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December 2011

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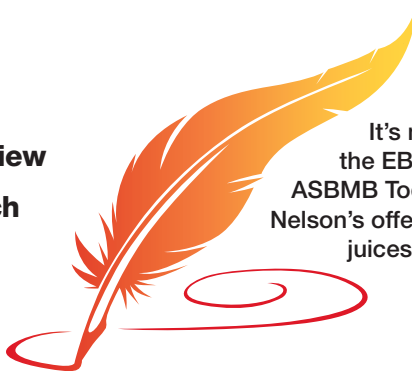
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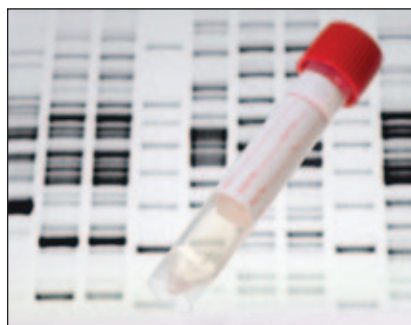


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Crowdsourcing biochemistry and molecular biology

BY SUZANNE PFEFFER

Crowdsourcing is responsible for the wonderful success of Wikipedia—who would ever have predicted that volunteer editors from around the world could generate a resource that is so valuable for all of us. Another type of crowdsourcing is used by computer games that simulate protein and RNA folding. David Baker and colleagues at the University of Washington have created a competitive protein-folding game called Foldit that takes advantage of the problem-solving skills of amateurs to tackle how polypeptides fold in three dimensions (1). Scientists at Carnegie Mellon and Stanford universities have created EteRNA, a computer game that enables amateurs to design RNAs that fold well (2). If a player wins the weekly competition, his or her RNA is synthesized and then scored for how well it folds. These games make use of the power of crowdsourcing to find solutions and offers new ways of looking at problems that workers in the field may have missed.

Are there additional ways that biochemists could benefit from crowdsourcing? What if there were a website for biochemists to compare notes in their roles as customers, regarding their experiences with journals and with vendors? For example, 2011 has been a good year for my research group in terms of paper publishing. Four original research articles made it through the evaluation process, and two more are about to be submitted. Each of these will appear in a different journal, and my experience with each journal was distinct. The manuscript-submission websites varied in terms of ease of use, clarity and time required to complete the submission; the time for review varied significantly; the quality of the reviews differed; and each paper was subject to a different level of academic editor oversight.

Scientists gossip about such differences, but what if there were a Biochemadvisor.com website with reviews of our experiences as customers of different journals? Whenever I plan a trip to a new destination, I check out Tripadvisor.com to read reviews of hotels in the city I will visit. I also contribute reviews to that site to help other travelers. Hotel managers are monitoring such sites very closely because travelers listen to the comments of other travelers. Although the online rebuttals of hotel managers sometimes seem gratuitous, managers are surely making changes at their hotels to avoid bad reviews in the future. We, as scientists, should speak out and understand that we have choices in the marketplace, and editors should care about the customer experience.

Journals need our feedback. Editors need to learn when their behavior is unacceptable. If referees are asked to provide feedback within two weeks,

authors should not have to wait more than four. There are journals that send a manuscript out to four reviewers, and then the editors aren't quite sure which of the four reviews is most important. One of my lab mottos is that I have never seen a manuscript that is not improved upon revision. That being said, four reviews are likely more than what is actually necessary, and editors have every obligation to provide timely and constructive feedback to authors.

ASBMB publishes three journals: the Journal of Biological Chemistry, Journal of Lipid Research and Molecular and Cellular Proteomics. The activities of these journals are overseen by the ASBMB Publications Committee, currently chaired by Charles Brenner of the University of Iowa. ASBMB journal editors also report to the ASBMB Council twice a year and must keep the publications committee and council members apprised of manuscript turnaround times and rates of acceptance. If you have complaints about one of our journals, the publications committee would like to hear from you.

eLife

A new type of manuscript review is coming to a new online journal, eLife, recently established by the Max Planck Society, the Howard Hughes Medical Institute and the Wellcome Trust. With ASBMB member Randy Schekman as the new editor-in-chief, this journal will assign papers for oversight by a member of a board of reviewing editors. The editor and one or two other experts will read each manuscript, and they will then confer to merge opinions into one coherent message to the corresponding author, offering specific guidelines for one round of revision or a firm rejection on the basis of substantial criticisms of the work. The idea is to take advantage of the collective intelligence of three expert referees to provide authors with the most intelligent and rational reviews. This approach is very welcome. "It is my strong feeling that there is a need for a scientific journal at the very high end



Brenner



Schekman

that is run by active practicing scientists embedded in an academic environment, individuals who experience both the frustrations and satisfactions of research," says Schekman.

Faculty of 1000

Another valuable, community-based service is provided by Faculty of 1000: Members contribute short, high-level summaries of papers they find interesting in their reading of the literature. I certainly appreciate papers being brought to my attention by colleagues in my field, and a single, weekly email summary makes it easy to stay up to date.

Scientists also need to share reviews of their vendor experiences. How many ASBMB Today readers have purchased an antibody or enzyme from a company and then discovered that it doesn't work? There is one vendor known to members of my lab for sending out useless antibodies, but I bet that company would be put out of business if all frustrated customers voiced their opinions on a single Biochemadvisor.com site. Think of how much money and time could be saved if we shared

this kind of information. Let's make use of the collective intelligence of our entire community of biochemists and crowdsource as much as possible to help each other be most successful. ∞∞∞



ASBMB President Suzanne Pfeffer (pfeffer@stanford.edu) is a biochemistry professor at the Stanford University School of Medicine.

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The public affairs staff's holiday wish list

BY JULIE MCCLURE



As the calendar year winds down and the holiday season approaches, the American Society for Biochemistry and Molecular Biology Office of Public Affairs is reflecting on 2011 and looking ahead. As tradition dictates, we have put together our own wish list of sorts for 2012 in the hope that our names are on the “nice” list and that we’ll receive everything we ask for.

A workable budget for FY12

After multiple continuing resolutions that allowed the government to keep functioning past the beginning of the fiscal year, the FY11 budget was approved in the 11th hour, narrowly averting government shutdown. While the final budget deal resulted in \$38 billion in spending cuts for FY11, science-funding agencies escaped relatively unscathed, receiving only minor budget reductions. Unfortunately, FY12 has started down an all-too-familiar path with the passage of two continuing resolutions since the beginning of FY12 on Oct. 1. Next year, the country would appreciate a budget *before* the fiscal year is half over. And if Congress would fully support science funding agencies, that sure would make those at ASBMB happy.

Open-minded and responsive NIH leadership

In 2011, there was a lot of discussion about the formation of a new National Institutes of Health center, the National Center for Advancing Translational Sciences. While NIH leadership was strongly supportive of NCATS, its purpose, structure and funding were widely debated within the scientific community, with many researchers questioning whether the center would pull the focus and funding away from the NIH’s core mission of supporting basic research. Recently, the NIH has begun to look for solutions to continue to fund outstanding scientific research in the face of a flat or, more likely, reduced budget. In an October blog post, Sally Rockey, deputy director of the Office of Extramural Research, requested suggestions on how to manage NIH resources in times of fiscal austerity. While we know there is no perfect solution, this year we ask all members of the research, administrative and legislative communities to come together with a certain

willingness to compromise so that the basic research enterprise as a whole can continue to progress.

Increased communication about science by ASBMB members

This year we hosted two Hill Days, during which 25 students, postdocs and primary investigators came to Washington to meet with their representatives and advocate for biomedical research. In 2012, we will continue to raise awareness about the importance of basic research to Congress and the public at large by providing you, our members, with information about opportunities to interact with your elected officials in your hometowns. We’d like to ask all members of ASBMB to reach out to colleagues, legislators and even neighbors to garner support for basic research funding. Improve your communication skills by participating in the 2012 Hill Day or consider attending the ASBMB special seminar at the 2012 Experimental Biology meeting. This year’s topic is communicating science to the public.

That the ‘super committee’ will play nice

While FY12 funding is in the forefront of everyone’s mind, we also have to think about the long haul. The Budget Control Act of 2011 raised the debt ceiling but also called for the formation of the Joint Select Committee on Deficit Reduction, otherwise known as the super committee, which is charged with finding \$1.2 trillion to \$1.5 trillion in spending cuts over the next 10 years. The super committee recommendations were due Nov. 23, and a full congressional vote must occur by Dec. 23 to avoid across-the-board budget cuts to all discretionary spending. (Scan the QR code or visit <http://bit.ly/vCnLwR> for updates to this story.) Santa, if you can only bring us one thing on our list this year, this would probably be it. ☺☺☺



Julie McClure (jmccclure@asbmb.org) is a science policy fellow at ASBMB.





HRUSKA



CHANG



FIERKE



BERTOZZI



GRONENBORN



BASSLER



SCOTT

Hruska takes top post at bone research society

Keith Hruska, who has spent his entire scientific career as a faculty member at Washington University School of Medicine in St. Louis, was named president of the American Society for Bone and Mineral Research. In a statement, Hruska emphasized that his appointment comes at a time when tens of millions of Americans, many of them seniors, are affected by bone diseases, and he underscored his optimism about future solutions that research will yield. Hruska's research focuses on the skeletal contribution to cardiovascular morbidity associated with kidney disease. He serves on the editorial board of the *Journal of Biological Chemistry*. XXXX

ACS honors Chang, Fierke, Bertozzi and Gronenborn

The American Chemical Society's biological chemistry division has named four ASBMB members the winners of its annual awards. Christopher J. Chang of the University of California, Berkeley, won the Eli Lilly Award in Biological Chemistry in recognition of his contributions to the discovery and understanding of new chemical signaling agents in biological systems. Carol

Fierke of the University of Michigan won the Repligen Award in the Chemistry of Biological Processes in recognition of her research of how protein and nucleic acid catalysts achieve high efficiency with rigorous control of reaction specificity. Carolyn Bertozzi of the University of California, Berkeley, who was recognized for her work on bridging the gap between molecular chemistry and biological function, will give the ACS Chemical Biology lecture at the society's spring meeting. Angela Gronenborn of the University of Pittsburgh, who was recognized for her development of nuclear magnetic resonance methodologies for determining biomolecular structures, will give the Gordon Hammes biochemistry lecture at the society's annual meeting next fall. XXXX

Obama nominates Bassler to National Science Board

President Obama nominated Bonnie Bassler of Princeton University to the 24-member National Science Board, which oversees the National Science Foundation. Bassler, a Howard Hughes Medical Institute investigator and the winner of the 2009 Wiley Prize in biomedical sciences, is known for her work with quorum sensing, through which bacteria communicate. Bassler was elected to the National Academy of Sciences in 2006. XXXX

Scott claims an ASPET early career award

Emily Scott of the University of Kansas was named the winner of the American Society for Pharmacology and Experimental Therapeutics's Early Career Achievement Award. Scott, who studies the structure and function of cytochrome P450 enzymes, is supported by the National Center for Research Resources and the National Institute for General Medical Sciences. XXXX

Four members elected to Institute of Medicine of the National Academies

CAROLYN R. BERTOZZI,
University of California, Berkeley

GEORGE GEORGIU,
University of Texas at Austin

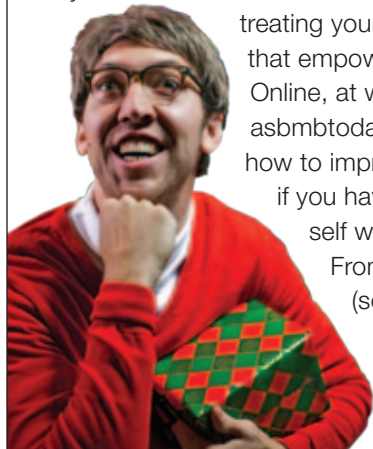
JONATHAN D. GITLIN,
Vanderbilt University
School of Medicine

RICHARD L. HUGANIR,
Johns Hopkins University
School of Medicine

Please submit member-related news and accolades to asbmbtoday@asbmb.org.

Gifts for geeks!

We've all been told to embrace our nature and to celebrate that which makes us individual. So, if your love for science runs to geekdom, consider



treating yourself to special gifts that empower your geekiness. Online, at www.asbmb.org/asbmbtoday, we'll show you how to impress your friends or, if you haven't any, yourself with thoughtful stuff.

From wearable to edible (somewhat), there are geeky projects for the family, too! Who says you can't buy "cool"? ☺☺☺

Bernard Axelrod: 1914 – 2001

Bernard "Barney" Axelrod, professor emeritus and former head of the biochemistry department at Purdue University, died at home Oct. 22. He was 87. Axelrod, who spent 15 years working at the U.S. Department of Agriculture before entering academia in 1954, along with his colleagues, established the presence of the pentose phosphate shunt, an important alternative pathway for the metabolism

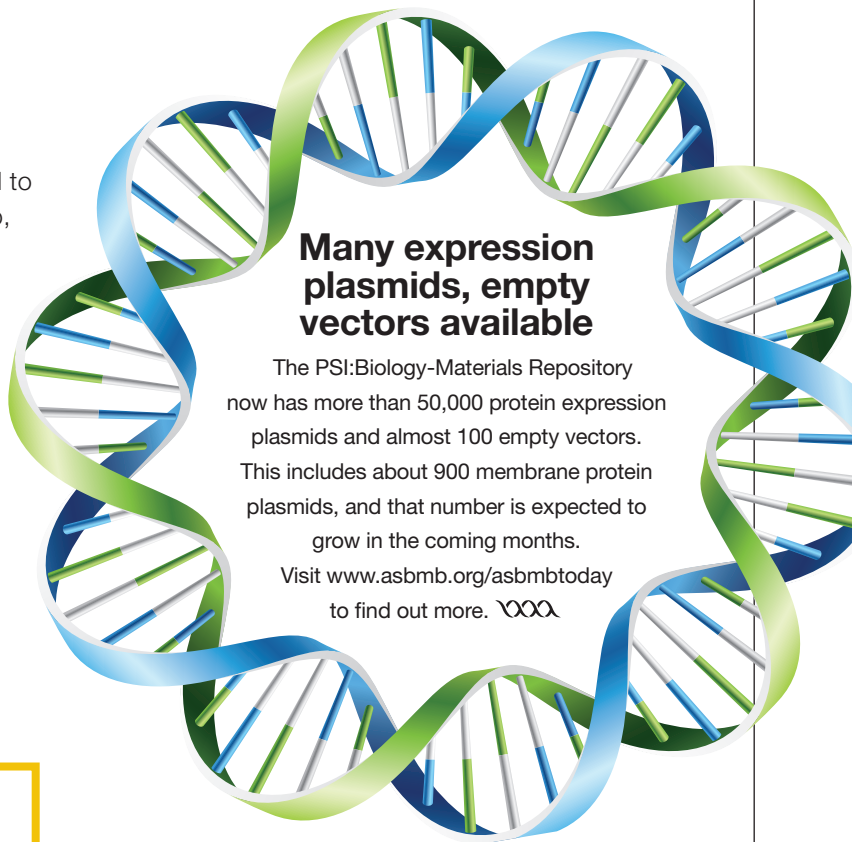


of glucose and other sugars in higher plants. He also developed methods to isolate intact mitochondria and study their role in the energy-production system of plants. For a full obituary, please visit www.asbmb.org/asbmbtoday. ☺☺☺

Many expression plasmids, empty vectors available

The PSI:BiologY-Materials Repository now has more than 50,000 protein expression plasmids and almost 100 empty vectors. This includes about 900 membrane protein plasmids, and that number is expected to grow in the coming months.

Visit www.asbmb.org/asbmbtoday to find out more. ☺☺☺



NIH taps Kaiser as NIGMS director

Chris A. Kaiser, a professor and head of the biology department at the Massachusetts Institute of Technology, will become the director of the National Institute of General Medical Sciences in the spring. He will replace Judith H. Greenberg, who became acting director in July after American Society for Biochemistry and Molecular Biology President-elect Jeremy M. Berg moved to the University of Pittsburgh to become associate senior vice chancellor. Read more about Kaiser at www.asbmb.org/asbmbtoday. ☺☺☺

BMB blogs in brief: lesson bank review

While those who work and study in the field of bioscience have a multitude of reading options, it's sometimes hard to know where to begin when it comes to the blogosphere. There is an ocean of interesting reading out there, and ASBMB Today contributor Aditi Das' monthly

online column is intended to help readers who aren't all that Web savvy yet to wade through it and pick out the gems. In this month's online issue, read her review of The Biochemistry Questions Site. Go to www.asbmb.org/asbmbtoday. ☺☺☺



Five years of giving rural students second chances

Billy Hudson's life continues to inspire the Aspirnaut Initiative for K-12 STEM education

BY RAJENDRANI MUKHOPADHYAY

At the age of 64, Billy G. Hudson, a renowned expert in the molecular basis of kidney diseases, one day returned to his rural Arkansas hometown after an absence of 50 years and got on a yellow school bus. Hudson wanted to help the children in his childhood community but had no idea how to go about it. He decided to ride the school bus. "I don't know why I did it," he says.

It was a chilly October morning in 2005, still dark at 6 a.m., when Hudson climbed up the bus stairs to start the one-and-half-hour trip to the local school on the street he lived on as a child. The bus jolted over gravel roads and went past densely wooded areas with only the occasional glimpse of a house, traveling over land Hudson knew intimately as a child.

Hudson had arranged to ride with the children, who ranged from kindergartners to high-school seniors; spend the six-hour day at school; and accompany the children on the ride back home. In the morning, the children were too wary and shy to speak to Hudson. But in the afternoon, some of them began to pipe up, with one preteen boy telling Hudson he loved math.

The nine-hour school day (including the three hours spent idle on the bus) gave Hudson the inspiration he was searching for to help rural children, who face unique challenges in getting an education. "Many of the children live in poverty and may come from dysfunctional families. They have limited exposure to professional people," says Hudson, a professor at the Vanderbilt University Medical Center who recently celebrated his 70th birthday. He adds that elementary and middle school teachers often don't have the technical expertise to teach science, mathematics,

technology and engineering adequately. On this point, he knew he could help.

With his wife, Julie K. Hudson, a physician and assistant vice chancellor for health affairs at the Vanderbilt University Medical Center, Billy Hudson launched the Aspirnaut Initiative in April 2006. The initiative began with an ordinary yellow school bus outfitted with laptops, iPods, and a mobile Internet router (a novelty back then) that directed

the children to online STEM educational programs so they could use constructively the three hours spent each weekday on the bumpy bus ride. Now, five years later, the initiative has grown larger and involves 500 students every year.

When he started the initiative with his wife, Billy Hudson was no stranger to hard

work. His scientific successes include the discoveries of two new collagen chains and a novel chemical bond that fastens them together. He received the National Institutes of Health Merit Award in 2002 and the Homer W. Smith award, the highest honor from the American Society of Nephrology, for his contributions to understanding kidney diseases in 2003.

But none of these accomplishments hints at the grueling road he took to his current position. Hudson's "life story is fascinating," says friend and colleague Richard W. Hanson at the Case Western Reserve University School of Medicine. "You couldn't do more than what he has done with his life."

From a rural gravel road to Vanderbilt

Billy Hudson grew up on a 15-mile gravel road in rural Arkansas. "My address was Grapevine, Arkansas. The street was 40th and Plumb, meaning 40 miles from town and plumb-back in the sticks, as we'd say," he says with a chuckle.

“ [I] knew I was going to destroy my life... There are champions who come into your life to help you. I was fortunate. ”



Children riding a school bus in rural Arkansas take in science lessons played on TV screens.

Hudson's childhood chores in the 1940s and 1950s included tending to cotton and taking care of 20,000 chickens and other livestock. The physical labor was accompanied by regular and spurious beatings, which his father meted out with tree branches with the message that Hudson was never good enough.

Unable to stand his father's abuse and threats of violence any more, Hudson decided at the age of 16 to drop out of high school to work on a cotton farm. His history teacher

of Environmental Medicine in Boston. It was work on the dialysis machines and a lecture by Robert Spiro of Harvard Medical School that got Hudson interested in diabetes and the havoc it wreaks on the kidneys. That interest has led to understanding the basement membranes of kidneys, which act as a filtration barrier. Diseases such as Goodpasture and Alport syndromes and renal failure arise when there are defects in the basement membrane. Hudson's research led to the discovery of the $\alpha 3$ and $\alpha 4$ chains of collagen IV, which,

and basketball coach, Robert Theus, "knew I was going to destroy my life. He was the one who first showed me a light and how I might get out of my circumstances," says Hudson. "There are champions who come into your life to help you. I was fortunate."

Theus took Hudson to Henderson State Teachers College (now Henderson State University) in Arkadelphia, Ark., where Hudson was allowed to enroll without a high school diploma. There he met chemistry professor and mentor Haskell Jones, who encouraged Hudson to complete a college degree in chemistry. A cafeteria supervisor, Alice Sloan, made sure Hudson had jobs to earn room and board. After Hudson completed one year of college, his high school decided to award him an honorary diploma. Several other mentors guided Hudson into getting a Ph.D. in biochemistry at the University of Iowa under the supervision of Rex Montgomery and Robert Barker. During that time, he studied carbohydrate chemistry.

The Vietnam War was on when Hudson graduated with his Ph.D. in 1966. He joined the army and was assigned to improve filtration membranes for dialysis machines at the Army Research Institute



Billy Hudson joins a videoconference science lab beamed to a rural Maine school.

Back to the roots to solve a problem

But even with decades of scientific success under his belt, Hudson hasn't forgotten his beginnings and has returned to rural America in hopes of helping younger generations replicate his success. "He hasn't turned his back on people who are in the same position as he was earlier in his life," says Hanson.

The current crisis in U.S. science, technology, engineering and mathematics education, caused by inadequate numbers of students taking an interest in these fields, could be helped if the needs of rural students were addressed, says Hudson. Twenty percent of the K-12 student population in the United States lives in rural areas. "It's an untapped pool of talent in rural America that can be brought into the STEM work-

along with the $\alpha 5$ chain, create the essential meshwork for kidney filtration. His work also has found its way into clinical applications. "Before there was such a thing as translational science, he was doing it," notes Hanson.

A company called NephroGenex is currently developing a compound discovered in Hudson's lab that protects against diabetic kidney disease. The U.S. Food and Drug Administration is getting close to approving a Phase III clinical trial to test the compound, Pyridorin, in more than 1,000 diabetic patients.

In 2009, Hudson and his colleagues discovered a novel sulfilimine bond, in which sulfur and nitrogen are double-bonded together, in type IV collagen. This bond exists in all animals but had not been found previously. Hudson says they have now established that an enzyme from the peroxidase family makes the unusual bond, and they think the enzyme and the sulfilimine bond emerged more than 500 million years ago as a primitive form of innate immunity.

force," he says. "The talent is there, but students need to be presented with opportunities."

Aspirnaut Initiative's first bus program rolled into something bigger within a year. Julie Hudson says it quickly



Students participate in a science lab run by the Aspirnaut Initiative.



High school student Jonathan Stroud is mentored by Mohamed Rafi, Billy Hudson's research assistant, during a summer internship. Stroud's program mentor was Roberto Vanacore, and his research project was on Goodpasture's syndrome.

became obvious that time on the school bus needed to be managed better, so the couple started an after-school class twice a week to work with the students. That class in turn grew into something else, which the Hudsons now consider to be the flagship of the initiative.

These days, researchers at Vanderbilt University hold weekly science labs via videoconference with children in rural schools. The Hudsons explain that they base the labs on those developed by the Vanderbilt Student Volunteers in Science program, which takes science kits to students attending Nashville-area schools. But with Internet-based videoconferencing capabilities, the Aspirnaut program now makes it possible to reach schools not physically near Vanderbilt. "We have a real-time interaction with the class, where we're bringing the intellectual assets of a research university, in partnership with the school, to give students hands-on, inquiry-based, critical-thinking activities," says Billy Hudson.

The science labs, built around real-world issues, now get beamed into classrooms in Arkansas, Tennessee and Maine. Hudson gives the example of the theme they built around his research area of diabetes. The children first learn about electricity, magnetism and the concepts of nuclear magnetic resonance spectrometry. Next, they learn about metabolism and how metabolic malfunctions cause diseases like diabetes. Then they hear about how researchers use tools like NMR spectrometry to develop therapies against a given disease. "Rather than say 'Here's a kit in chemistry. Good luck,' we try to relate science and math concepts to their everyday lives through hands-on activities," explains Hudson.

While many scientists immediately see the value of helping with K-12 STEM education, Hudson acknowledges that some say that they have pressures of their own and feel they can't spare the time. Hudson says all that is required of a scientist is to devote an hour once in a while to show up for

a videoconference with a lesson prepared for grade-school children. “We have a responsibility for educating our citizens in science,” urges Hudson. “You’re not going to turn all these teachers out there into STEM experts. You’re not going to turn the scientists into K–12 teachers. But as a partnership? It’s a winning strategy.”

Path out of poverty

In addition to the bus and the videoconferenced science lessons, the initiative has a third program that involves six-week summer internships for high school students doing fundamental research in various Vanderbilt laboratories. “They come from rural communities, earn a stipend, and are provided their room and board,” explains Hudson. “We challenge them to help advance our scientific objectives.”

The students are immersed in the daily pace of research and return to high school in the fall with new experiences that inspire them to work harder in school, says Hudson. The students help the teachers organize the videoconferenced science classes and earn an hourly wage while doing so.

Out of the 36 high school students who have gone through Aspirnaut internships, 26 have finished high school, and 25 of those are now in college. (The math-loving boy Hudson met on the school bus in 2005 participated in some of the Aspirnaut programs and now is in college.)

The Hudsons visualize the Aspirnaut Initiative as a pipeline. Students first get on the school bus and start learning about science, medicine, engineering and mathematics. In elementary and middle school, they get exposed to the videoconferenced labs. Then in high school, they get hands-on experience in research laboratories and find mentors to guide them to college.

The Hudsons’ biggest wish for the initiative is for it to serve as a model for other major research universities, according to Julie Hudson. “While Vanderbilt has an enormous bandwidth, we certainly couldn’t, nor do we wish to be, the end-provider for the entire nation. We have demonstrated that the model is replicable in other rural states.”

Because of the intense mentoring that goes on with the summer interns, the Hudsons get to know the teenagers intimately. “Almost every one of these students has an incredible life story,” she says. One student was born in prison and handed off to his grandmother “in a Christmas stocking” when he was three-weeks old, recounts Hudson. The boy’s grandmother became his legal guardian. Hudson says, “They lived on almost no money for many years because all they had was her pension. That was \$9,000 a year.”

From a young age, the boy was very motivated to change his circumstances. He excelled in school and read a lot. In high school, he taught himself the curricula of a number



Billy and Julie Hudson founded the Aspirnaut Initiative.

of Advanced Placement courses and sat for the exams. He passed 11 AP courses eligible for college credit with flying colors. He applied to the Aspirnaut summer intern program between his junior and senior years of high school and had “an outstanding summer of research,” says Hudson. He maintained ties with Aspirnaut during his senior year of high school by helping with the bus and videoconference programs in his community. “He served as a junior mentor to the students,” she says. “He’s now a sophomore at Vanderbilt and has an excellent academic record. He’s going to apply for early decision to medical school” and is hoping to earn an M.D./Ph.D.

Students like this young man are the ones Billy Hudson always looks out for to introduce to the Aspirnaut Initiative, mindful that he broke out of the circle of poverty and abuse at the age of 16. “We show them education is a way of breaking free of difficult situations,” he states. “That’s the path I know out of poverty and out of abuse. It’s what education can do, but it can’t happen unless an opportunity passes your way.” ∞∞∞



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Synthetic biology: edging toward the clinic

Researchers are carefully moving forward in creating engineered biological systems for applications such as drug production and cell-based therapies

BY RAJENDRANI MUKHOPADHYAY

Slowly, slowly, synthetic biology has been inching toward clinical applications. Those closest to this decade-old field say the time has come to test it against some of the most pressing global clinical challenges.

The goal of synthetic biology is the manipulation of biological cells in a predictable and rational fashion at the molecular level to carry out a given task efficiently and reliably at a cost of mere pennies. James J. Collins, a Howard Hughes Medical Institute investigator at Boston University, explains that over time, the community has become more efficient and savvy in manipulating biomolecules “to reprogram organisms and endow them with novel functions.” While some researchers are focusing on environmental, energy, and commodity chemical production issues, others are tackling longstanding biomedical problems (1, 2).

Some significant steps have been taken recently on the clinical front: Specially designed microorganisms can synthesize critical drugs, and a device has been created to track ovulation in cows for the dairy and livestock industry. Academic research laboratories are pushing for human therapies, such as re-engineering probiotic bacteria to tackle cholera. The brass ring in the field is to re-engineer cells taken from patients and put them back in to cure complex diseases.

What’s in a name?

But in discussing synthetic biology, a schism appears. A PubMed search for “synthetic biology” in journal article titles pulls up 310 articles since 2003. Obviously, there are researchers who believe that synthetic biology is a bona fide field. But some researchers, like John C. March of Cornell University and Andrew D. Ellington at the University of Texas at Austin, assert that “synthetic biology” is just a buzz phrase.

“What does synthetic biology have to offer? Perhaps it is a new way to look at things, but really many of the same

thrusts have been proceeding under the rubric of biotechnology, molecular biology and bioengineering,” says Ellington. “This cobbled-together field adopted a name, but that doesn’t mean it has any sort of intellectual center or gravitas.”

March says he hasn’t seen anything in the literature that suggests synthetic biology is a new science. He sees it largely as sophisticated genetic engineering. Journal articles about synthetic biology don’t describe anything more than “taking genes out of one organism and putting them in another and looking more at the transcriptional control of gene expression,” which has been done for more than 30 years, says March.

Collins says he understands the criticism. Synthetic biology is closely related to genetic engineering and “utilizes the tools and methods that were developed as part of genetic engineering,” says Collins. “It’s genetic engineering on technological steroids.” He and other self-described synthetic biologists say genetic engineering tends to focus on individual genes, while synthetic biology strings together a series of molecular components, such as DNA, RNA, proteins and cells, into circuits and networks.

“Conventional genetic engineering often refers to cutting and pasting genes from one place to another without fine control over how the genes are regulated or a clear understanding of all the detailed molecular mechanisms,” explains Timothy K. Lu at the Massachusetts Institute of Technology. “Synthetic biology puts a lot more emphasis on separating out components into individual modules and functions,” such as understanding how to quantitatively control translation and transcription rates. In addition, synthetic biologists don’t want to pursue the one-time genetic engineering of an organism but want “to build a set of tools that will allow you to do many types of modifications, regardless of your end application, much more rapidly, quantifiably and predictably,” says Lu.



First indications of clinical applications

Regardless of whether you call it synthetic biology or improved genetic engineering, the field has begun to make some headway in clinical applications, such as using engineered microorganisms for cost-effective, timely and robust drug production. An example is artemisinin, an antimalarial drug whose extraction from the Chinese sweet wormwood plant is inefficient and expensive. Given that every year malaria infects 300 million to 500 million people and causes 1 million to 2 million deaths, mostly in the developing world, cheaper and more readily available sources of artemisinin-type drugs are urgently needed.

Jay D. Keasling's laboratory at the Lawrence Berkeley National Laboratory and the University of California, Berkeley, armed with a \$42.5-million grant from the Bill and Melinda Gates Foundation, engineered *Saccharomyces cerevisiae* to produce artemisinic acid, which is readily converted into artemisinin by chemical means. To engineer the yeast, the researchers first created a new metabolic pathway in the microorganism. Next, they placed bacterial and wormwood genes in the yeast genome so that the products of those genes interacted in the new metabolic pathway to produce a precursor to arte-

misinic acid. The researchers then added the wormwood cytochrome P450 gene so this precursor would be converted to artemisinic acid.

The researchers estimated their method could produce the drug for 25 cents per treatment. The conventional approach of extracting artemisinin from the plant costs about \$2. This year, Sanofi-Aventis licensed the technology to optimize it and scale it up. The company hopes to have synthetic artemisinin in the supply chain by 2013.

A more complicated application of synthetic biology involves engineering biological components to work inside a mammal. In the dairy and livestock industries, farmers struggle to determine when a cow is ready to be impregnated, which they do by observing the cow's behavior.

But even if they correctly guess when a cow is ovulating, artificially inseminating the cow with sperm from a plastic tube has only a 40 percent success rate.

Earlier this year, Martin Fussenegger's group at the Swiss Federal Institute of Technology in Zurich developed a capsule made from cellulose polymers (3). Into the capsule they placed sperm and engineered mammalian cells that detected luteinizing hormone (the ovulation signal) and produced cellulase in response. The capsule works like this: A farmer tracks an animal's 21-day ovulation cycle and notes when ovulation is most likely to start. The capsule keeps the sperm fresh for three days, so a vet inserts the capsule into the cow's uterus a day or two before ovulation. When luteinizing hormone surges through the cow, the engineered cells inside the capsule detect it and initiate the expression of cellulases. The cellulases degrade the capsule and release the sperm. In the first trial run carried out in Switzerland, Fussenegger says the device had a 100 percent success rate.

Other efforts to develop clinical therapeutics are still in the laboratory testing phase. For example, researchers are looking to exploit the commensal bacteria that reside in the gut.

“There are a number of things these bacteria normally do daily in the intestine that we just haven’t tapped into,” says March. “There is no reason why we couldn’t engineer them to act on the behalf of their host rather than just on their own behalf.”

March’s team has manipulated commensal bacteria to treat cholera. *Vibrio cholerae*, the bacterium that causes the infection, populates the upper intestine and reaches a certain density after which it stops making its colonization proteins. It then exits the body by diarrhea, causing life-threatening dehydration in victims. March’s team decided to beat *V. cholerae* at its own game by getting a probiotic *Escherichia coli* strain to produce the signature quorum-sensing *V. cholerae* proteins. “If [*E. coli* bacteria] were making the signal and a *V. cholerae* bacterium came in, it would think other *V. cholerae* were already there. It wouldn’t attach,” says March. The investigators were successful in getting the method to work in a mouse model last year (4).

Cholera is rampant in the developing world, where affected populations often can’t afford the two vaccines currently available for more than \$1.50 per dose. March’s approach with engineered commensal bacteria would be relatively inexpensive: The bacteria could be laced into fermented foods, such as yogurt, and passed through communities as fermentation starters without incurring costs.

Cancer therapies also are being pursued. Current methods often cause unpleasant side effects in patients, because they take down healthy as well as cancerous cells. Ron Weiss’ group at MIT, in collaboration with the laboratory of Yaakov Benenson at ETH Zurich, described a system earlier this year that distinguished HeLa cells from normal ones in a mixed-cell culture with great specificity (5). The system used small interfering RNA to measure the expression of six microRNAs that marked cells as cancerous: Three of the microRNAs were typically overexpressed in HeLa cells, while the remaining ones were expressed at extremely low levels. When the magic combination of the six different expression levels of the microRNAs identified the cell as being HeLa, the artificial system triggered



apoptosis in the cell. Weiss says the approach of using six different microRNA markers is much more sophisticated and specific than current therapies, which often rely on a single biomarker and are more prone to mistakes.

The approach can be generalized for other types of cancer cell types and could accommodate other types of biomarkers, such as messenger RNAs and proteins, because “we look for the symptoms, not the underlying cause” of the cancer, says Weiss. Because each cell type has a unique combination of biomarkers, he says, it’s a matter of identifying the unique features of each cancer cell type for targeting purposes.

Technical difficulties

As with anything scientifically ambitious, the technical hurdles in synthetic biology are enormous at the early stages. To begin with, the experts say they need to expand the number of well-characterized molecular tools. “It would be so great to have a whole toolkit of well-characterized components sitting on the shelf that we could mix and match,” says Keasling. Meanwhile, Collins explains that the present-day tools of molecular biology “are relatively small and narrow, whether it’s Tet- or Lac-based systems or T7 phage.” He says there are numerous molecular parts that “are not sufficiently characterized or developed to be used as tools in synthetic biology.”

This is where the trove of molecular biology literature comes in, points out Pamela A. Silver of Harvard University. The old literature, she says, is “ripe with things that we can use as parts to build devices.” Silver gives the example of lambda phage, the subject of much research over the past 30 years. “The beauty of that work is that it was done in a lot of detail, and now we can turn around and apply it in a very quantitative and predictable way.”

The complexity of biology is challenging on two levels. First, interactions of synthetic components with endogenous players in different pathways within a given cell are inevitably a problem, says Keasling. Modern technologies that look at large ensembles of molecules, such as DNA arrays, proteomics and metabolomics, help us to understand how pathways are connected to one another. However, the introduction of a synthetic pathway may accidentally set off different pathways, he says, adding that, with the knowledge gained from these technologies, it’s often possible to re-engineer synthetic components to minimize interference.

Then there is the interaction of the engineered entity with the mammalian system. Fussenegger explains that researchers are just coming to grips with the complexities of human systems. “We still do not understand the dynamics of systems biology. We do not even understand the differences among humans in terms of genome,” he says. “If you want to implant something which interfaces with a very complex system, this is very difficult.” The complexity worries March: He says purported synthetic biology tools currently developed may get lost in the noise of complex systems.

This is why “synthetic biology is giving way to systems biology,” says Ellington. He explains that no matter how independent a synthetic pathway appears to be from endogenous pathways in a cell on paper, it’s “going to interact with transcription, translation and signal transduction. Many of the ways in which it does interact are going to be unknown prior to implantation.”

Ellington says molecular biologists can’t always predict outcomes of genetic manipulations. If the outcome of a simple genetic manipulation can’t be predicted with certainty, it’s “very difficult to predict the outcome of a complex engineered biological system within a human. It’s a fact we encounter regularly at a simpler level with the unanticipated consequences of gene therapies,” he says.

Synthetic biologists disagree. “Synthetic biology aims at creating new forms of life, genetic circuits and behaviors in cells. Systems biology looks at existing natural systems and tries to understand how they work,” says Weiss. Although the two may have some procedures in common, they have “very different perspectives but more importantly, different goals,” he says. Lu further expands by saying the modus operandi of synthetic biology is to have better quantitative control over “molecular

engineering techniques that others have been doing over the last 20 years” with higher throughput and predictable and logical properties.

‘Why wait?’

By any name, the endeavor to create artificial biological systems for clinical applications will raise some fundamental questions: What happens to engineered cells when they enter complex mammalian systems? How stable will these engineered entities be in complex environments, and how long will they last? Can parts engineered for one particular mammalian system be translated easily to another? And do the engineered components actually do what they are supposed to do and not unwittingly unleash more havoc? Because of these unanswered questions, synthetic biologists are taking it slowly, keenly aware of the possibility of a backlash like the one that followed early attempts at gene therapy. Those interviewed for this story say it will be at least five years before there are clinical trials using synthetic biology components.

But with all these questions hounding the field, one may very well ask if synthetic biology is even ready for clinical applications. Keasling says he has heard the criticism before. But his response is this: “Why wait?”

Keasling says there is enough knowledge in some areas of biology to have well-characterized components that can be used for initial synthetic biology applications. By pushing the boundaries of the unknown, both synthetic biology and its foundation, molecular biology, stand to benefit. For example, Lu says, by delving into the mechanics of how to solve certain disease states, “synthetic biology can help us understand disease processes more efficiently” at the molecular level.

But he and others say synthetic biologists will need time, investment and collaborative efforts to figure out the best means of delivering safe and effective therapeutics to patients. As Lu notes, “The road is going to be a long one.” ∞∞∞



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Tips for writing your first scientific literature review article

BY EMILY CRAWFORD

When I undertook the task of writing a scientific literature review article last year, I had hoped that a Google search would reveal a handful of how-to pages thoughtfully created by veterans of this particular writing process. I found nothing of the sort, so I plowed ahead on my own, inventing techniques for myself. I'm now offering this piece for other young scientists who find themselves in similar situations. What you're reading now is basically a case story with an N of one, but it is the sort of essay I wish had been available to me when I started.

I was running a protein over a nickel column on a Sunday evening in February 2010 when my adviser approached me about co-authoring a review article for *Annual Review of Biochemistry*. My adviser is a busy guy, with a lot of papers and grants to work on, so I knew that by "co-author" he meant that I would be the main researcher and writer, getting mostly broad, guiding suggestions from him. That was fine with me — as a fifth-year graduate student, I had learned to cope with, and even prefer, extreme independence. To be honest, I was excited to have this opportunity to examine the literature in depth and to create something useful out of it. The due date was August, so I had six months to synthesize decades' worth of research papers on our topic into one conveniently sized, nicely packaged bundle of facts and interpretations.

Getting started

Our topic was caspase substrates, a diverse group of proteins essential for programmed cell death and thus important to our understanding of how to kill cancer cells. A PubMed search for "caspase substrates" yielded more than 2,000 research papers. I had no illusion that this project could approach comprehensiveness, and luckily my adviser didn't either. I would have to assess the limits imposed by the journal (30 pages, six months) as well as my own limits and the necessity to balance the writing project with lab work that was essential to finishing my Ph.D.

Narrowing the scope of the article to conform to these boundaries was perhaps the biggest challenge of this process.

Knowing that I work better when I focus on one project at a time, I spent the next two months carrying out all of my regular lab work while only pondering the review article and skimming the literature when I had time. After that, I transitioned to full-time reading and writing. I found a café that I liked in

my neighborhood and spent nearly every morning there that summer drinking tea, eating pumpkin muffins and working on my laptop. Afternoons I often spent writing at my apartment or at the library on campus. I knew that concentrating on the article in my crowded, noisy laboratory would be impossible, but it also was essential to spend some time there each week consulting with my labmates on my literature research, keeping up with lab business and gossip, and retrieving my ergonomic pipettes from other peoples' benches around the lab (they always seemed to get kidnapped as soon as I posted a "working from home" status update on Facebook).

The finished product

There were many points at which I felt overwhelmed by the task and didn't see a clear path to finishing the article on time. I tried to reassure myself by remembering that I had been rather good at writing term papers in college; but this was a larger task and one with the potential for having an impact on someone, somewhere, sometime who wanted to learn about caspase substrates. In the end, I finished by the deadline (well, plus one two-week extension the editor agreed to grant me) and was very happy with the product and with all I had learned about caspase substrates, about the scientific literature and about the review-writing process. Yet I estimate that the next time I undertake a task like this, I'll be able to do it in half the time. I hope the following tips will help other scientists who find themselves in this kind of uncharted territory.

I'll end by mentioning that, for me, this was one of the most rewarding experiences I've had during my time as a Ph.D. student. Distilling all sorts of data from experiments done by scientists all around the world into a coherent story turned out to be very satisfying. I look forward to doing it again someday, perhaps in a somewhat more efficient manner.

1. Define the scope of the article. Make an outline, keep lists of topics that are and are not within your scope, and remind yourself to stop any time your reading wanders outside your scope. My adviser and I settled on devoting the first half of our article to a broad survey of a few key research topics (for example, the physical details of the caspase-substrate interaction) and devoting the second half to a few highly detailed vignettes about some of the hundreds of known caspase substrates.



Emily Crawford often retreated to her apartment rooftop in San Francisco to write her review. PHOTO: MATTHEW PERRY

2. Your labmates and collaborators

are invaluable resources. Each has a specific area of expertise that's probably slightly different from your own.

Ask colleagues which papers they'd give to a rotation student to read and what the most important recent advances are in the field. (Be careful not to let this lead you too far astray. Your colleagues' ideas may help you define your scope when you are starting out, but you do not have to incorporate all of their suggestions if you don't feel they're relevant.)

3. Don't dwell on previous review articles that have been written on your topic (this quickly can become a black hole that sucks up time and gives you unnecessary insecurity about the contribution you're trying to make to the field), but do familiarize yourself with their content. Look for areas that have not yet been thoroughly reviewed or areas for which you think you have a fresh take on old data. One of the most painful things that can happen is to spend days reading and writing about a topic only to notice later that there's a section of another review article that explores the same area, references the same set of papers and comes to the same conclusions.

4. Make yourself comfortable. This may seem obvious, but I think it's important. Find places to write where you can concentrate, and take breaks often to stretch, get a snack or even step outside for a few minutes. On days when I struggled with concentration, I often used a timer to structure my day. I would work for 60 minutes, then take a sanity break, then work for another 60 minutes, and on and on.

5. Impose some structure on the mess that is the scientific literature. I developed a strategy for each research topic that I wanted to review (including the broad survey section in the first half and the vignette sections in the second half). First, I found the most recent papers on the topic and went through them, picking out what looked like important references. I worked my way backward to a set of about 10 key papers. Then I quickly read and made a summary for each, usually in the form of a bulleted list of the conclusions drawn from each figure. Next, I combined those summaries into a single table. (I did this by hand on paper; an Excel spreadsheet also would work). Each research article was one row (arranged by publication date), and the columns were results or con-

clusions reached. I then easily could see which papers agreed on which topics, what trends emerged over time and where the controversies in the field lay. I found that once I had made a table, the narrative of that particular research topic almost wrote itself.

6. Spend some time writing with all your PDFs and Web browsers closed and your desk cleared of any paper.

This was advice my adviser gave me about a month before the due date, when he could tell that my brain and my PDF library were so overflowing with data that I was struggling with actually producing any text. I didn't find it easy at first. I didn't want to get anything wrong, even in a draft, so I was afraid of typing even a single sentence without references to back me up. On the other hand, with the Internet and all my PDFs in front of me, I tended to generate sentences that were very dense with information but not necessarily closely related to each other — and not always pertinent to the specific scientific narratives I was attempting to compose. I started making real progress on the writing only

when I spent a few August afternoons sitting on the roof deck of my apartment building with a pen and paper and no Internet-capable devices. Yes, I sometimes wrote things that were wrong (or at least imperfect) when constructing a section from memory. However, I often ended up with a strong scaffolding onto which I could later add some of those dense, fact-laden sentences.

7. Don't be shy about clearly defining your role relative to that of your co-author(s)

before you begin, or even along the way, if you feel amendments are needed. This was easy in my case, because my adviser and I both preferred that I be the main researcher and writer and that he act as a consultant on high-level issues. However, I am keenly aware of other cases that did not work out nearly as congenially.

8. Read the journal's instructions for submissions carefully.

You should have the email address of an editor at the journal; don't be shy about asking questions. Do not ignore the journal's page limits or formatting requirements. Pay very close attention to the graphical requirements for figures. Make sure to get permission to reproduce any figures in your review. (This usually is done by following the permissions instructions on the website of the journal in which the original figure appeared. It's also not a bad idea to email the authors who made the figures to let them know that you will be using their work).

9. Get familiar with software like Papers (or any other PDF-management software), EndNote and Adobe Illustrator (or whatever graphics program the journal suggests). For me, online Adobe Illustrator tutorials provided nice breaks when I'd been reading for hours and hours.

10. Your labmates and collaborators also can help you with the editing process.

Rather than asking one or two people to help you edit the entire article, break it up into sections and ask a different colleague for his or her expert help in revising just one section on a topic with which you know he or she is familiar. Another strategy is to give part or all of your article to a first-year graduate student or to a scientist in a slightly different field. He or she is your target audience and will let you know if there are sections that need to be revised for clarity. ∞∞∞



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The Department of Integrative Biology (<http://www.ucdenver.edu/academics/colleges/CLAS/Departments/biology/Pages/Biology.aspx>) on the University of Colorado Denver campus seeks to fill three new tenure-track faculty positions: Assistant Professor in Molecular Biology (Job #815425 at www.jobsatcu.com); Assistant Professor in Genetics (Job #815436 at www.jobsatcu.com); and an Assistant Professor in Systems Biology (Job #815434 at www.jobsatcu.com). **Review of applications will begin as they are received, and will continue until the positions are filled.**

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A shot in the arm for outreach

ASBMB members, staff tackle public's questions about flu

Last month the American Society for Biochemistry and Molecular Biology partnered with the Rockville (Md.) Science Center to co-sponsor an event dubbed “Flu Fest.” The event, which included a public discussion on the science of the flu and offered free flu shots to local residents, was held Nov. 16 at the Universities at Shady Grove.

One of the discussion leaders was ASBMB member Barney Graham of the National Institutes of Health Vaccine Research Center, who stressed to participants the importance of getting vaccinated.

“The [flu] vaccine really does work,” he said, crediting vigilant vaccination campaigns for the low mortality rate during the 2009 H1N1 outbreak in particular.

Anna Ramsey-Ewing, who also works at the NIH, focused on a similar theme in her presentation, pointing out historical examples of diseases tamed through vaccination. Ramsey-Ewing also responded to questions from participants, allaying audience members’ fears about getting the flu from the shot and debunking media-fueled chatter suggesting links between vaccines and autism.

For the event organizers, the discussions exemplified the type of public outreach that is becoming increasingly prominent among scientists.



Hunt



Ramsey-Ewing



Graham

ASBMB member Ed Eisenstein, who is a professor at the Universities of Shady Grove and who serves on the board of trustees of the Rockville Science Center, praised the event as “another wonderful example of ASBMB working with our community to increase their interest and awareness of the science and technology underlying health care.”

ASBMB staff member Geoff Hunt, who headed up the society’s part in the event, echoed Eisenstein’s sentiments: “The presenters enjoyed interacting with nonscientists, and the audience asked really insightful questions. Hopefully, Flu Fest will serve as a catalyst for future ASBMB outreach events.” ∞∞∞

‘Show-Me’ science outreach to adult populations

A University of Missouri science-outreach course gives graduate students the skills to present science to the public

BY MELODY KROLL

For many scientists, outreach means working with the K – 12 community or museums. Outreach to the adult public is often neglected, even though we may find ourselves in personal and professional situations where we need to speak to the adult public.

“Adults are generally overlooked in terms of science outreach,” said Gavin King, assistant professor of physics at the University of Missouri. “If you didn’t engage in science as a kid or you’ve gone through life as a nonscientist, then you tend to be ignored by the scientific community as a whole.”

Well, not at the University of Missouri, where a model graduate-level course is giving students the skills, experience and confidence to communicate effectively with the adult public.

The vision

The course is the brainchild of Hannah Alexander, an adjunct associate professor of biological sciences in the College of Arts and Science at the University of Missouri.

Alexander credits the impetus for the course to a conversation she had with a woman who proclaimed that she would refuse to immunize her daughter.

“When I asked her why, the woman said ‘my girlfriend says I don’t need to,’” Alexander recounted. “I recall thinking: There is 150 years of science, and there is her girlfriend, and her girlfriend has more weight than science.”

Alexander’s eureka moment, however, came later: “It hit me that if, in this day and age, her girlfriend has more credibility than I do, then it’s my fault, it’s our fault as scientists collectively, that we never explained it to her.”

Having just spent two hours explaining vaccines to this woman, she was aware that talking science to adults is tricky. “It requires certain skills and practice that most scientists, let alone graduate students, do not necessarily have,” said Alexander, who has more than 40 years of experience as a molecular biologist. She decided that she would teach those skills to the next generation of scientists.

“That’s what is unique about Hannah’s vision,” said King. “She sat down and actually said let’s break this down into nuts and bolts and actually teach the skill set that is necessary to effectively communicate research to the adult public.”

The course

The outcome of Alexander’s vision is Science Outreach: Public Understanding of Science, a graduate-level course designed in collaboration with her now-deceased colleague Sandra Abell. The semester-long course is divided into three parts: The first two occur in the classroom and focus on choosing topics and crafting presentations, and the third includes presentations around the community.

Students construct presentations that emphasize the role of science in everyday life. For example, the presentation “Why is it getting harder to see as I get older?” covers how laser surgery is the result of years of basic research on the physics of lenses and light waves, neuroscience, the anatomy of the eye and so on. Presentations purposefully avoid political, cultural or religious agendas and focus instead on the scientific process.

Deliberately, students choose a topic other than their research. The reason is to put students in the public’s shoes: “They’re learning about a topic for the first time. It forces them to question jargon and use words they might not have thought to use to describe the topic,” Alexander said. Each student is paired with a faculty mentor who is familiar with the topic and willingly provides guidance on the science, talk and presentation.

Students deliver their presentations in class for feedback on their efficacy, interest and impact. These critique sessions are friendly but fierce, providing praise and pointing out weaknesses in clarity, organization and delivery.

Science & Me

At the heart of the course are the presentations for real audiences. The presentations are billed under the banner “Science & Me,” a title that Alexander said captures the course’s goal:



Jennifer Hamel, a doctoral student in the Division of Biological Sciences at the University of Missouri, explains her research on parent-offspring communication in insects at the Ordway-Swisher Biological Station in Gainesville, Fla. She is using the lessons she learned about presenting research to adult audiences in the Science & Me initiative to explain her own research at different outreach events.

PHOTO: JOHN P. HAYES

“to highlight the pivotal and irreplaceable part that science plays in our lives on a daily basis.”

The presentations occur in a variety of public venues, including independent-living facilities and a public library. Surprisingly, identifying venues is not a challenge, according to Alexander. “Groups are elated to have us, particularly the assisted-living facilities.”

The titles of past presentations illustrate the variety and range of topics: “The aging brain: what to remember about memory loss,” “The physics of flushing— how science is improving the most commonly used seat in our house,” “The science behind the sounds of music,” “My family’s genes: Do I have to be a chip off the old block?” and “Critters in my back yard: Why do deer keep eating my flowers?”

Class time after each public presentation is dedicated to

debriefing. Students share their experiences, the reception they received, and the range and types of questions asked. “It’s an iterative process,” said Alexander. “Each student gives their presentation several times and refines it for clarity, interest and impact.”

To date, 27 graduate students from nine departments have gone through the course and given 103 presentations. This year the program has been expanded and is being offered at Westminster College in neighboring Fulton, Mo.

Learning firsthand

Jennifer Hamel is a fifth-year doctoral student in biological sciences at MU. She was among the first cohort of students to take the course with Alexander. The opportunity to give lectures to older audiences drew her to the course, she said.

"I was intrigued. I had done some outreach with children in the past but never with older adults. They are a really different audience and have to be approached in a very different way," said Hamel.

Hamel's doctoral research is on parent-offspring communication in insects, but for the course she prepared a presentation on amphibian conservation. Presenting on a topic unrelated to her research was, she said, a great learning experience. "I had to read and think about a field of research that is not so far from my own, but it's not what I've been doing for the past five years. I had to read about it, think about it and then think about how to tell that story with no jargon and no preexisting knowledge."

The experience also pushed her to be prepared. "When you get a Ph.D. in biology, a member of the community or your family expects you to be an expert in biology and to interpret biology for them. It was a really good preparatory exercise in that way," said Hamel.

At her first presentation, she got firsthand experience of the challenges of presenting science to the public. During her talk, an audience member became increasingly upset and confrontational, particularly taking issue with her use of data from United Nations-funded projects as evidence that biodiversity was declining. Hamel recalled the experience as uncomfortable but ultimately positive.

"It was my first experience presenting information to the person who really needs to hear it," she said. "He had strongly held misconceptions about science, scientists, the agenda of scientists, conservation, biodiversity, about all of it. I am actually quite glad it happened when I was still in graduate school."

Hamel subsequently gave the same presentation at additional venues, including two adult-living facilities, an alumni event, the local library and on a local television show.

For Hamel, the course has better prepared her as a scientist: "I see it as just one more thing in my toolkit: How am I going to speak to the public about this topic that they don't know anything about? I think that is a really valuable skill set to have as a scientist."



Hannah Alexander (AlexanderH@missouri.edu) is an adjunct associate professor of biological sciences at the University of Missouri. For more on Alexander's work see www.scienceandme.org.

'Show Me' more

In 2010, Alexander initiated a graduate-level certificate of science outreach at the University of Missouri and recruited King, a physicist and strong advocate for science outreach, to co-chair the program. The purpose of the certificate is straightforward, said Alexander: "to cultivate the sense that public engagement is an ordinary part of the professional life and to recognize students who make efforts to develop in this area." She is confident the program will be a significant asset to future scientists who will be asked to demonstrate the broader impact of their research.

Alexander has co-authored two articles about the Science Outreach: Public Understanding of Science course, one in the *Journal of Intergenerational Relation-*

ships and one in the *Journal of College Science Teaching*. Although a successful and productive author of research articles, Alexander has new insights into the difficulties of getting the word out about such programs.

"Many outreach programs do not start as controlled experimentation in science outreach but rather as an initiative by a scientist who believes in talking to the public," she explained. "As such, they lack formal assessment and evaluation, which are required for scientific publication."

She has since been encouraging scientific societies and journal editors to consider allotting a small space in their publications in which science-outreach programs can be advertised and shared.

If the recent attacks on federally funded science programs (e.g., the "shrimp on a treadmill" study blasted by AARP) in Congress and in the news are an indication, the need for more science outreach to adults is ever more pressing.

As King said, "It's no longer taken as a given that science is a good thing. We have to convince the public that what we're doing is beneficial." ∞∞∞



Melody Kroll (krollmm@missouri.edu) is executive staff assistant for the Division of Biological Sciences at the University of Missouri.

The evolution of genomics

BY ROZA SELIMYAN

What more powerful form of study of mankind could there be than to read our own instruction book?

— Francis S. Collins

WHITE HOUSE PRESS CONFERENCE, JUNE 26, 2000

Earlier this year, we celebrated the 10th anniversary of a historic moment for humankind: In February 2001, *Nature* and *Science* published papers on the first draft version of the human genome. Sequencing of the human genome was completed in the most efficient way available at that time both in terms of time and costs (1). This efficient approach is also characteristic of the other goals articulated in the Human Genome Project and would not have been possible without strong collaborations between different groups, institutes and international consortia. According to the third and final five-year plan of the HGP, one-third of the human genome was to be sequenced by the end of 2001 and the entire genome by the end of 2003 (1). However, in June 2000, the International Human Genome Sequencing Consortium announced the completion of a rough-draft sequencing of the entire human genome — an astounding achievement.

Much progress has been made between the pre- and post-genomic eras. Here, I will attempt to touch on some of the most important milestones achieved so far. In order to appreciate fully the evolution of technology and our knowledge, let us compare where we stood before the launch of the HGP with where we stand now.

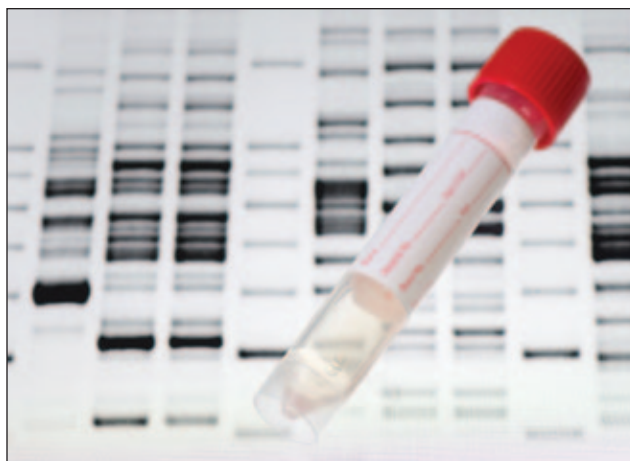
Advances in technology have made sequencing more time- and cost-effective, more accurate, and easier. Sequencing capacity has increased more than 10^{12} -fold (2) since the pre-genomic era, and the cost-effectiveness associated with increased sequencing has improved at least 15,000-fold (3). Developments in sequencing technologies have outstripped

Moore's Law and outpaced progress in computational performance. Progress in sequencing even has made it possible for new disciplines like metagenomics to be born.

Advances arising from the HGP ended the era of coarse-resolution maps and provided scientists with much higher resolution maps, readying them to ask more sophisticated questions. Such maps now model 3-D folding, epigenetics, cancer genes, evolutionary conservation, evolutionary selection and disease association.

Questions that cannot be answered by human research because of either ethical or technological limitations can still be posited and addressed through the study of model organisms. Sequencing the genomes of model organisms

also has been of the utmost importance. When we understand how a given species' genes function, this information becomes very helpful when attempting to predict how genes of other species function. Indeed, as Jacques Monod said, "Once we understand the biology of *Escherichia coli*, we will also understand the biology of an elephant." The successful completion of the sequenc-



ing of the entire genome of a live organism — *Haemophilus influenzae* (1.8 Mb) — for the first time in 1995 marked a new era in the evolution of the biomedical field. Up until then, only a handful of viral and organellar genomes had been sequenced, including bacteriophage Φ X174 (5,368 bp), which was the first DNA-based genome to be sequenced, as well as bacteriophage I (48,502 bp), cytomegalovirus (229 kb), vaccinia (192 kb), mitochondrion (187 kb), chloroplast (121 kb) and smallpox (186 kb).

At the turn of the millennium, before the sequencing of the human genome, the genomes of four eukaryotes (*Saccharomyces cerevisiae*, *Caenorhabditis elegans*, *Drosophila melanogaster* and *Arabidopsis thaliana*) and a few dozen prokaryotes were sequenced. The size of the sequenced genomes combined was less than 500 Mb. Nonetheless, at

that point, only five years had passed since the completion of the first sequencing of a live organism's genome. But, now, after 10 years, we have sequenced more than 250 eukaryotic and 4,000 prokaryotic and viral genomes, the total size of which is greater than 130 Gb!

The successful sequencing of small genomes gave the HGP several advantages. For example, improved sequencing techniques finally made the HGP feasible and brought its completion before the originally planned deadline. But more importantly, sequencing of the genomes of various organisms has allowed us to address questions relevant for both biology and medicine. Although it is important to identify those genes that are conserved, much may also be gleaned by studying gene divergence between species. Comparative genomics continues to provide helpful information about the structure, function and regulation of genes and how they relate to disease susceptibility and other issues by comparing the genomes of different species, whether they are evolutionarily distant or closely related like humans and Neanderthals.

When the HGP first launched, humans were thought to have nearly 100,000 genes. In 2001, it was clear that the actual number was much lower, and it was estimated to be between 30,000 and 40,000 genes. We now know that the actual number is even lower: approximately 20 to 25 percent of the originally predicted amount. This finding has sparked a renewed interest in the study of alternative splicing. We now know that even though many eukaryotic genes operate according to the one gene, one protein scenario, 94 percent of human genes undergo alternative splicing, a very effective tool that allows human genes to make up at least three times as many proteins.

We have discovered that less than 10 percent of the human genome encodes proteins and that what we have called "junk DNA" carries out important functions. We have gained an appreciation for the importance of noncoding RNAs, including piRNAs, microRNAs and lincRNAs. With regard to mutations, researchers have identified approximately 4,000 genes that cause genetic diseases. Among them are not only single-gene Mendelian disorders but also complex diseases such as cancer.

Progress in genome sequencing has not benefitted only researchers, doctors and patients; farmers and pet owners have profited as well. Besides making a difference in

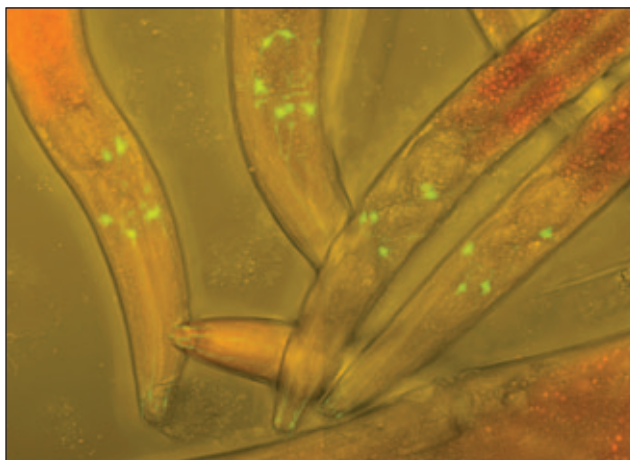
agriculture, sequencing the genomes of domestic animals enriches our knowledge of conserved evolutionary pathways and genetic mechanisms of disease in those animals and in humans. Also, sequencing the genomes of disease-causing organisms is very important for the medical and veterinary fields.

Many of the achievements we have accomplished over the last decade were inconceivable at its beginning. However, many projects once considered overly ambitious now appear reasonable. For example, for years the thousand-dollar genome project sounded like science fiction; yet now the expectations are even higher, and we look to the day when we can sequence our own personal genomes for a more affordable price.

There remains a huge amount of work ahead of us. Although it may have seemed that the final sequence of the human genome had been determined in 2006, it is not yet

complete. Human DNA fragments are still being sequenced, resequenced and analyzed. The genomic databases will be updated with the revised sequences. And there are many projects to complete, including characterization and cataloging of all transcript variants and epigenomic modifications as well as all intermolecular interactions between DNA, RNA and proteins.

We have made great progress in understanding the molecular mechanisms of diseases and developing diagnostic tools and effective treatments. Thanks to advances in genomic sequencing, we are moving away from the chemotherapy era and toward personalized medicine. But we cannot rest comfortably on our laurels, because, the more we learn in the post-genomic era, the more we realize how much more there is to know and explore in our instruction book. ∞∞∞



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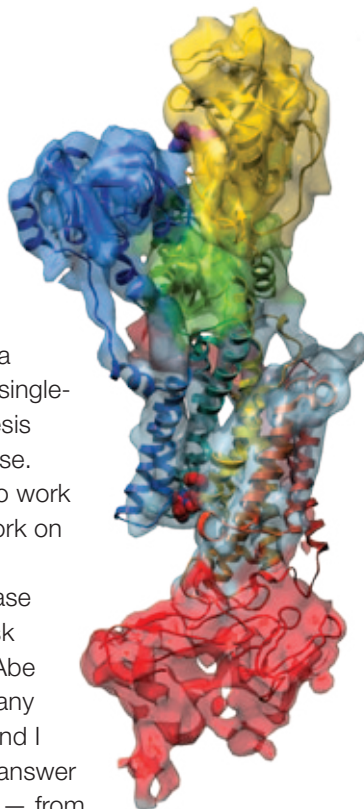
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Pumped up about ATPases

Kazuhiro Abe, a postdoctoral researcher at Kyoto University, won a Journal of Biological Chemistry/Herb Tabor Award for his studies of the molecular mechanisms of a P-type ATPase.

A native of Sapporo, Japan, Abe earned his Ph.D. at Hokkaido University under Kazuya Taniguchi. There, using classical kinetics and single-molecule fluorescence measurements, his thesis was on the mechanism of gastric H^+/K^+ -ATPase. He subsequently moved to Kyoto University to work under Yoshinori Fujiyoshi and do structural work on H^+/K^+ -ATPase.

“Gastric H^+/K^+ -ATPase has the remarkable task of pumping protons,” Abe says. “But there are many remaining questions, and I do hope to be able to answer them in the near future — from the structural and functional point of view.” XXXX



Gastric H^+/K^+ -ATPase



Kazuhiro Abe was named the winner at the 13th International ATPase Conference held in late September in Pacific Grove, Calif., and attended by Journal of Biological Chemistry Associate Editor Jerry Lingrel.

HERBERT TABOR YOUNG INVESTIGATOR AWARD

On top while Down Under

Stephan Reitinger, a researcher at the Institute for Biomedical Aging Research of the Austrian Academy of Sciences, was named a Tabor award winner for his structural studies that identified a hyaluronan unbinding domain that governs the enzymatic activity of hyaluronidases.

Reitinger, who collaborated with researchers from the Hungarian Academy of Sciences and the University College Dublin, Ireland, is interested in how the activation of hyaluronidases is controlled by a bulky surface loop



near the active site. His hyaluronan metabolism work is supported by a Marie Curie International Reintegration Grant from the European Commission.

Reitinger completed both his undergraduate and graduate work at the University of Salzburg, Austria, and a postdoctoral stint at the University of British Columbia in Vancouver. XXXX

Stephan Reitinger was named the winner at the 7th International Conference on Proteoglycans held in October in Sydney, Australia, and attended by Journal of Biological Chemistry Associate Editor Vincent Hascall.

Clever cytokine work



ABOVE Niamh Mangan was named a Tabor award winner at the International Society for Interferon and Cytokine Research meeting held in October in Florence, Italy, and attended by Journal of Biological Chemistry Associate Editors Charles Samuel and Luke O'Neill.

BELOW Solenne Vigne was named a Tabor award winner at the International Cytokine Society's meeting held in October in Florence, Italy, and attended by Journal of Biological Chemistry Associate Editors Charles Samuel and Luke O'Neill.



Niamh Mangan and **Solenne Vigne** were named winners of Tabor awards at a joint meeting of two organizations dedicated to cytokine and interferon research.

Mangan, a postdoctoral fellow at Monash University in Australia, was recognized for her work on the role of interferon cytokine and receptor signaling in immune regulation in infection and inflammation — and, more specifically, the characterization of the cytokine interferon epsilon, which may be important for infections in the female reproductive tract.

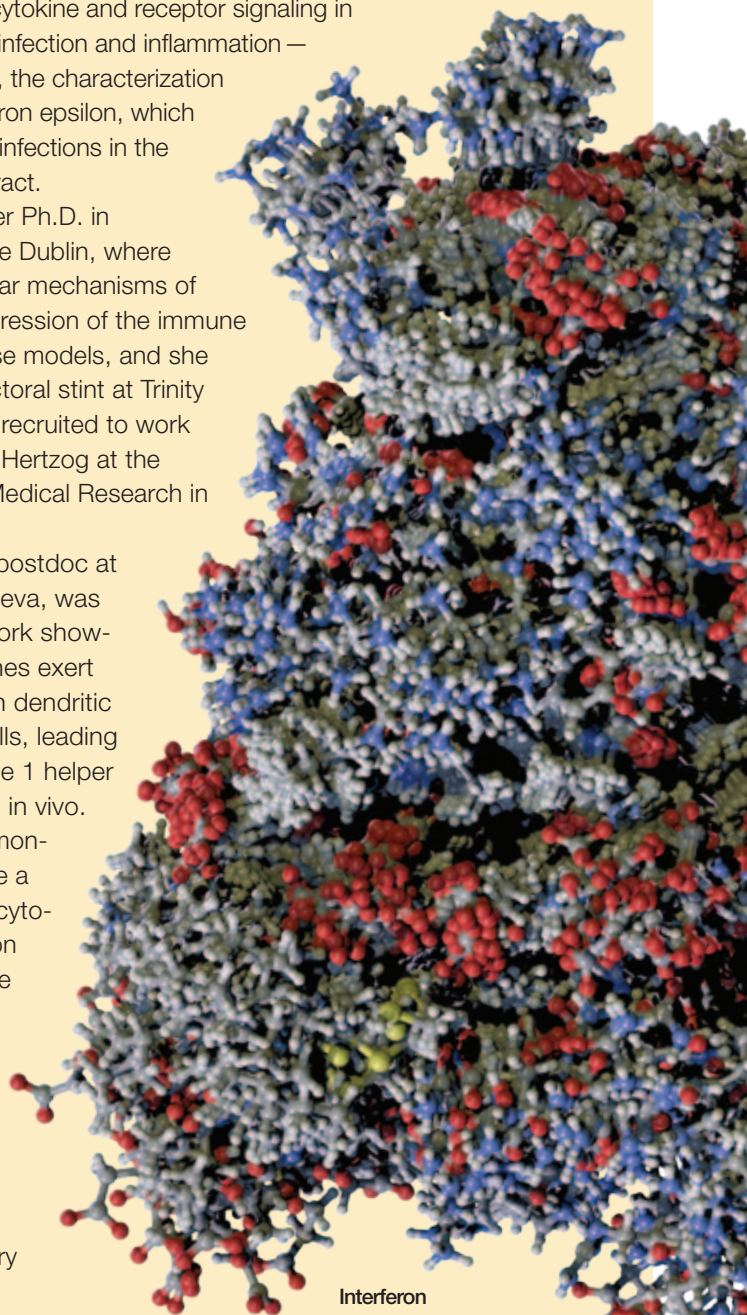
Mangan earned her Ph.D. in 2005 at Trinity College Dublin, where she studied the cellular mechanisms of modulation and suppression of the immune response using mouse models, and she completed a postdoctoral stint at Trinity College before being recruited to work in Australia with Paul Hertzog at the Monash Institute of Medical Research in Melbourne.

Solenne Vigne, a postdoc at the University of Geneva, was recognized for her work showing that IL-36 cytokines exert stimulatory effects on dendritic cells and T helper cells, leading to a predominant type 1 helper response in vitro and in vivo.

"These results demonstrate for the first time a critical role for these cytokines in the stimulation of innate and adaptive immune responses," Vigne says. "Therefore, our findings indicate that these cytokines may represent potential targets for immune-mediated inflammatory conditions." ∞∞∞

HERBERT TABOR

YOUNG INVESTIGATOR AWARD



Interferon

A nice mix of experiences

Lydia Chávez-Vargas, a graduate student at Mexico's Center for Research and Advanced Studies at the National Polytechnic Institute, won her Tabor award for her studies of the molecular intricacies of endothelial-cell migration in response to angiogenic signals acting on chemotactic G-protein-coupled receptors

Chávez-Vargas, a native of Morelia, Mexico, studied biochemical engineering as an undergraduate and worked for a pharmaceutical company after graduation before continuing her studies at CINVESTAV under the mentorship of José Vázquez-Prado.

Her overall project will contribute to (a) our understanding of signaling pathways' roles in activating Rho GTPases in tumor-induced angiogenesis and (b) the identification of novel antiangiogenic targets. XXXX



Lydia Chávez-Vargas was named the winner at the Cell Signaling Networks Conference held in late October in Merida, Mexico, and attended by Journal of Biological Chemistry Associate Editor Judith Bond.

Wound-healing studies recognized

Ulrich auf dem Keller, a senior research assistant and junior group leader at ETH Zurich, won his Tabor award for his studies of proteolytic events in the skin.

Auf dem Keller, a native of Mülheim an der Ruhr, Germany, completed his undergraduate studies at the Universities of Tübingen and Munich and his graduate studies at ETH Zurich, where he worked under Sabine Werner and focused on cytoprotection of keratinocytes in the skin. He later completed a postdoctoral stint with Chris Overall at the University of British Columbia in Vancouver and then returned to the ETH Zurich unit led by Werner.

Auf dem Keller was recognized for identifying, along with Paul Hartmann AG, proteolytic signatures in the acute wound-healing process.

"In future work, those signatures will be compared to signatures from impaired skin repair, such as in diabetes," auf dem Keller says. "The final goal is to apply this knowledge in the clinics for assessing if a wound might turn bad and for defining the appropriate strategy for therapeutic intervention." XXXX



Ulrich auf dem Keller was named the winner at the 7th General Meeting of the International Proteolysis Society held in October in San Diego and attended by Journal of Biological Chemistry Associate Editor Judith Bond.

New protein sensors to quantify phosphoinositides in situ

BY ROBERT V. STAHELIN

Cellular membranes harbor receptors, ion channels, lipid domains, lipid signals and scaffolding complexes that function to maintain cellular growth, metabolism and homeostasis (1). Abnormalities in lipid metabolism attributed to genetic changes, among other causes, are associated with a host of diseases (2). Thus, there is a need to understand molecular events occurring within and on membranes as a means of grasping disease etiology and identifying viable targets for drug development.

The lipid bilayer has a highly polarized structure that consists of a central hydrocarbon core and two flanking interfacial regions that are highly dynamic and could contain thousands of different lipids (1). This dynamic variety of glycerolipids, sphingolipids and sterols in membrane organelles provide spatial and temporal cues to direct signaling processes through target proteins (3). However, there remains a large gap in our understanding of the spatial and temporal dynamics of the lipids that produce these bioactive signals.

Given that nearly half of all proteins are located in or on membranes, it is not surprising that there are a variety of conserved lipid-binding domains in eukaryotes. Some of these domain families rank in the top 15 modular domains in the human genome and are most often found in signal-transduction and membrane-trafficking proteins (4). To date, fluorescently tagged lipid-binding domains

(such as the PH domain) that harbor high specificity and affinity for phosphoinositides (PIs) have most often served to study PI dynamics and localization (5). While the overall spatial distribution of lipids such as PI(3)P and PI(4,5)P₂ (5) is well appreciated, the actual concentration, distribution and spatiotemporal dynamics have not been determined quantitatively. Thus, real-time lipid sensors that could provide high sensitivity for a specific PI to quantify its role in a cellular-signaling cascade would be a great advantage to researchers.

Recently, Wonhwa Cho and his colleagues developed

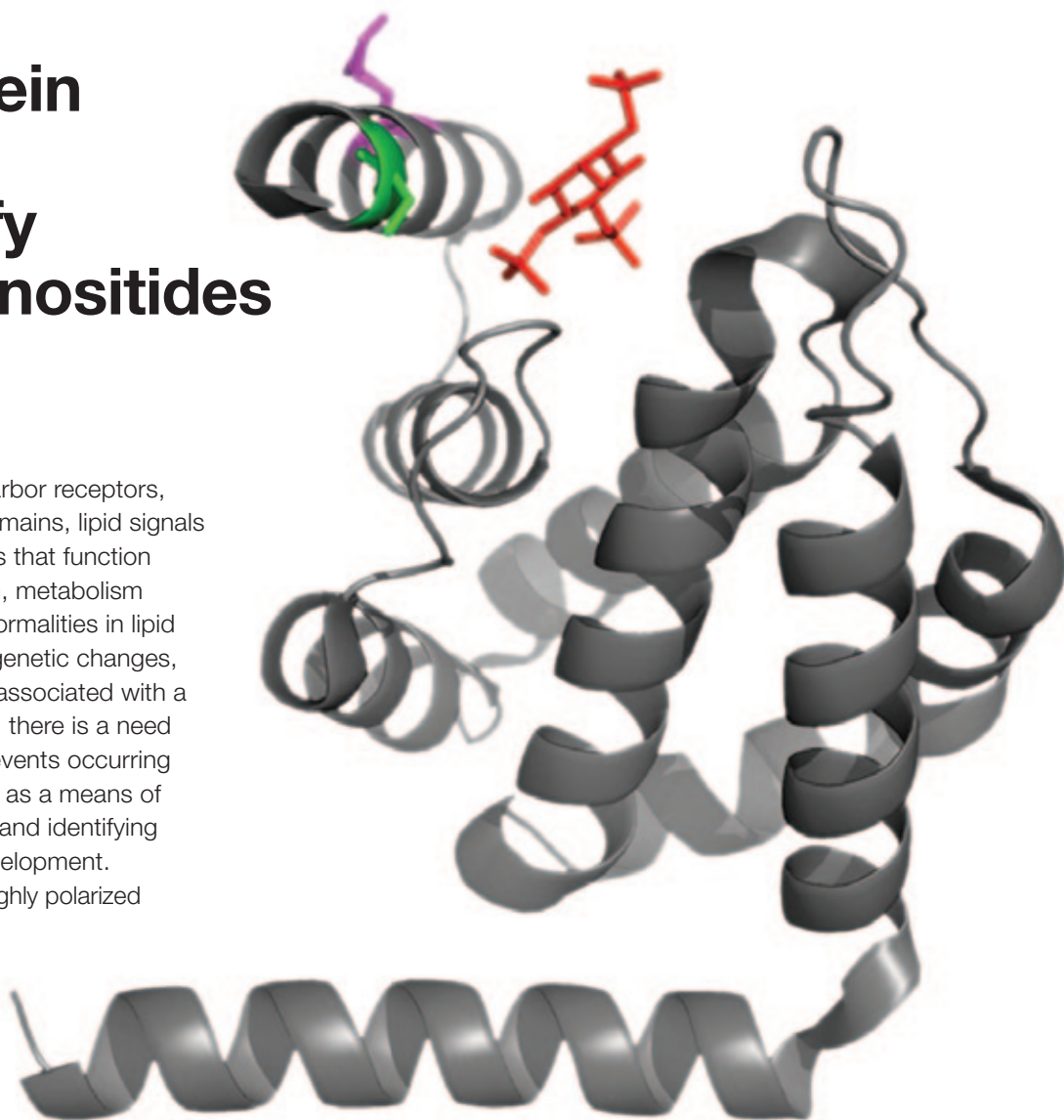


Figure 1. The epsin1 ENTH domain (PDB 1HOA) was used to engineer a high-affinity PI(4,5)P₂ binding reporter. Methionine 10 (magenta) was mutated to cysteine to attach the environmentally sensitive probe, while serine 4 (green) was mutated to tryptophan to increase membrane affinity. Inositol(1,4,5)P₃ bound to the ENTH domain is shown in red.

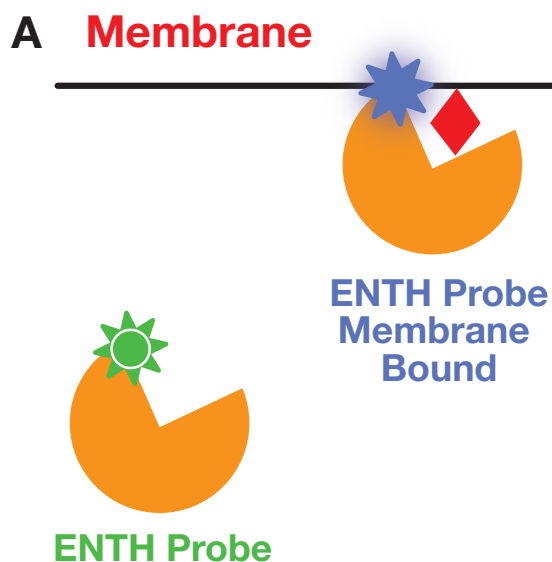
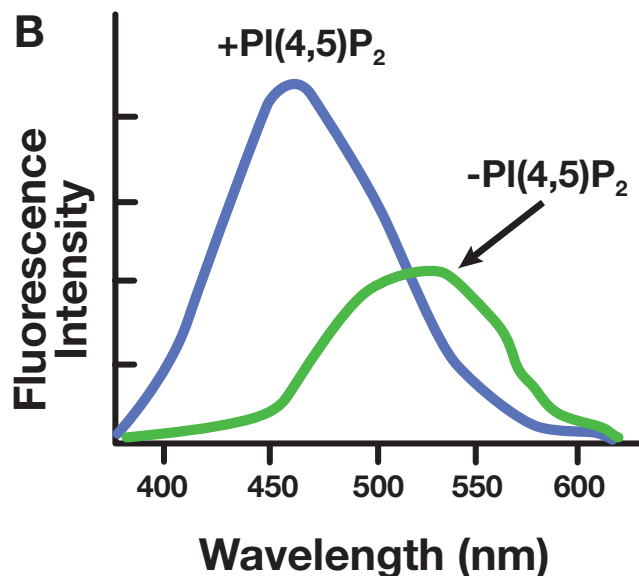


Figure 2. A. The engineered PI(4,5)P₂ sensor undergoes an increase and blue shift in fluorescence upon binding PI(4,5)P₂-containing membranes.



B. The fluorescence shift and increase observed with PI(4,5)P₂ binding can be quantified to determine the concentration of PI(4,5)P₂ in cellular membranes.

such an approach to quantify PI(4,5)P₂ using a chemically modified lipid-binding domain (6).

The probe was first engineered for optimal lipid-binding properties and minimal affinity for cellular proteins. Through the introduction of an environmentally sensitive chemical probe on a free cysteine, the engineered domain serves as a turn-on sensor that undergoes a large increase in fluorescence upon lipid binding.

In addition, the probe undergoes a blue shift upon PI(4,5)P₂-dependent membrane binding, which allows ratiometric detection of PI(4,5)P₂ in vitro and in cells. The ratiometric approach will allow researchers to overcome obstacles associated with fluorescently tagged domains, such as photobleaching.

The probe's successful microinjection, or liposome-mediated delivery, into multiple cell lines further demonstrated its applicability. Ultimately, Cho and colleagues were able to use the probe to investigate the threshold level of PI(4,5)P₂ required to trigger phagocytosis in immune cells. Taken together, environmentally sensitive lipid probes will be applicable to studying the quantitative role of lipids in signal transduction, membrane trafficking, apoptosis and cell migration and may serve as readout assays for therapeutic efficacy and potency.

The approach designed by Cho and colleagues will be

of much use, as structural and functional knowledge of lipid-binding domains, including the C1, C2, PH and PX domains (4), are available and should allow the engineering of lipid probes for diacylglycerol, phosphatidylserine and PIs. Although it may now be difficult to sense both sides of membrane organelles in an unbiased manner using this chemical approach, this is a significant leap forward in studying real-time lipid signaling. ∞∞∞



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MCP MOLECULAR AND CELLULAR PROTEOMICS

Chemical proteomic method reveals new target for treating head and neck cancers

BY RAJENDRANI MUKHOPADHYAY

Nearly 600,000 new cases of head and neck squamous cell carcinomas are reported globally each year, making it the sixth-most-common form of cancer. The disease prognosis isn't encouraging, with a 40 percent to 50 percent survival rate over five years. In a recent *Molecular and Cellular Proteomics* paper, a multinational research team described a potential new therapeutic target for the disease by using a chemical proteomics approach.

Stephan Feller of the Weatherall Institute of Molecular Medicine in the U.K. explains that head and neck cancers are the type that "arguably most devastates a patient's life

at the most basic personal levels." He says because the cancers affect the head, they attack most of the senses, including taste, hearing and vision.

Feller and Bernhard Kuster of the Technical University in Munich led a team to investigate possible targets for therapeutic agents using a chemical proteomics approach. The approach probes

the activities and interaction partners of proteins using small-molecule inhibitors. "Chemical probes allow purification and analysis of a relevant sub-proteome that is often not accessible to whole proteome expression profiling," explains Kuster. The investigators specifically looked at kinases, a class of proteins that, according to Feller, is insufficiently explored for oncologic drug targets.

The investigators studied 146 kinases in 34 cell lines of

head and neck squamous cell carcinoma using quantitative mass spectrometry and small interfering RNA assays for loss of function. Their analyses showed some of the previously known kinases involved in the disease, such as EGFR, but also revealed a novel drug target, EPHA2.

The discovery of EPHA2 has opened up several new avenues of investigation, says Kuster. The researchers are now investigating how EPHA2 expression levels correlate with patient prognosis, and they are searching for small-molecule inhibitors against EPHA2 that can be used in studies using cell lines and animal models to find new drugs. Feller says that they also plan on using the same chemical proteomic method to work on other types of cancers. ☺☺☺

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JLR THE JOURNAL OF LIPID RESEARCH

Although expensive, the 'cleaning' of blood (apheresis) is a viable option for people with severe hypercholesterolemia

BY MARY L. CHANG

Familial hypercholesterolemia (FH) is a genetic disorder characterized by high levels of cholesterol, especially the "bad" cholesterol LDL. In extreme cases, such as in patients who don't respond to regular medical treatment or suffer from muscle breakdown (rhabdomyolysis) related



to the disorder or coronary heart disease, LDL-apheresis is an option. In a process similar to dialysis, a patient's blood is removed from the body and cleaned of LDL, its subparticles and apolipoproteins, and other molecules involved in lipoprotein production before the blood is returned to the patient. The high expense of the procedure has so far restricted its widespread use.

Alexina Orsoni of INSERM and Pierre and Marie Curie University in Paris, tested the efficacy of LDL-apheresis once every two weeks over a minimum of two years in patients with severe FH, comparing pre- and post-LDL-apheresis lipid levels and levels of specific types of HDL that are known to protect against cardiovascular disease. All participants concurrently received the lipid-lowering drugs atorvastatin and ezetimibe. This study, "LDL-apheresis depletes apoE-HDL and pre-beta1-HDL in familial hypercholesterolemia: relevance to atheroprotection," published in this month's *Journal of Lipid Research*, confirmed that LDL-apheresis was successful in significantly lowering total cholesterol, triglyceride and other molecules involved in lipoprotein production, such as apolipoproteins B and E.

Because there are different genes implicated in the development of FH, it was of particular interest that this study showed that LDL-apheresis selectively removed apolipoprotein E-HDL. ApoE-HDL possesses high electrostatic affinity for vascular walls and may exacerbate cholesterol deposition in plaques. Thus, removal of apoE-HDL2 via apheresis may have an atheroprotective effect. XXXX

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jbc THE JOURNAL OF
BIOLOGICAL CHEMISTRY

Enzyme oxidizes fatty acids based on environmental cues

BY RAJENDRANI MUKHOPADHYAY

Carnitine palmitoyltransferase 1 is an enzyme in the outer mitochondrial membrane of mammals that is critical for metabolism. Researchers in the U.K. and U.S. now have shown how an important isoform of the enzyme, a potential target for several drug therapies, is regulated by environmental cues.

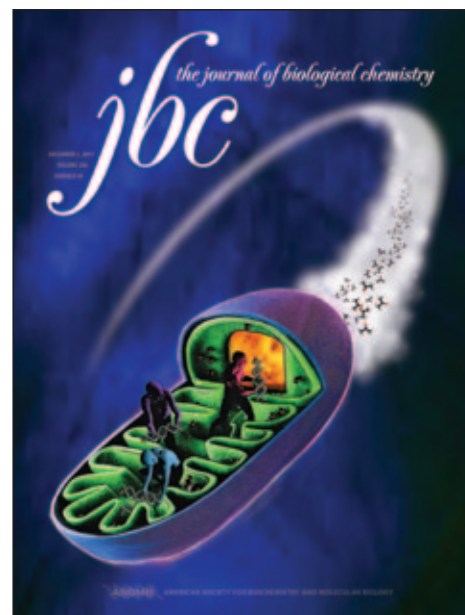
CPT1 controls the rate-limiting step in fatty acid β -oxidation. Because of the enzyme's importance, CPT1A, one of the three isoforms of CPT1 found in several organs, presents a prime target for drug treatments. It is inhibited by

malonyl-CoA, the first intermediate of fatty-acid synthesis and a signal for the short-term metabolic state of the mammal. The enzyme also is regulated by the curvature of the mitochondrial outer membrane, which defines its location within the oxidative phosphorylation complex. CPT1A also is sensitive to long-term nutrient levels or disease states, such as Type 2 diabetes or obesity, which change the fluidity and lipid composition of the outer membrane. But the question dogging researchers has been this: How does the enzyme take in these three different signals to control its function?

In a recent *Journal of Biological Chemistry* "Paper of the Week," Tobias S. Ulmer and colleagues at the University of Warwick in the U.K. and the University of Southern California showed that, depending on the malonyl-CoA concentration, membrane composition and curvature, CPT1A's N-terminal regulatory domain adopted one of two structural states, called $N\alpha$ and $N\beta$. $N\alpha$ inhibited the enzyme's activity, but $N\beta$ didn't have an inhibitory effect. $N\alpha:N\beta$ ratio tuned the enzyme's sensitivity to malonyl-CoA.

Ulmer says it's the first time that an on-off switch has been described for a membrane-bound protein that can integrate several environmental cues. Victor A. Zammit, one of Ulmer's co-authors, emphasizes that the work can help the pharmaceutical industry in finding small molecules that "can affect the molecular switch in the direction in which the patient needs it." For example, he says, drugs can be developed for those patients suffering from diabetic ketoacidosis, a condition when insufficient insulin causes the body to start breaking down fat, so the CPT1A is inhibited to oxidize fewer fatty acids. Alternatively, CPT1A could be activated with a drug to prevent fatty liver disease from developing, a condition that accompanies insulin resistance and diabetes. XXXX

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Advice for new assistant professors

BY PETER J. KENNELLY

As someone who has observed many assistant professors over the years and lived to get tenure himself, I have observed certain patterns that appear to hold true for assistant professors who aspire to be tenured. When I became department head, I put together a list of these items to pass on to newly arrived faculty members.

Although the list was generated with the environment and expectations of a research university in mind, most of these items also apply to new faculty members at primarily undergraduate institutions, medical schools, and so on.

Work with a sense of urgency.

Time is a nonrenewable resource, and the probationary period before submitting your promotion-and-tenure dossier will pass quickly.

Get to the bench!

It takes considerable time to recruit and train graduate students, technicians and postdoctoral fellows to the point at which they produce publication-quality results with some consistency. In the interim,

the most experienced and skilled set of hands in your lab will belong to you, the principal investigator. Make time, especially during the first two to three years, to get to the bench and generate the data for a manuscript or two.

Be opportunistic.

Opportunities rarely come along at convenient times; to put it another way, it is the nature of passionate, self-motivated people to be perpetually overcommitted. Invitations to review papers and grants, to give talks

or write reviews or chapters, to participate in site visits and the like represent golden opportunities to raise your visibility among your peers across the globe, to establish relationships with program officers and journal editors, and to document respect and recognition by the scientific community for your promotion-and-tenure committee. You also will find reviewing manuscripts and grant applications teaches you more about writing and grantsmanship than attending a dozen workshops.

Recruit self-motivated, responsible students.

Talent is of no value if a person does not possess the passion or work ethic for research. Do not underestimate the potential of a single irresponsible, disrespectful, intolerant or lazy individual to sap the morale and cohesion of your entire research group. Screen applicants carefully with respect to goals, motivation and expectations. Check references when possible. Have members of your group meet candidates, and listen to their feedback.

Attend conferences early and regularly.

Your attendance helps establish your new identity as an independent investigator in the eyes of your colleagues, helps you to keep current with developments and opportunities in your field, and may attract a seminar invitation or recruit a collaborator.

Invite potential outside evaluators to be seminar speakers.

Meeting you, interacting with your lab group and hearing your ideas will enable external evaluators to write more informed and dynamic letters



of evaluation than those working from your curriculum vitae. Seminar visits also provide your department head and tenure chairs the chance to assess the suitability of potential evaluators.

Treat staff with courtesy and respect.

You are all members of the same departmental team. Avoid crying wolf. Your procrastination does not constitute another person's emergency.

Be proactive.

Identify service and teaching assignments you find most rewarding, and seek them out. If you wait passively, you will end up with the leftovers. Getting your service credentials established early leaves you with one less thing to worry about later in the tenure process. Saying "yes" now makes it much easier to say "no" somewhere down the line.

Define the issues.

When writing a paper or a grant application, anticipate and address likely questions or weak points. Ignoring them leaves you vulnerable to misconception or confusion. You want to define the issues rather than have them defined for you.

Think like a reviewer.

Focus on demonstrating proof of concept or expertise when amassing preliminary data for a grant application. An experienced reviewer will see the masses of routine, descriptive preliminary experiments for what they are.

Avoid arguing with reviewers.

The vast majority make constructive, good-faith efforts under difficult circumstances. Treat them with respect and adopt a gracious, constructive tone in your responses. Avoid scolding the reviewer for missing something already in the manuscript, for in

the end, as the author, you are responsible for making critical points clear and noticeable. Think strategically when framing your response. Identify the critical area in which you need to convert the reviewer to your point

of view — perhaps regarding the need for an additional experiment. Concede the small points and those readily addressed by simple experiments. But remember Clausewitz: If you try to defend every little thing, you likely will prove completely unconvincing overall.

Think of your research program as an investment portfolio.

If you put all your assets into one high-risk venture, you may reap great rewards, but you also may crash and burn. Develop a diversified portfolio. In addition to your main, bread-and-butter effort, establish a low-risk project (or two) that is likely to produce useful, if unspectacular, publications particularly during off years. Look for opportunities to spin off a methods paper in addition to a research manuscript. Talented undergraduates represent an excellent source of labor for carrying out low-risk projects as well as for exploring novel, high-risk ideas. XXXX



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Creating your own path: a bioinformatics case study

Faced with the reality that the majority of my time would be spent on the job, I was on a quest to find one that I love.

BY EWY MATHÉ

As early as elementary school, I was fascinated by science and medicine and was convinced I would become a brain surgeon. By the time I went to college, this changed toward forensics, and by the end of college I was thoroughly confused and realized that I hadn't quite found my greatest interest yet.

Having been fortunate to find a job in a yeast genetics laboratory, I sequenced and ran Westerns for a year and realized that bench work was not my forté. Importantly, though, bench work provided a lot of downtime that I, like most everyone else, used to browse the Internet.

During that time, as I was waiting for my timer to go off, I found my new calling: bioinformatics—specifically, protein-structure modeling. I started calling around to different academic institutions that offered bioinformatics degrees and decided to embark on a Ph.D. at George Mason University. The learning curve was steep (I had no computer-science classes under my belt when I applied), but the field switch was exciting and proved to be the best decision.

Why bioinformatics?

One of the most exciting aspects of bioinformatics for me is its collaborative nature. Indeed, the field would not exist without large masses of raw data being generated that are of little worth without bioinformatics interpretation.

This dependency requires building a bridge between related yet diverse fields, both linguistically and knowledgewise, and thus provides opportunities to step out of your scope to better understand the challenges at hand. I find this aspect very exciting, as it allows me continuously to learn new biological aspects that I might not necessarily explore on my own.

Furthermore, bioinformatics can be thought of in the context of team-science approaches that are becoming more prevalent as scientific projects grow in size and complexity. Indeed, the high level of expertise required and the increasing demands from publishers make it difficult to address thoroughly all aspects of a given project.

Nowadays, bioinformatics is most always a component of larger scale projects that require a team of experts who may or may not know each other.



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This team-science approach requires strong communication and the ability to coordinate efforts and keep the project moving along. Keeping everyone in line with the vision of the project and making expectations clear are critical for building a successful team.

Another stimulating aspect of bioinformatics for me is that it is not routine. The majority of the projects I undertake require novel applications and interpretations. A typical project requires unique ways of looking at the data and thus also requires a strong understanding of the biological question at hand. Furthermore, the field is very fast paced. While this attribute may be daunting, it is also very exciting, as bioinformatics is always at the forefront of new technologies and applications.

A whole new world

Just as the bioinformatics field is very broad, the topics that I touched on in my

training (and I am still training!) are also broad. During my Ph.D., I took advantage of lab rotations to touch on very different aspects, including image analysis, Monte Carlo simulations, genetic algorithms and computational geometry/protein-structure modeling.

While my thesis was centered on computational geometry and sequence alignments, I again switched gears in my postdoc and delved into genomics and metabolomics, all with a molecular epidemiology flavor. This switch has opened a whole new world for me, and, importantly, I had chosen to be in a wet lab environment as opposed to a purely computational laboratory.

The reason for this choice was to make sure that I stayed up to date with biology and learned how to communicate well with different participants in a given project. While you can stay up to date via the literature, I found it extremely valuable to be able to interact directly with bench scientists and have learned a lot from this direct interaction.

Life can shape your career path

On a more personal note, my career path also has been molded by the fact that cancer has plagued my family, as it has a large number of families. Right after applying to Ph.D. programs, my brother was diagnosed with stage 3 melanoma.

It was at that moment that I decided I wanted to invest my efforts in cancer research. I found a way to fit cancer research into my Ph.D. thesis by studying the p53 protein and mutations, which are very common in various cancer types. Since then, I have focused on finding diagnostic and prognostic markers in early stages of esophageal and lung cancers. This additional personal dimension to my research makes my work more personally valuable and drives me to do the best I can do.

Charting your path

As you are reading this, you may be asking yourself, "What is the best trajectory for a successful career?" My answer to this is none. I do not think there is a best trajectory. This last statement should be more reassuring than alarming.

Indeed, I believe that everyone has to carve his or her own trajectory, as there is most likely a variety of definitions of a successful career. Do you define success as having achieved independence? Or perhaps by how much recognition or awards you are getting? Or perhaps by salary? By having achieved a good balance between family and work? By doing "good science"?

I find it very important to do a bit of soul searching to determine what makes you happy and how you envision your success, with the understanding that another person's idea of success may not necessarily fit yours. Furthermore, recognize that your vision of success is not static and that it will probably evolve with time.

In this sense, it is useful to self-evaluate regularly and make changes accordingly. After all, your happiness in your work is directly correlated with drive and desire to accomplish tasks well. In other words, ensuring satisfaction with your work makes you most productive.

Finding and using mentors

It is very useful to discuss professional development with mentors. Often, a laboratory chief or primary investigator is a default mentor. However, mentors can also be peers and collaborators from within or outside your institute.

Seeking outside mentors can be beneficial, because there is less fear of crossing a line that may affect daily work.

In addition, being a mentor can be quite fruitful in that it may force self reflection, deepen your knowledge,

help build leadership skills, establish valuable professional relationships and provide a sense of gratification from contributing to someone's advancement.

Taking this even a step further, it is essential to network. Participating in committees, attending and presenting at conferences, and forging collaborations are all avenues for networking. The ability to delineate clearly your work and interests is very important, and the ability to break past shyness or reservations and ask questions about others' work and interests is very rewarding.

In my experience, many scientists love to talk about their work and interests and are flattered by inquiries. Opening up communications can be a great self-confidence builder and can establish important relationships.

Overall, I apply all the various aspects I have mentioned here in my career as I advance on my journey toward my self-defined success. I hope at this point that one main message is becoming apparent: Following a career path is a personal journey that may be redefined as you move forward. Also, acquiring expertise and knowledge should not be the only aspirations, for they are baselines.

With lots of Ph.D.s and brilliant people out there, we are all competing against the cream of the crop. With this in mind, it is critical to evaluate yourself frequently, redefine your vision, network and communicate clearly. These are very high expectations, and some aspects come more naturally to some than others. However, the same drive that kept us working long hours to finish our theses should be kept alive so that we continuously challenge ourselves to keep improving and learning.

After all, continual learning may be the most exciting aspect of working at the doctoral level! XXXX



Oh, how we love odes!

*It's not too late to submit your entry
for the Experimental Biology 2012
poetry contest sponsored by ASBMB.*

We know some of you are probably on the fence about this whole poetry-contest thing, so we thought we'd give you a little more information about what we're looking for.

We want you to send us lines that will make us laugh, that will make us feel warm inside, that will make us shiver, that will make us say to the person next to us, "Hey, you've got to hear this." Put simply, we want to be moved one way or another.

For those of you who might still be hesitant to expose your inner poet, **ASBMB Today Editor-in-Chief John Nelson** was willing to expose his own by allowing us to publish the poem below. We hope you'll enjoy it and then share your poems with us.



GUIDELINES: Entries should be unpublished free-verse poems up to 25 lines long in the EB2012 "bench-to-bedside" theme. Simultaneous submissions are allowed, but notify us immediately to withdraw your entry if it is accepted for publication elsewhere. Send your poem as an attachment, without identifying information on the file, to asbmbtoday@asbmb.org.

ELIGIBILITY: Members of the societies participating in EB2012 and registered attendees may enter. Each entrant is allowed only one entry, so send us your best work.

WINNERS: The top 10 finalists will be invited to read their work at EB2012, if they plan to attend. Attendance is not required for submission to the contest. The top three prizes will be \$100, \$75 and \$50. Finalists' poems will be published in ASBMB Today.

JUDGES: The panel includes both scientists and poets.

DEADLINE: Dec. 31, 2011

*The day I left the bench,
I felt relief.
But soon after, relief turned to
green-minded regret. It took years
to wash out the green;
it faded rather than washed away.
I should have stayed in the sun more.*

*Anchors keep us stable in torments.
They also
chain us in calm waters.
Being free is being ready
to move (on)
when the wind is right and the seas are still.*



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