAs. To this end, the lab purchased a Sun Microsystems workstation with an 86-MB hard drive and recruited an undergrad to develop a multiple-sequence alignment

program. Carl Woese, at the University of Illinois at Urbana-Champaign, and Noller together used an approach they called "red dot-green dot" to visualize complementary sequences showing mirror-symmetric patterns of red trans-versions and green-dotted transitions.

Because the protein-centric view of ribosome function still pervaded, Noller's group studied rRNA with little competition for a decade until the 1980s, when self-splicing introns were discovered. From the work of his students Danesh Moazed, Seth Stern and Ted Powers "came the hybrid-states mechanism for translocation, the placement of antibiotics in functional sites in the ribosomal RNA, and an initial model for the three-dimensional folding of 16S rRNA," Noller notes. Jostled by future Nobel laureate Phil Sharp's 1987 quip – "So, Harry, why don't you nail it?" – Noller performed his seminal work, published in the journal Science, from whence the function of enzymatic rRNAs became widely accepted. He showed peptide bond formation from SDS-treated, SDS-and-proteinase-K-treated, and SDS-and-proteinase-K-treated and phenol-vortexed ribosomes.

Noller then moved on to a three-dimensional crystal structure of the entire ribosome with substrates mRNA and tRNAs in place. He recruited Jamie Cate as a postdoc and invited Marat and Gulnara Yusupov to UCSC from the CNRS lab in Strasbourg. Together they crystallized and phased the Thermus thermophilus 70S ribosome at 5.5-Å resolution. The initial lower resolution structures with and without bound tRNA helped in phasing and revealed an L-shaped tRNA in the ribosome A site. Across the continent and ocean, three other groups also solved the atomic structures of the ribosomal subunits. Noller writes, "Although at lower resolution, we could see the whole thing: how the subunits fitted together with their dozen intersubunit bridges; how the tRNAs bound to the A, P, and E sites of the ribosome; and the path of the mRNA through the ribosome. As we anticipated, all of the functional sites were made almost exclusively of ribosomal RNA." Noller closes his "Reflections" article by alluding to the RNA world in a comment on the ongoing search for the secret of life, marveling at his fortune in being able to have a singular career focus.

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Long-distance relationships in gene regulation

BY KAMALIKA SAHA

In a recent minireview in the Journal of Biological Chemistry, Zong Wei and colleagues at the University of Southern California give an extensive account of the significance and biological implications of long-range chromosomal interactions.

The human genome has more than 20,000 genes distributed across 22 pairs of autosomes and two sex chromosomes. Regulation of gene expression is critical for efficient functioning of a cell, be it developmental processes or stress adaptations. The chromosomal organization in the nucleus follows a hierarchal system ranging from nucleosomes to higher-order chromatin fibers. This organization modulates chromosomal condensation, which plays a pivotal role in gene transcription by masking the transcription-factor-specific regulatory sequences.

The classical perception of transcriptional gene activation involves a one-dimensional model of binding of transcription factors to specific regulatory sequences followed by RNAP and associated factor recruitment to drive the process. The advent of novel chromosome-capture techniques has revolutionized the field of long-range chromosomal interactions between regulatory elements across the genome during transcription, enabling a three-dimensional approach.

The JBC minireview authors discuss the evolution of the state-of-the-art techniques used to study the long-range interactions ranging from fluorescent in situ hybridization to powerful chromosome-capture methods. While highlighting the technical details, the authors compare the applications of chromosome conformation capture, chromosome capture-on-chip and chromosome conformation capture carbon copy, known as 3C, 4C and 5C, respectively.

Subsequently, the minireview delves into the fascinating concept of transcription factories, wherein genes as far as 40 MBs away share the same transcriptional foci, reiterating the principle of long-range interactions. Additionally, the authors highlight the application of the chromosome-capture techniques to identify these transcription factories. The minireview concludes with an explanation of the ubiquitous nature of long-range interactions in fundamental physiological processes, such as chromosome translocation, nuclear organization and X chromosome inactivation.

This minireview, titled "The biological implications and regulatory mechanisms of long-range chromosomal interactions," outlines the significance of the current research in the field, helping readers to gain an appreciation of the extremely dynamic nature of chromatin, which loops within the intra- and internuclear compartments to regulate fundamentally important cellular processes.

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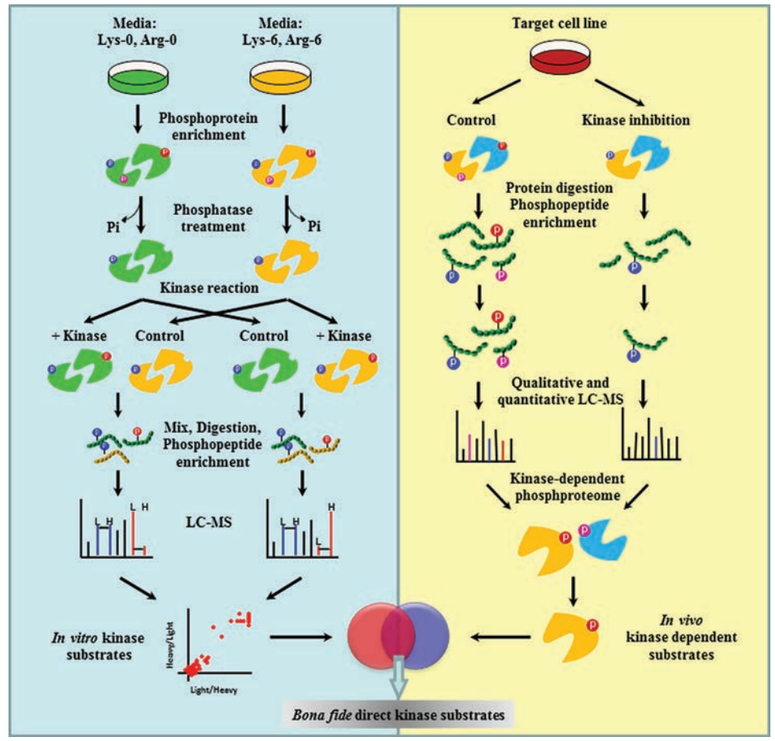
MCP MOLECULAR & CELLULAR PROTEOMICS

Keeping up with kinases

BY RAJENDRANI MUKHOPADHYAY

Without protein kinases, we wouldn't have much signal transduction in cells. But identifying the relationship between these critical molecular machines and their numerous substrates has been a challenge. In a paper in a recent issue of Molecular & Cellular Proteomics, a team led by W. Andy Tao at Purdue University described a proteomic approach to identify directly the substrates of tyrosine kinases.



Tao's group's approach involved two steps. In the first step, the investigators did an in vitro screen to look for substrates phosphorylated by a particular kinase. In the second step, with an in vivo assay, they looked for which substrates were phosphorylated when human lymphoma cells were treated with an inhibitor against the same kinase.

By comparing and contrasting the two datasets, Tao and colleagues were able to identify many of the substrates for a given kinase. (As proof of principle, the investigators studied the kinase SYK.) Their approach identified many more substrates than the traditional molecular-biology approaches, which can identify only one substrate at a time.

The work has potential clinical implications. "Many kinases, in particular tyrosine kinases, have been discovered as oncogenes in a number of cancer types," explains Tao. "While they are targeted to develop inhibitors as drug candidates, their network, in particular the precise relationship between kinases and their substrates, is not clear in most cases. The lack of specific knowledge has hindered us from developing better and more potent drugs and from addressing the difficult issue of drug resistance in chemotherapy."

The investigators intend to extend their strategy to serine/threonine kinases and look at diseases caused by mutated kinase–substrate interactions.

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Deciphering the role of CGI-58 in lipid regulation

More than one way to trim the fat?

BY KENT D. CHAPMAN, JOHN M. DYER AND ROBERT T. MULLEN

Comparative gene identification-58, or CGI-58, is best known as the causative gene in Chanarin–Dorfman syndrome, a rare neutral lipid-storage disease in humans (1) that results in an abnormal accumulation of triacylglycerol, or TAG, in nonlipid-storing cell types such as muscle, heart and skin (1, 2).

CGI-58, also known as alpha-beta hydrolase 5, or ABHD5, is a member of the large alpha/beta-hydrolase-fold-domain family of proteins. However, unlike many members of this family, CGI-58 itself lacks lipase activity and instead regulates TAG turnover by serving as a co-activator of major adipose triacylglycerol lipase ATGL (3). Yet beyond its interaction with ATGL, many of the mechanisms of CGI-58 action remain somewhat unclear, including its inherent lysophosphatidic acid acyltransferase activity (4, 5) and its potential role in lipid-signaling pathways (6).

Homologues of CGI-58 have been identified in diverse eukaryotes, including invertebrates, yeast and plants (7, 5), and in several cases there appears to be a remarkable conservation of function at the cellular level. For example, in the model plant Arabidopsis thaliana, loss of CGI-58 activity results in a Chanarin–Dorfman-like phenotype – a hyperaccumulation of TAG and lipid droplets in leaves where lipid droplets normally don't accumulate (8).

However, instead of interacting with an ATGL-like lipase, Arabidopsis CGI-58 interacts with the peroxisomal ABC transporter 1 protein, also known as PXA1 (9), which is responsible for the uptake of fatty acids into peroxisomes for β–oxidation (10, 11, 12). Hence, despite the overall similarities in lipid accumulation phenotypes in plants and animals with disruptions in CGI-58, the underlying mechanisms involved in lipid regulation appear to be quite different.

Notably, PXA1 recently was shown to act as an acyl-hydrolase toward fatty acyl-CoA substrates as part of the transport cycle (12), suggesting that CGI-58 in plants and animals might stimulate hydrolytic activity similarly, albeit of different proteins, to promote lipid turnover ultimately.

Still, because some cell types in animals use peroxisomal β-oxidation extensively for the metabolism of fatty acids and also possess ABC proteins for transport of fatty acids into peroxisomes (13) and mitochondria (14) and across the plasma membrane (15), it is possible that CGI-58 (or other related ABHD proteins) interacts with ABC transporters in a similar way to regulate other aspects of lipid metabolism and signaling in nonlipid-storing cell types of mammals (16, 17).

One additional and interesting aspect of CGI-58 in plant cells is that the protein is positioned at a key point in the regulation of lipid turnover and lipid signaling in plants (see figure). For instance, PXA1, in addition to playing a role in the uptake and turnover of cellular fatty acids for energy generation, also facilitates the uptake of lipophilic hormone precursors of the jasmonate and indole acetic acid pathway for their subsequent activation through β-oxidation (18, 19). In CGI-58 loss-of-function mutants of Arabidopsis, in addition to the increase in TAG content in leaves, the production of jasmonic acid and IAA, or auxin, are significantly impaired (9), implying that CGI-58, through its interaction with PXA1, participates in the regulation of both lipid homeostasis and hormone signaling in plants (see figure).

Hence, CGI-58 interaction with peroxisomes may be an evolutionarily ancient means for the coordination of energy supplies and regulation of growth in multicellular eukaryotes. It will be interesting to identify additional functions for CGI-58 in diverse organisms and to test such possibilities.

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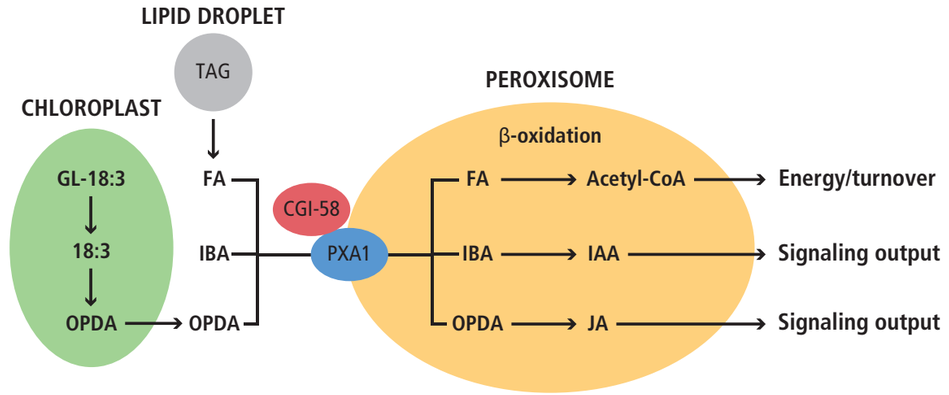

FIGURE CREDIT: ADAPTED WITH PERMISSION FROM PARK ET AL. PLANT CELL 25, 1726 – 1739 (2013). SOURCE: WWW.PLANTCELL.ORG. COPYRIGHT: AMERICAN SOCIETY OF PLANT BIOLOGISTS.

Model depicting the interaction and cooperation of CGI-58 and PXA1 to cellular lipid homeostasis and signaling in Arabidopsis. OPDA, 12-oxo-phytodienoic acid; IBA, indole butyric acid; FA, fatty acid; IAA, indole acetic acid; JA, jasmonic acid; GL, galactolipid; TAG, triacylglycerol.

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A random walk to the career I never knew I always wanted

BY JOANNA DOWNER

My high-school plan to major in chemistry, earn a Ph.D., become a faculty member and cure cancer worked to a point. I did major in chemistry, and undergraduate research experiences led to graduate school. But in graduate school, I realized I wasn't happy in the lab. However, with no Plan B, I stuck with Plan A.

Plan A involved some magic: I thought that at some point an aspect of my graduate school research would speak to me and become my life's work. So I was surprised when — just two-and-a-half years in — my adviser asked me to figure out what I wanted to do with my life so he could help me get there.

I started by considering the obvious — my own projects and then others in the group. I quickly dismissed them all. I wondered whether I should be in genetics or high-energy physics. After a few days, I knew the answer was no.

My consideration of these possible fields revealed two ways in which doing science was counter to my nature: I didn't want to abandon an infinite number of interesting options to pursue a single avenue, and the process of science was too slow. To be motivated and satisfied, I needed more frequent deadlines and more frequent closure.

Frustrated, I wondered if I had enjoyed anything since beginning graduate school. A little voice inside me said yes — writing and editing. My adviser had asked me to research and draft a textbook chapter and to edit manuscripts authored by others in the lab. I'd poured myself into those projects and found great satisfaction in their completion.

While I knew only that I wanted to incorporate science and writing or editing, my adviser was a step ahead — he said he thought I'd like to be a science writer. "Great," I said. "What's that?"

True to his word, he helped me become a science writer, translating technical information into stories for a general audience. He connected me with a magazine editor at the university, for whom I wrote a number of articles. Those were my ticket to a 10-week Mass Media Fellowship from the American Association for the Advancement of Science, which I spent at Time Magazine in Washington, D.C. Once back at graduate school, I turned my experience into paying freelance jobs that I learned about through the National Association of Science Writers.

After finishing my doctorate, I started at Duke University Medical Center doing science writing and media relations for basic and clinical cancer research. A few years later, I left for Johns Hopkins Medicine, where I was a news writer dedicated to the basic sciences, cell engineering and genetic medicine.

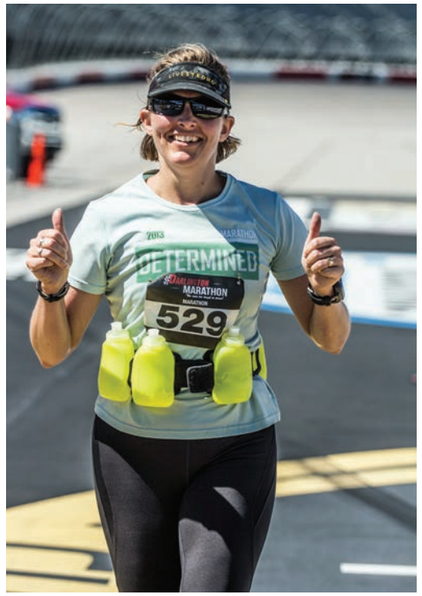
An impetus for both job decisions was my desire to choose positions where I could learn from those around me, use skills I already had and build new skills by taking on new challenges. In each position, I also built strong relationships at every opportunity.

After a few years at Hopkins, I realized I didn't want my boss's job or her boss's job, both of which involved being on call 24/7. I needed another new path. I could have stayed in science writing, perhaps switching to writing for internal publications instead of news, or at a college instead of an academic medical center.

Instead, I was offered and accepted an opportunity to return to Duke in 2006 at the invitation of Nobel laureate Peter Agre, whose work (and Nobel) I'd covered at Hopkins. After a few years of writing and managing projects for Agre and other medical center leaders, the economic downturn altered the landscape. Among my major projects at the time was a fledgling effort to create a large statewide innovation fund — now an instant nonstarter.

So I offered the medical school my scientific editing skills — which I'd used only as a freelancer — to help the institution apply for stimulus funds. My offer was readily accepted, and in five months I wrote three high-scoring institutional construction grants (one was funded for $15 million). Due to their success, I was invited by the medical school's dean's office to help faculty members develop complex research grants, an area in which Duke had been struggling.

On each grant team, I play whatever role necessary: leading, providing direction behind the scenes or picking up balls that have been dropped. I help the team establish and meet agreed-upon responsibilities and timelines. I pay attention to "boring" grant components, such as biosketches and management plans, and I make sure the grant manager — the financial expert — is engaged early. I help teams keep their science true to the funding opportunity requirements and intent, and I edit each application to ensure it is clear, compelling, consistent, concise and complete — my five C's. I approach every piece of every grant as if it were my own.



A few years ago, Downer gave up competitive volleyball to take up long-distance running. She warns that some grants are marathons and some are sprints. Here she crosses the finish line of her second full marathon, held Sept. 28, 2013, in Darlington, S.C., her first of three marathons this fall.

My current job is part of a relatively new profession: research development. It unites my skills in building teams, explaining science, crafting compelling messages, editing scientific documents and doing all of it under deadline pressure. Each day, I use my existing skills and find new challenges. In the past few years, I've added three staff members to my team. Last year I started offering writing workshops to help faculty members learn to revise their own work more effectively. I'm still learning new things nearly five years in and with nearly three dozen complex research grants under my belt.

The hardest part of my job is meeting demand — and saying no. As the funding climate has tightened, good research-development professionals — or even freelance scientific editors — provide critical support to faculty members who need to make the strongest case for their research.

In some ways, I feel I found this career accidentally, just by following my nose. In other ways, it seems I have been training for it all my life — from playing competitive volleyball, to editing my high-school yearbook, to telling stories of discovery, to education and research in chemistry. I just love it when a plan comes together.

Is research development for you?

- Team oriented
- Exceptional attention to detail
- Excellent writing and editing skills
- Energized by deadlines
- Can balance multiple shifting priorities
- Finds inherent satisfaction doing high quality work
- Enjoys helping others

For more information, visit www.NORDP.org, the website of the National Organization of Research Development Professionals.

Joanna Downer is director of research development at the Duke University School of Medicine. Previously, she was associate director of science communication at Johns Hopkins Medicine, and before that she was a science writer in the Duke University Medical Center News Office. She earned a B.S. with honors in chemistry from Carnegie Mellon University in 1993 and an M.A. and Ph.D. in nuclear chemistry from Washington University in St. Louis.

How to get teaching experience that will help land you a job

BY SARAH PERDUE

There are several avenues you can take to show future employers that you're serious about becoming a classroom leader

One of the more popular career choices in which I've heard fellow early-career scientists express interest is that of the teaching-focused college professor. Such positions allow scientists to stay active in research while being able to focus on teaching more than they would at a large research institution.

I am pursuing such a career path, although not necessarily in the most traditional way. In the two years since finishing grad school, I have worked as a visiting professor at two primarily undergraduate institutions, or PUIs, and after completing a postdoc position, I hope to be hired in a tenure-track position at such a school. As a visiting professor, not only was I able to gain invaluable experience in the classroom, but I also served on hiring committees and got a glimpse into what will and will not help applicants in pursuit of teaching-focused jobs.

Unlike being a successful candidate for faculty positions at R1 schools, where applicants are evaluated mostly on their research, securing a position at a PUI demands both modest success as a researcher and "a demonstrated interest in teaching" (to quote a number of job announcements).

First, the bad news: No, your two semesters of being a teaching assistant aren't going to cut it; nor is your week of guest lecturing for your adviser's class. The good news: There are a number of ways to demonstrate interest in teaching, and showing a pattern of interest and taking opportunities as they come often is sufficient.

In writing this article, I'm hoping to provide anyone who thinks he or she might want to pursue this career path with the impetus to get started teaching as soon as possible. I'm also hoping to provide a (not entirely inclusive) list of ways to access teaching opportunities and to share the experiences of people who have done so.

Teaching your own course

After my doctorate, I spent one year teaching at the University of Wisconsin–Parkside, a small public university, and then another year at Providence College, a private Catholic liberal arts college. While I might be biased, I think most hiring committees would agree that a visiting or adjunct professorship is easily the best way to gain the type of teaching experience they are looking for in their candidates. It was also a way to test-drive my desired career path and check out different types of institutions (public vs. private, religiously affiliated vs. not).

As a visiting professor, I was a faculty member of my departments, and I was treated as such by my colleagues. The responsibility for putting together a syllabus, assigning point values to assignments, writing homework assignments, determining lab schedules, writing exams and doing all the grading for the equivalent of three courses each semester fell squarely on my shoulders. It sounds overwhelming – and at times it was! It helped that I was given materials from previous instructors on which to build, and a few times I was teaching second sections of a course, so I had another instructor with whom to share some of the work and to bounce ideas off of. Unlike my tenured or tenure-track colleagues, I had no research or service requirements, so my teaching load was about one more course per semester than theirs.

I could not envision a better job for me after graduate school. Yes, it was a ton of work. (I easily spent more time per week at these jobs than I did as a graduate student.) Yes, I had students try to make me feel responsible for their poor grades, and I dealt with sticky situations like plagiarism. And yes, sometimes I felt like I was in way over my head, and I wondered how I was ever hired in the first place. But now if I do land a position at a PUI, I'm already ahead of the curve in terms of teaching and interacting with students. And if I am interviewed at a PUI, I can answer their questions about how I would handle certain situations with an example drawn from reality instead of one I role-played in teaching workshops.

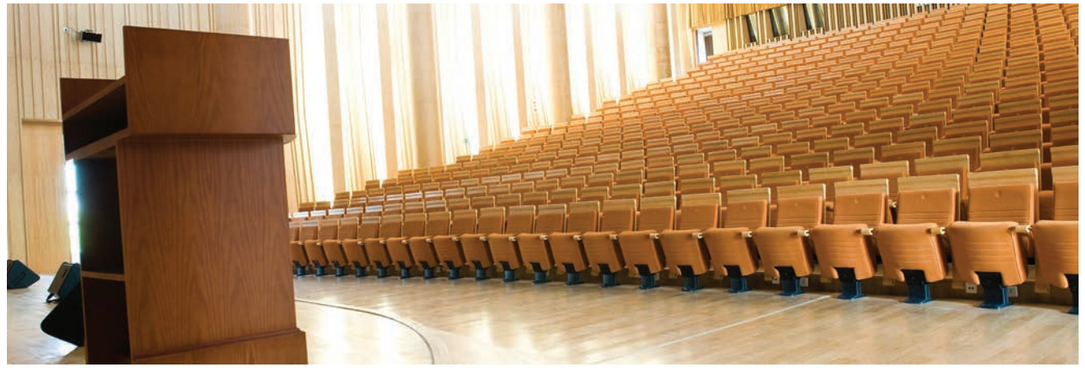


IMAGE CREDIT: ZHANG XIANGYANG

Full-time visiting professorships are not for everyone, though. Aside from being very competitive and essentially requiring candidates already to have some teaching experience, they typically require a doctorate and cannot be done concurrently with full-time postdoctoral research. They are usually guaranteed for only one academic year, so they require a certain degree of flexibility in terms of relocating and then relocating again when the year is up. (Luckily, moving expenses may be covered.)

If a full-time teaching position isn't for you, consider an adjunct spot. Adjunct positions are part time, sometimes for only one course. The experience gained is as good as with the full-time positions, and this job can be done in addition to full-time research (although you first will want to discuss with your adviser how to handle the situation when the teaching cuts into expected time in the lab). The downside is that the pay stinks, there are no benefits and the positions are usually dependent on enrollment, meaning that courses can get cut right at the start of the semester.

Teaching postdocs

Noting the need to train top scientists also to be good teachers, organizations like the National Institutes of Health and the Howard Hughes Medical Institute have started teaching postdoctoral fellowship programs that integrate research with teaching. These programs require fellows completing traditional mentored research to participate in workshops on teaching and learning strategies and to apply that training in the classroom. These fellowships usually are awarded to institutions, not individuals, so the first step is to find those institutions that offer them and then apply.

"The goal is to prepare (fellows) for a successful career in academia where they will do research and teaching," said Shiva Singh, chief of the Undergraduate and Predoctoral Training Branch at the National Institute of General Medical Sciences, which oversees the Institutional Research and Academic Career Development Awards program. "Our expectation is that these fellows will bring new excitement and courses to research institutions, to minority institutions, and to liberal arts institutions, and they do." He added that about two-thirds of fellows are hired into academic positions.

The hands-on teaching component of the IRACDA program at the University of California—San Diego has fellows team-teach a course at partnering San Diego State University. "The setup of that program helped me get teaching experience, and I used that to get my foot in the door to adjunct at SDSU," said Karen Resendes, now an assistant professor of biology at Westminster College in Pennsylvania. She believes that her adjunct position was a significant factor in landing her current job.

Another benefit of teaching postdocs is that the program, not the principal investigator, funds the postdoc for up to three years. "When I knew I was in the program, it was very easy to get a lab to take me, because it covered my stipend," Resendes said.

Before diving into a teaching postdoc position, there are a few things to note. IRACDA programs are offered at only 19 institutions, limiting the research options available to candidates. They are competitive: Singh said the acceptance rate is about 10 percent overall, but it varies at the individual institution level. Resendes noted that each school's IRACDA program is run differently, and UCSD's was more focused on large lecture courses. "My program was good for people who wanted to move on to R1 schools but have some teaching experience," she said.

Teacher-training programs and other opportunities

If you don't have the previous options available to you, you're still in luck! Plenty of schools have mentored teaching programs, and while they can be competitive and often do not provide a stipend, they show that participants are making the effort to become more effective teachers.

For example, the University of Wisconsin-Madison offers a selective HHMI-funded Teaching Fellows program open to graduate student and postdocs in any biology-related discipline. It is a two-semester program during which the fellows learn different approaches to teaching and learning in the first semester and then apply that training in the classroom during the second semester.

"The spring semester is a class for them, and the first half of the class is really an introduction to what we know about how people learn and exposure to pedagogical approaches and raising awareness of effective teaching habits," said Kristin Jenkins, director of the Pre-Faculty Programs at UW-Madison's Center for Biology Education.

During the second semester, fellows team-teach a freshman seminar course while each fellow leads a smaller discussion section. "You learn all the logistics of laying out a course, you have to plan the syllabus and get everything ready ahead of time, you get to give a big lecture and design the material (for the discussion section activities), and then you also get feedback on how the activity worked," Jenkins said. She added that the fellows always are trying to incorporate different strategies in the freshman course, such as focusing on active learning and reading primary literature.

Many other schools offer similar, if not externally funded, programs. "I realized colleges and universities are looking for more than standard department TA experience, so I signed up for this fellowship," said Bradford Condon, a recent plant pathology graduate who participated in the Cornell University Center for Teaching Excellence's Graduate Teaching Assistant Fellows program for two years. The two-semester program requires fellows to host teaching workshops on a range of teaching topics, such as identifying learning outcomes as the basis for instruction and assessment and using library resources to enhance students' research skills. Fellows also meet about once a month with CTE staff to discuss innovations in teaching approaches.

"I think it's an awesome value time wise," Condon said. "I really encourage any grad student interested in teaching to at least try a workshop, if not sign up to be a fellow."

If your school does not offer these more formal training programs, try taking an education course or seek science-outreach opportunities through your institution or local venues, such as museums or nature centers. Outreach "demonstrates your interest, it gives you experience and it connects you to people who are teaching," noted Jenkins. And it works! I participated in science outreach as an undergraduate and graduate student, and I'm sure that taking that initiative was a factor in my hiring at UW-Parkside.

The bottom line: If you think you want to pursue a career at a PUI, you need to have some teacher training or experience beyond your required teaching assistantship to be an attractive candidate. That extra experience not only shows your interest but makes you a better teacher too. The sooner you get involved and the greater your experience level, the better.

Links for teaching opportunities

NIH IRACDA teaching postdoctoral fellowships:
http://1.usa.gov/1a06vV0

The best place to find visiting or adjunct professor listings:
http://www.higheredjobs.com/faculty/

American Society for Microbiology online Science Teaching Fellowship:
http://bit.ly/lfeK9y

UW HHMI Teaching Fellows program:
http://biology.wisc.edu/1282.htm

Cornell's Graduate Teaching Assistant Fellow Program:
http://bit.ly/1iOQpW3

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Editor's Note: *The ASBMB, as part of its Promoting Concept-Driven Teaching Strategies in Biochemistry and Molecular Biology project, is hosting a series of free workshops around the country focusing on scientific teaching tools and student-assessment techniques. Graduate students and postdoctoral fellows who are interested in undergraduate science education are welcome! Learn more at www.asbmb.org/bmbconcept.*

An introduction to the scientific communities on Reddit

BY ANNA SHIPMAN

There are multiple online sources for scientific content; however, there are not necessarily many places online where people with varying scientific backgrounds are able to come together to discuss science. One place online where people can casually come together to discuss a variety of scientific topics is Reddit.

Reddit is an Internet link aggregator where people can post links or text posts (called "self-posts"), and then users in the community can comment and up-vote or down-vote the post and comments. Up-voting a post or comment makes it more visible to the rest of the community, allowing Reddit users to decide which content is most relevant.

There are myriad topic categories on Reddit, which are divided into "subreddits." Each subreddit has its own set of rules concerning the nature of acceptable posts. There are several science-related subreddits where users can view and submit a variety of different posts, from asking serious questions about an everyday concept to making a joke about something that happened in the lab. The scientific communities within these subreddits are a way for people with professional scientific backgrounds as well as people who simply have an interest in science to come together and discuss new things.

Two of the most popular science subreddits, /r/AskScience and /r/Science, cover a variety of scientific topics. /r/AskScience is where anyone can ask a well-thought-out scientific question and get a proper answer from a panel of scientists or other users who are familiar with said topics. /r/AskScience is heavily moderated to keep jokes and memes to a minimum, allowing people to focus on the science instead. In /r/Science, there are only direct links to articles or summaries about recently published, peer-reviewed research. This subreddit also is heavily moderated to keep nonserious discussion to a minimum.

However, there are also more casual subreddits with more specialized topics, such as /r/chemistry, /r/biology, /r/biochemistry, /r/LadiesofScience and /r/labrats. The rules pertaining to acceptable submissions are more relaxed in some of these subreddits compared to /r/AskScience and /r/Science. In /r/chemistry, /r/biology and /r/biochemistry, it is more acceptable to ask questions about career paths and lab work related to the subreddit topic. /r/LadiesofScience is meant for women who are involved in science to ask questions and talk about their experiences, although everyone is welcome to post there. In /r/labrats, users can request advice regarding new protocols or experiments gone awry, as well as tell funny lab-related stories. A couple of other specialized subreddits are /r/physics and /r/math.

Tips for new Reddit users

- **Read the rules:** Every subreddit has different rules about what content can be posted and what kinds of comments are acceptable.
- **Be considerate of other users:** Remember, there is a person on the other side of that username, so don't be rude to him or her.
- **Use correct grammar and spelling:** Check over your post or comment before submitting. Be especially careful with post titles, considering that you cannot edit them after the fact.
- **Don't be so quick on the draw:** Read the article or post before voting on it.
- **Don't down-vote simply because you disagree or dislike the person who posted it:** Down-vote if a comment doesn't contribute to the conversation.
- **Make comments that contribute to the conversation:** Comments consisting only of "I agree," "up-vote" or "lol" don't add to the conversation.
- **Post content to the most appropriate subreddit.**
- **Avoid re-posting links that have been posted recently.**

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Special symposium recap

Membrane-anchored serine proteases

BY TONI M. ANTALIS AND THOMAS H. BUGGE

Proteases comprise more than 2 percent of the known proteome, with the family of serine proteases constituting one of the largest protease families. The trypsin-like serine proteases long have been recognized to be critical effectors of biological processes as diverse as digestion, blood coagulation, fibrinolysis and immunity.

The complete sequencing of several vertebrate genomes at the turn of the millennium unexpectedly revealed a new group of serine proteases that are structurally distinct and anchored directly to the plasma membrane. These enzymes, broadly termed the membrane-anchored serine proteases, are synthesized with amino- or carboxy-terminal extensions that serve to anchor their serine protease catalytic domains (1 – 3).

Since the emergence of this subfamily, researchers have begun to investigate the biochemical and physiological activities of these enzymes and have come up with some surprising results. The 2013 American Society for Biochemistry and Molecular Biology special symposium on membrane-anchored serine proteases, held in September in Potomac, Md., brought many of these researchers together for the first time, revealing that while there are structural and phylogenetic commonalities among these enzymes, there are also stark differences in biological function.

The conference opened with a keynote lecture from Qingyu Wu (Lerner Research Institute, The Cleveland Clinic) titled "The membrane serine protease corin: from physiology to pathology." This enthusiastic and entertaining talk focused on a journey of discovery into corin biology, physiology and pathways to the clinic. It was an inspiring start to the conference.

Talks covering wide-ranging combinations of biochemical analyses, animal models and human studies were presented, revealing that the membrane-anchored serine proteases are key pericellular contributors to processes vital for development and the maintenance of homeostasis. They regulate diverse fundamental biological processes including epithelial barrier function, water transport, iron homeostasis, blood-pressure regulation, hearing, fertilization and embryonic development. Their misuse in many cellular contexts contributes to human illnesses including cardiovascular disease, cancer and viral infection.

Several attending researchers have focused on the identification of target substrates for the membrane-anchored serine proteases and the regulation of their protease activities; however, as the meeting progressed it became clear that the biology is not as simple as first thought. Endogenous protein substrates targeted by membrane-anchored serine proteases include peptide hormones, growth and differentiation factors, receptors, enzymes, adhesion molecules and viral coat proteins.

A significant research focus of several groups is the regulation and activities of the epithelial type II membrane-anchored serine protease called matriptase. The serine proteases share a common catalytic mechanism for selective cleavage of specific substrates and frequently are involved in consecutive proteolytic reactions or protease cascades, where one protease precursor or zymogen is the substrate for an active protease. Provocative new data relating to the matriptase pathway was presented at the meeting suggesting that membrane-anchored serine proteases may serve as non-enzymatic, allosteric cofactors for activation of other protease zymogens.

We had an outstanding selection of junior investigators present their research results in the oral sessions, indicating that this is a young field that will remain vibrant for many years to come.

Several studies presented indicate that these enzymes are interconnected with known zymogen activation cascades at the cell surface, including the coagulation and fibrinolytic cascades. Furthermore, there is evidence that proteases within this family can constitute a cell-surface proteolytic cascade within themselves and act upstream of effector proteases, providing the capacity for unleashing a burst of proteolytic potential. Several of the membrane-anchored proteases, such as matriptase and testisin, are capable of activating G-protein–coupled receptors, such as protease-activated receptor type 2, and receptor tyrosine kinase ligands, such as pro-hepatocyte growth factor, on the surface of different cell types, thus potentially constituting a so-called missing link from the extracellular protease cascades to intracellular signaling pathways.

We had an outstanding selection of junior investigators present their research results in the oral sessions, indicating that this is a young field that will remain vibrant for many years to come. Participants came from U.S. and international laboratories and included researchers from academic institutions, government and industry. The meeting had an encouraging and informal atmosphere, which undoubtedly fostered collaborative interactions among the researchers. The poster session also attracted a lot of interest. It was a challenging and rewarding experience and provided some thought-provoking suggestions for future research.

Overall, the meeting was entertaining, interactive and motivating while covering a variety of areas in the emerging field of membrane-anchored serine proteases. The challenges ahead include the development of unique tools with which to study these enzymes to show how these proteases are used and modulated by the cell and how they can be exploited for therapeutic benefit.


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What BMB students are saying about their profs on Twitter

(Don't worry, students. We picked only the tweets that wouldn't get you in trouble. #gotyourback)

agrommons @agrommons
"I'm loopy from all my medicine. Is it cocaine or codeine? I don't know." -biochem prof. #party

Vineet G. @VineetGoopta
Biochem prof: "I tried to come up with a Miley Cyrus joke but it just wasn't twerking"#jokess

Gabby maxwell @gabbytennn
"Trying to get into your bacteria is like trying to get onto Death Star." Yes ladies and gents. My biochem prof made a Star Wars reference

Taghreed Mohamed @taghreedmhassan
'Don't waste your time trying to understand, just memorize it.' My biochemistry professor.

PreMedProblems @Pre_Med_Probz
Biochem prof copies and pastes his lecture notes from the internet....CAUGHT YA pic.twitter.com/qohEzRurM7

Stephen Raines @stephenraines
"If you review everything from all the material this semester, you will do well on the final" Thank you Biochemistry professor

Laura Fitz @lilfitz1
New biochem prof starts the class off by blaring music #Jeanne

Amanda Kramer @_shmanders
Just had my entire biochem class turn and look at me as the prof pointed out I'm the only American. Gonna be a long semester

Anny Bae @annybae
"Your girlfriend has 67 protons, or in other words, she's a Ho!" -biochem prof

Yule Mbois Mndialala @ French_Freddy
The question of how an epileptic seizure starts. "That's the holy grail of epilepsy research," says Molecular Cell Bio Prof Robin Williams

Raven @ravenrockstar09
You might be a nerd if your biochem prof talks about thrombin and all you can think of is how that sounds like a dwarf's name. #nerdalert

Anna Wu @annnawu
My biochem professor just started lecture with "I'm not gonna ask for blood but.."

Audrey Jeon @aauds
I had the COOLEST biochemistry professor/professor out of all my 3 yrs @ UGA... ever! Honestly gonna miss him....#torn #enjoyedit...

Jessica Kabigting @JessKabigting
my cool biochem prof just took a swig of beer to show the effects of lacking acetaldehyde dehydrogenase. #BAMF (+ now I know why I turn red)

silvia dhia fairuz @silviadhiaaa
"looks like we need to start drinking blood instead of water as the Fe main supplies" Prof Anton in biology molecular class ._.

Natasha Tripp @nsytripp
"Keep warm, stay cool"- wise words from my biochem prof #lifeadvice

Brent Thomas @breinhart65
My biochemistry professor is one of the funniest ladies I know.

2014

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- Emerging Roles of Mitochondria in Cell Signaling, Physiology and Disease
- Enzyme Mechanisms & Chemical Biology
- -Omics, Systems Biology and Their Translational Applications
- Membrane Biology
- Frontiers in Glycobiology
- Signal Transduction
- Science of Addiction
- 21st-Century Approaches to Teaching and Communicating Biochemistry and Molecular Biology

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Building A Sustainable Research Enterprise
Sun., April 27

ASBMB Welcome And Networking Reception
Sun., April 27

Women Scientists Networking Event
Tues., April 29

Late-Breaking Abstract Deadline:
Feb. 21

Early Registration Deadline:
Feb. 21

Housing Deadline:
March 21

www.asbmb.org/meeting2014

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