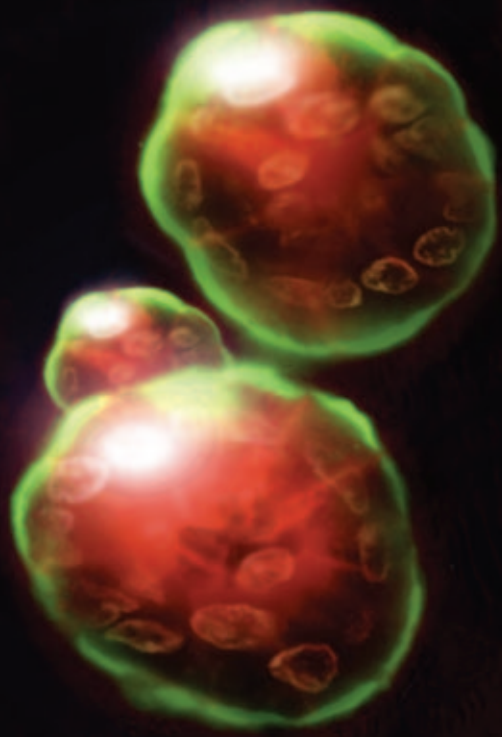
ASBMB today

October 2010



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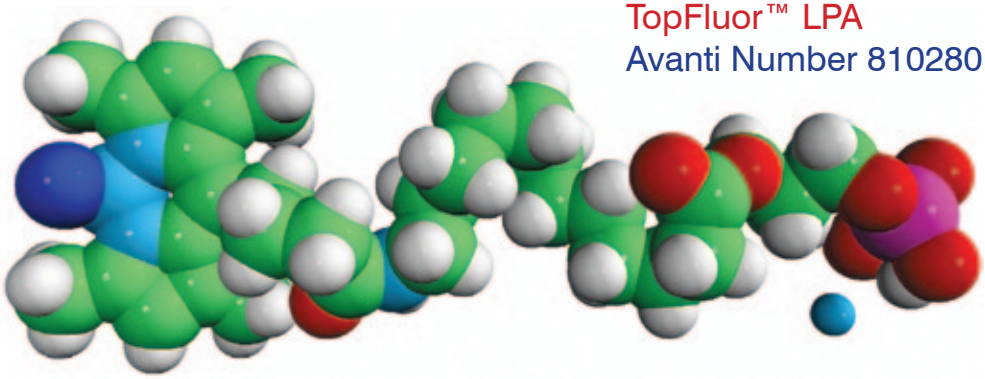

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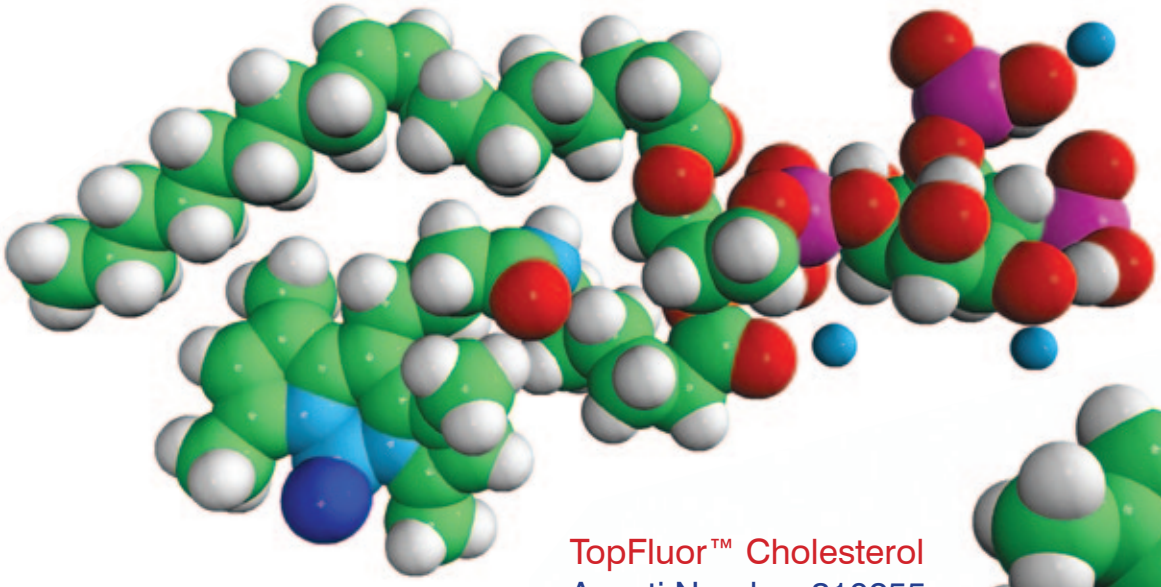

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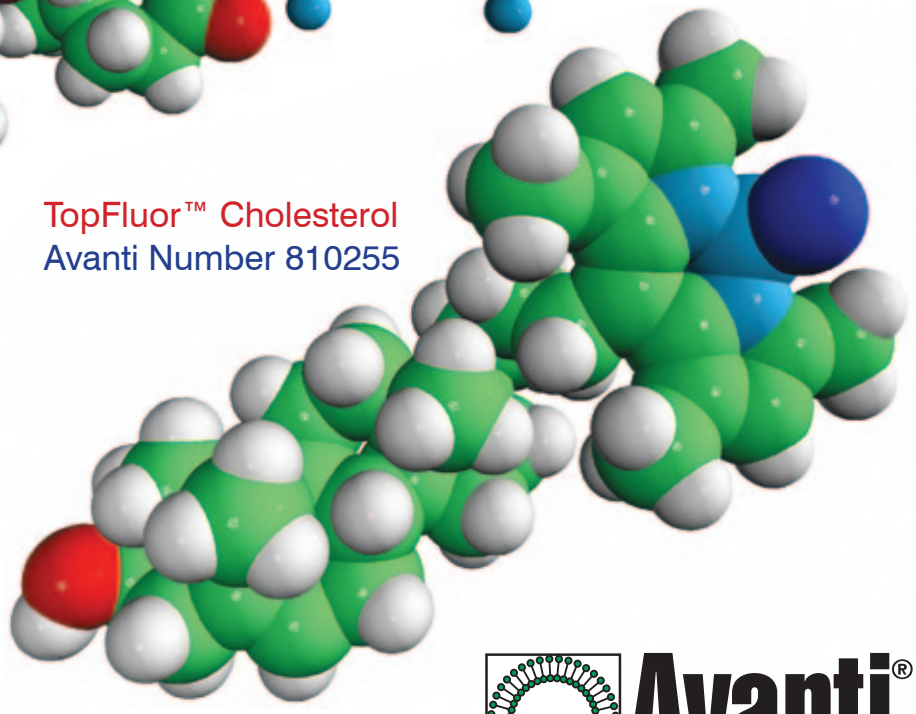

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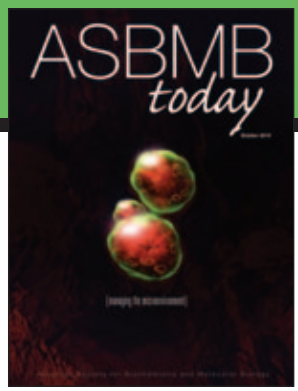

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Mina Bissell uses innovative 3-D cell culture systems to study the cell microenvironment. 14

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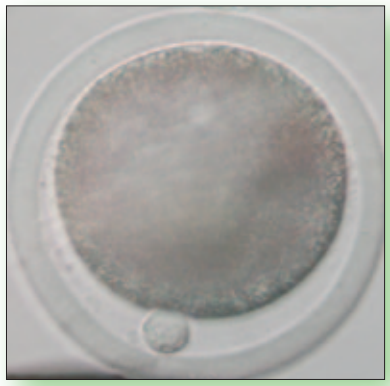

A day of science at the School at Columbia University. 20

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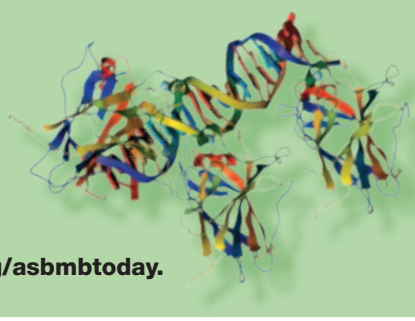

ASBMB today

A monthly publication of
The American Society for
Biochemistry and Molecular Biology

ASBMB Today

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2008 APEX AWARDS FOR PUBLICATION EXCELLENCE

president's message

Time to Degree — Are Changes in Publishing to Blame?

BY SUZANNE PFEFFER

Today, most doctoral students in biomedical sciences will not pursue a career as a research university faculty member. Instead, they are moving on to wonderful roles in biotech, teaching, science museums, consulting, law, advocacy, writing, policy and so on. Yet, our graduate-training programs seem to be stuck in a time warp, setting universal expectations commensurate with eventual faculty positions at top Ivy League institutions. Are the current definitions of what constitutes a doctoral thesis appropriate for the discipline? Is it harder to comply with those definitions than it used be?

Obviously, we want our students to conceive bold and significant hypotheses and use their graduate careers to take risks and push the field forward. But I have seen too many students reach their fifth year of training, worried about their futures because they have not yet had a chance to publish a first-author paper. Graduation seems unimaginable and exactly what constitutes a thesis seems less clear by the day.

Why don't more of our students publish sooner? Part of the problem is that reviewers and journals are demanding more. In the late 1970s and early 1980s, the sequence of an important gene was sufficient for publication in the flashiest of journals. I envied those manuscript reviews — what could the referees criticize when a sequence was a sequence? Now, journals quibble over whether to publish entire genomes. A referee can always ask for more experiments, another mutant, another control, and, because most journals want to maintain the highest standards, the editors agree. Such an approach may make for great papers, but it actually can be harmful to younger workers in our field because it sets the bar for publication further from their grasp.

Two-author papers are much less common than ever before. Don't get me wrong: Collaborations enable us to accomplish so much more and to apply multidisciplinary approaches to questions under study. But when there are multiple authors, there only is one "first" author, and it is still the first-author papers that are weighted highly in fellowship and job application evaluations. It takes multiple, shared first-author papers to count as much as one with a single first author. And students want to publish their own "big" story because they believe it to be important for their future successes.

All authors remember their first papers, seeing their name in print, with the figures and text formatted professionally. A result isn't real until it is published; publishable findings can be communicated at meetings and provide the heart of a postdoc interview. More important than all of this is the fact that the process of publication helps young scientists understand the meaning of a "publishable unit," the importance of duplicates and replicates, experimental details, the

significance of the project and how it relates to previous work in the area.

What if all first- and second-year graduate students were encouraged to publish a "least-publishable unit" paper? This type of paper can almost be outlined before the experiments are initiated — a process that could be part of a first-year graduate course. Faculty advisors would work with students to design a project that was guaranteed to yield useful information; the work could be published in an appropriate venue.[1]

Then, students would gain a sense of what a paper represents and would try to generate figure-quality results with every subsequent experiment, including positive and negative controls. They would gain self-confidence and, upon publication, would feel like they were true members of the biomedical research "guild." This new status would carry them more sturdily through a second, more challenging project. (Kudos to all programs that do this already.)

The American Society for Biochemistry and Molecular Biology publishes three excellent journals: the Journal of Biological Chemistry, Molecular and Cellular Proteomics and the Journal of Lipid Research. These journals exist to serve our members (and nonmembers) by providing a quality venue for presentation of their research. Discounted page charges are available as a benefit of membership in ASBMB. According to its new mission statement, "The Journal of Biological Chemistry publishes papers based on original research that are judged to make a novel and important contribution to understanding the molecular and cellular basis of biological processes." Although this would not likely include a manuscript in the "least-publishable unit category," the breadth of topics included in this description are likely to encompass the interests of all ASBMB members. As scientists, we hold the power to determine which journals have the opportunity to publish the best science — because we decide where to submit our best work. The ASBMB journals exist for our benefit, and we enhance our community when we publish papers in them.

> "The sooner our students can experience the thrill of publication, the sooner they will be hooked."

What can all journals do on behalf of our students? During manuscript evaluation, editors and reviewers should try to use care to not ask for more than is needed to substantiate the authors' conclusions. When drafting a review, referees should remember that a paper's first author is likely to be a graduate student; they should temper their language and always include some positive comments in their reviews. We all find it easier to accept a review that acknowledges a paper's strengths. Doctoral mentors also should teach their students how to review manuscripts — how to be constructive and how to evaluate overall significance. Reviewing papers teaches students a great deal about how to best write them. And, no matter how difficult some reviewer comments may be to digest, I have never seen a manuscript that was not improved upon revision.

Yes, there always is an element of luck in research. Some proteins form tight complexes and some enzymes seem to pop out of E. coli in milligram quantities. That is why we carry out experiments — the outcome is not guaranteed. But the pleasure of making a discovery — and working it out — is at the heart of why all of us chose science. It would be a travesty if tougher biomedical science publishing standards drive away talented individuals because of long doctoral tracks and years of feeling inadequate and/or discouraged. The sooner our students can experience the thrill of publication, the sooner they will be hooked.

P.S. We welcome all suggestions regarding how to improve your online journal experience! XXX

FOOTNOTE

1. Appropriate venues include PLoS ONE, a journal that presents primary scientific research not published elsewhere, performed to a high technical standard, described in sufficient detail and with conclusions supported by the data. BioMed Central also includes this category of paper.

Stem Cells: Back in the Spotlight

BY GEOFFREY HUNT

After simmering for nearly a decade on the backburner of public awareness, stem cells moved back to the forefront Aug. 23, when Judge Royce C. Lamberth of the District of Columbia District Court issued a preliminary injunction halting the use of federal funding for research done using human embryonic stem cells. In his ruling on the case of Sherley v. Sebelius, Lamberth found that using funds from the National Institutes of Health for human embryonic stem cell research violates a federal law, which states that federal funding of work resulting in the destruction of a human embryo is prohibited. Along with reigniting the ethical controversy over human embryonic stem cells, this court case promises to have far-reaching effects on the entire field of stem cell research.

A History of Stem Cells

Stem cells have traveled a long path to the present. The idea that a cell capable of regenerating damaged tissue existed in the body originated during the 19th century. However, the first true stem cells, by definition able to both self-replicate and differentiate into other cell types, were not isolated until hematopoetic stem cells were derived from bone marrow during the 1950s. Later work identified so-called adult stem cells in various other tissue types, including neural and intestinal tissues. Though used successfully to treat ailments such as leukemia, adult stem cells generally are constrained to forming a limited subset of cell types, exist at an exceedingly low frequency and are difficult to isolate. Researchers realized that an ideal treatment would instead use a highly pure, highly plastic, easily obtainable cell source.

The search for cells that could meet these high standards began in earnest in the 1970s, when researchers turned their attention to mouse tumors known as teratocarcinomas, in which random collections of cell types, such as teeth and hair, grow. The presence of such a diverse group of cells in one location led to the idea that the tumors contained highly plastic progenitor cells that were capable of differentiating into all somatic cell types. However, initial attempts to isolate these progenitors, termed embryonic carcinoma cells, directly from teratocarcinomas were plagued by inefficient yields and variable developmental potentials.

After years of trying, the holy grail finally was obtained when embryonic stem cells were isolated directly from early stage mouse embryos in 1981. Compared with heterogeneous embryonic carcinoma cells, these cultures contained homogeneous populations of pluripotent cells able to form unique cell types from each of the primary germ layers (endoderm, mesoderm and ectoderm). Subsequent work led to the development of protocols for efficient transformation of embryonic stem cells into a plethora of somatic cell types, including pancreatic, neural and even hematopoetic cells.

Embryos and the Question of Life

It took another 17 years before human embryonic stem cells could be successfully cultured in lab. Relying on excess, nonviable embryos donated from in vitro fertilization clinics, researchers ultimately were able to generate pluripotent human cell lines from which all adult tissue types could be obtained. To date, human embryonic stem cells successfully have been differentiated into numerous cell types, including pancreatic and cardiac cells, and, in 2009, the first clinical trial was approved by the U.S. Food and Drug Administration for use in treating spinal cord injuries.

Ethical issues immediately arose after the derivation of human embryonic stem cells, as groups questioned the morality of destroying human embryos for research purposes, leading to an extended legislative tug-of-war. The Dickey-Wicker amendment, which was added as a rider to the 1996 federal appropriations bill, prohibits “research in which a human embryo or embryos are destroyed,” thus apparently scuttling embryonic stem cell research. However, in 1999, Health and Human Services general counsel Harriet S. Rabb determined that federal funds could, in fact, be used for research on human embryonic stem cells, as this work did not involve the actual destruction of an embryo. Yet, no defined guidelines for funding human embryonic stem cell research existed until Aug. 9, 2001, when President Bush issued an executive order permitting the use of federal funds for research on established human embryonic stem cell lines but prohibited federal funds from being used to study any lines created subsequent to his announcement. Though initially

AN ASBMB POSITION STATEMENT ON THE STEM CELL RULING.

ASBMB Disappointed By Stem Cell Decision

The American Society for Biochemistry and Molecular Biology expresses its supreme disappointment with the decision by the U.S. District Court for the District of Columbia to grant a preliminary injunction that will effectively put a halt to research on human embryonic stem cells in this country. Not only will this ruling stall scientific progress and delay potential medical cures for millions of sick Americans, but it also poses a grave threat to the peer-review process used to evaluate funding proposals strictly on their scientific merit. We urge the U.S. Congress to act swiftly to pass legislation that will restore federal funding to embryonic stem cell researchers while upholding peer-review-based scientific evaluation.

ASBMB previously has expressed its enthusiastic support for the government's policies promoting stem cell research. We trust that the oversight provided by governmental guidelines, developed and enforced by the National Institutes of Health, ensures appropriate regulation of research practices while allowing scientific progress. In addition, we fully support congressional efforts promoting human embryonic stem cell research, in particular H.R. 4808, the Stem Cell Research Advancement Act of 2009, the contents of which have been approved by a bipartisan coalition of lawmakers. The guidelines promulgated in that bill, which simultaneously balance respect for ethical concerns and scientific advancement, will greatly expand the capacity for, and efficacy of, human embryonic stem cell research.

A broader, unintended consequence of this ruling strikes directly at the heart of the peer-review process used to identify the best scientific proposals. Allowing the judicial system to determine the merits of particular types of research based on an argument of competitive disadvantage is a blatant disregard of the expert-based system that is the gold standard of scientific review. Funding of basic biomedical research is not a zero-sum game in which particular lines of research are supported at the expense of others; rather, the system has evolved so that each proposal is evaluated on both its merits and its future benefits for easing the burden of disease. Though the process is by nature competitive, it consistently has resulted in new biomedical methodologies and technologies that continue to benefit society at large. Constraining funding to a limited subset of applications doubtless will limit discovery and hurt those who rely on those discoveries the most.

This lawsuit represents a crossroads in U.S. scientific policy. We urge our leaders in Congress and the administration to move us down the right path.

encompassing 78 lines, researchers soon discovered that only 21 were viable for research and, that, having been derived before conditions had been optimized, even these lines were not ideal for use.

Hoping to further scientific and biomedical progress, Congress repeatedly attempted to expand on Bush's decree, even passing two separate bills that would have allowed use of federal funds for stem cell lines derived after Aug. 9, 2001. But, each time, Bush vetoed the bills, claiming that, by allowing further destruction of human embryos, they would cross "a moral boundary" that "society needs to respect." In March 2009, President Obama issued his own executive order that allowed for federal funds to be used for research on additional stem lines, that had been derived and propagated since 2001 using private funding. Obama's ruling expanded the number of human embryonic stem cell lines approved for use by the NIH Human Embryonic Stem Cell Registry to 75, with more than 150 lines in line for review. However, neither Congress nor the administration altered the language set forth by the Dickey-Wicker amendment.

Loopholes and Legalese

The lack of congressional action to alter the Dickey-Wicker amendment was exploited by pro-life advocates James Sherley of the Boston Biomedical Research Institute and Theresa Deisher of AVM Biotechnologies, who, along with several religious groups, filed suit against the federal government, claiming that funds distributed by the NIH were being appropriated illegally for use on human embryonic stem cells, as they were derived via destruction of human embryos. The plaintiffs also claimed that, as adult stem cell researchers, they were at a competitive disadvantage when applying for NIH funds, as federal funding for human embryonic stem cell research "increase[d] competition for NIH's limited resources."

The district court originally rejected the lawsuit, finding that the plaintiffs lacked standing and had not suffered

from "irreparable injury." Upon appeal, the District of Columbia Court of Appeals found that the two researchers did, in fact, have standing and overturned the earlier decision. Forced to now consider the case on its merits, Lamberth found in favor of the plaintiffs, agreeing that their injury was "of such imminence that there is a 'clear and present' need for equitable relief to prevent irreparable harm" and that the injury was "beyond remediation." His ruling rested on an unambiguous interpretation of the Dickey-Wicker amendment as prohibiting "all 'research in which' an embryo is destroyed." By contrast, the federal government has maintained that federal funding of human embryonic stem cell research does not violate the Dickey-Wicker amendment, as federal funds are still prevented from being used for the actual derivation of human embryonic stem cells and that the statute is ambiguous in its definition of the term "research."

Future Potential

As the fate of stem cell research plays out in the courtroom, it seems that patients and researchers can only sit and hope for a positive outcome. However, their focus need not be limited to lawyers and judges: Congressional leaders have indicated their willingness to enact legislation that will continue to support stem cell research. Moreover, scientists recently have developed alternative techniques to deriving human embryonic stem cells that do not rely on the destruction of human embryos, using both induced pluripotent stem cells and preimplantation genetic diagnosis-based technology.

The seemingly unlimited potential of human embryonic stem cells provides researchers with heretofore unknown hope for cures to diseases such as diabetes, Parkinson's and Alzheimer's. Everyone can agree that helping those suffering from these ailments should not be constricted by politics. In that light, as public support continues to grow, it seems that human embryonic stem cell research will soon be the rule rather than the exception.

Geoffrey Hunt (ghunt@asbmb.org) is an ASBMB science policy fellow.

JBC Editor-in-Chief Calls For New Leadership Search

The longtime editor-in-chief of the Journal of Biological Chemistry has asked that a search begin for a new leader to take the reins of the journal in 2011.

Herbert Tabor, a distinguished researcher at the National Institute of Diabetes and Digestive and Kidney Diseases in Bethesda, Md., and who has led the journal since 1971, said he will assume the role of emeritus editor when his predecessor is ready to take over. He notified the American Society for Biochemistry and Molecular Biology leadership of his decision in late August.

"As you can understand, I made this decision reluctantly, as I am still fully active all day at the lab and working for the journal in the evening," Tabor told the members of the JBC editorial board. "Still, I feel that this change is necessary for the good of the journal, and I want to ensure we have a smooth leadership transition."

While at the helm of the JBC, Tabor has witnessed a revolution in scientific publishing, and, in many ways, it was his journal that forged it. In 1995, for instance, the JBC was the first journal of its kind to begin publishing online. Today, it remains one of the most-highly cited scientific journals in the world.

"I cannot imagine a more devoted editor for any journal than Dr. Tabor; his shoes will be impossible to fill. Words cannot adequately express our gratitude to Dr. Tabor for his more than 40 years of leadership, thoughtful oversight and vision," said Suzanne Pfeffer, president of ASBMB and faculty member at Stanford University School of Medicine.

Pfeffer said a search committee has been formed, and nominations of candidates will be accepted through Nov. 1. The committee includes two former society presidents and several JBC associate editors.

"We will do our best to identify a suitable successor," Pfeffer said. "We have already received the names of several highly qualified candidates and welcome nominations from all ASBMB members."

The new editor's term will begin Jan.1, and he/she will be co-editor with Tabor for the first year.

jbc the journal of biological chemistry

Search for Editor-in-Chief, *The Journal of Biological Chemistry*

The American Society for Biochemistry and Molecular Biology welcomes nominations (including self-nominations) for the position of Editor-in-Chief of *The Journal of Biological Chemistry*. The JBC publishes papers based on original research that are judged to make a novel and important contribution to understanding the molecular and cellular basis of biological processes. The Editor-in-Chief advocates in the interests of both contributors and readers by ensuring that the *JBC* offers fair, prompt and thorough reviews, responsible editorial adjudication and thoughtful suggestions for revision and clarification.

Candidates should have demonstrated success in research in one of the fields about which the *JBC* publishes and should possess:

- A broad, general knowledge of biological chemistry
- A commitment to publishing the very best science
- The ability to recruit outstanding scientists to serve as contributors, Associate Editors and Editorial Board members
- A willingness to provide sustained and consistent editorial direction

A candidate should have an active scientific research laboratory and a broad knowledge of biological chemistry. He or she should have demonstrated communication, leadership and coalition-building skills and scientific editorial experience.

Responsibilities of the Editor-in-Chief include:

- Overseeing the peer-review process, editorial direction and journal mission
- Working with ASBMB leadership to develop strategic direction and vision for the future of the *JBC*
- Overseeing the selection of highlighted papers and short review topics
- Reporting semi-annually to the ASBMB Council and Finance and Publication Committees about the state of the journal and pending developments
- Assisting the ASBMB Publications Committee and Council in setting policy related to journal operations
- Leading meetings of the *JBC* Editorial Board members and Associate Editors

The Editor-in-Chief will be appointed to a five-year term, with the possibility of reappointment, formally beginning in January 2011. A staff support network is available, and a stipend is provided.

Nominations will be reviewed by a search committee appointed by the President of ASBMB. Each nomination should include a summary of the candidate's career and research interests. If self-nominating, the candidate should include a statement about his or her approach to leading the *JBC*.

Nominations should be sent electronically by November 1, 2010 to the ASBMB Editor-in-Chief Search Committee c/o ASBMB Publications Director Nancy Rodnan: nrodnan@asbmb.org

THE RUTH KIRSCHSTEIN DIVERSITY IN SCIENCE AWARD

Inaugural Diversity Award Bestowed upon University of Colorado Professor

Gutierrez-Hartmann's efforts described as "tireless" and critical to young investigators' success

BY ANGELA HOPP

The American Society for Biochemistry and Molecular Biology has named Arthur Gutierrez-Hartmann, a professor at the Anschutz Medical Campus of the University of Colorado-Denver School of Medicine, the winner of its inaugural Ruth Kirschstein Diversity in Science Award.

The award was established to honor an outstanding scientist who has shown a strong commitment to the encouragement of underrepresented minorities to enter the scientific enterprise and to the effective mentorship of those within it.

"This is a terrific honor, not only because it is the inaugural diversity award from ASBMB, but in particular because it is given in honor of Dr. Kirschstein, who worked tirelessly for trainees and their support at NIH/NIGMS. Importantly, this award also calls attention to the URM student group and that we need to do a lot more to increase this group in science."

ARTHUR GUTIERREZ-HARTMANN, professor at the Anschutz Medical Campus of the University of Colorado-Denver School of Medicine.

"Arthur has been tireless in his efforts, giving freely of his time to help numerous [underrepresented] and disadvantaged students as they progress through the key transitions in their careers in biomedical sciences," explained John D. Baxter of The Methodist Hospital Research Institute in the Texas Medical Center in support of Gutierrez-Hartmann's nomination. "Being a Mexican-American physician-scientist who has firsthand knowledge of the disadvantages and prejudices that [underrepresented minority] trainees must overcome has given him insights that resonate with trainees he mentors."

Sonia C. Flores, a colleague at the Anschutz Medical Campus, emphasized how scarce role models like Gutierrez-Hartmann were back when she was a trainee and how important his efforts are for trainees today: "As a woman from Puerto Rico… I commend his unwavering commitment to the advancement of not only ethnic minorities but women in science. Arthur is always gentle, always right and always finds the time to tell every student what they need to accomplish."

Gutierrez-Hartmann completed his bachelor's degree at the University of Texas at Austin in 1971. He attended graduate school and medical school from 1971 to 1977, receiving his medical degree in 1975 from University of Texas-Southwestern Medical School. He went on to complete a residency from 1977 to 1980 at the Stanford University Medical Center and a fellowship from 1980 to 1983 at the University of California, San Francisco, serving under Baxter. He served on the Journal of Biological Chemistry's editorial board from 2001 to 2006.

Angela Hopp (ahopp@asbmb.org) is managing editor for special projects at ASBMB.

About the award

The Ruth Kirschstein Diversity in Science Award includes a plaque, a $3,000 cash prize and travel expenses for the ASBMB annual meeting. Gutierrez-Hartmann will present his award lecture, titled "The Role of the ETS Transcription Factor ESE-1 in Breast Cancer," at 9:03 a.m. Sunday, April 10, at the 2011 annual meeting in Washington, D.C.

THE AVANTI YOUNG INVESTIGATOR AWARD IN LIPID RESEARCH

Young Scientist at Virginia Commonwealth University Wins Avanti Award

Chalfant lauded for research productivity and emerging leadership in the study of lipids

BY ANGELA HOPP

The American Society for Biochemistry and Molecular Biology named Charles E. Chalfant, an associate professor at Virginia Commonwealth University School of Medicine in Richmond, Va., the winner of the Avanti Young Investigator Award in Lipid Research. Chalfant also is a research career scientist at the Hunter Holmes McGuire Veterans Administration Medical Center in Richmond.

In support of Chalfant's nomination, Lina M. Obeid, professor of medicine at the Medical University of South Carolina in Charleston, said he "exemplifies the ideal young scientist in the lipid community."

"He is enthusiastic, always willing to help, participates in several important initiatives in the field of lipids and is clearly a highly positive influence to the lipid scientific community. These include organizing and obtaining NIH funding for lipid-related scientific conferences and serving on [National Institutes of Health] study sections as an advocate for lipid-related research," she wrote. "In fact, it is astounding how much Dr. Chalfant has been able to accomplish in advancing lipid research at such an early stage in his career while carrying a solid load of a productive scientist and academician."

Chalfant joined the faculty of VCU and began doing research at the VA medical center in 2003. He has been a member of ASBMB since 1999 and now serves as an editorial board member of the Journal of Lipid Research.

"His groundbreaking studies on regulation of alternative splicing of Bcl-X and caspase-9 by ceramide provided an answer to the long-sought-after function of ceramide in apoptosis. His seminal discovery that ceramide-1-phosphate is a direct allosteric regulator of cPLA2 has uncovered a novel function of this sphingolipid metabolite in regulating eicosanoid biosynthesis. These discoveries already have established him as a rising star in lipid research," said VCU colleague Sarah Spiegel, who nominated Chalfant for the award.

"I am truly humbled by receiving such national recognition for something I love to do."

CHARLES E. CHALFANT, associate professor at Virginia Commonwealth University School of Medicine in Richmond, Va.

Chalfant completed his bachelor's degree in 1992 at the University of Tampa and his doctoral degree in 1997 at the University of South Florida College of Medicine. He also served as a research associate at Duke University and completed a postdoctoral fellowship at the Medical University of South Carolina.

Angela Hopp (ahopp@asbmb.org) is managing editor for special projects at ASBMB.

About the award

The Avanti Young Investigator Award in Lipid Research consists of a plaque, $2,000 and travel expenses to the ASBMB annual meeting. Chalfant will present an award lecture, titled "Ceramide and Ceramide-1-phosphate: Enigmatic Lipids Generating New Signaling Paradigms," at the 2011 annual meeting in Washington, D.C.

THE ASBMB YOUNG INVESTIGATOR AWARD

UMass Professor Wins Emerging Investigator Award

Dekker developed tools to probe 3-D structure of chromosomes, opening an entirely new field of study

BY ANGELA HOPP

Job Dekker, an associate professor at University of Massachusetts Medical School, is the winner of the American Society for Biochemistry and Molecular Biology 2011 Young Investigator Award.

Dekker, a member of UMMS's program in gene function and expression in the department of biochemistry and molecular pharmacology, studies chromosome structure, and he is credited with developing early in his career a suite of extremely powerful methodologies to probe the 3-D structure of chromosomes at remarkably high resolutions. Since then, he has developed a method of using deep sequencing that allows analysis of millions of chromosome interactions in parallel.

"It is especially rewarding to see that our genome technologies have become so widely used."

JOB DEKKER, associate professor at University of Massachusetts Medical School.

When nominating Dekker, UMMS professor and department chairman C. Robert Matthews emphasized that the methods have brought previously invisible aspects of chromosomes into view, opening an entirely new field of study.

"Job Dekker embodies all that one might expect in the next generation of leaders in science," Matthews said. "Job sees the big picture, he is very creative, he is ambitious and he gets things done."

Tom Misteli, a senior investigator and the chief of the National Cancer Institute's cell biology of genomes arm, echoed Matthews' sentiments in support of Dekker's award: "[He] is an extraordinary scientist in many ways. He is ingenious, persistent to a fault, creative and a big thinker. While many have shied away from tackling the big question of how genomes are organized in vivo, Job Dekker fearlessly and relentlessly developed a method to pursue the answer to a very big question. His work has changed how we study gene expression, and the methods he has developed will shape the way we study genomes for many years to come."

Dekker received his bachelor's and doctoral degrees from the University of Utrecht, the Netherlands, in 1993 and 1997, respectively. He joined UMMS after a stint as a postdoctoral fellow at Harvard University from 1998 to 2003.

His pioneering approach has garnered considerable recognition and awards, including selection as a W. M. Keck Foundation Distinguished Young Scholar in 2007.

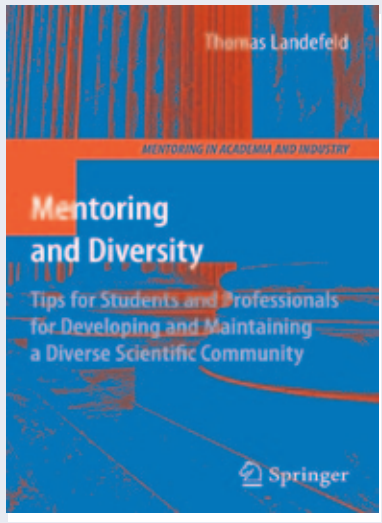
Angela Hopp (ahopp@asbmb.org) is managing editor for special projects at ASBMB.

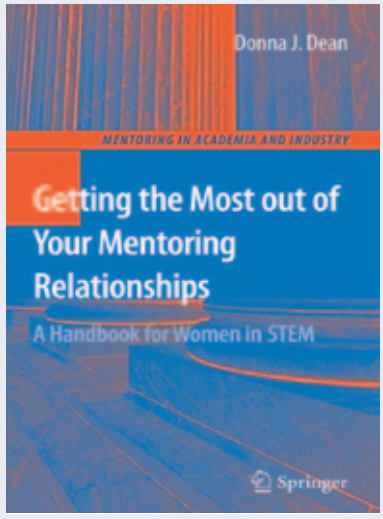
About the award

The ASBMB Young Investigator Award recognizes outstanding research contributions to biochemistry and molecular biology by those who have no more than 15 years of postdoctoral experience. It consists of a plaque, a $5,000 prize and travel expenses to the ASBMB annual meeting. Dekker will present his award lecture, titled "Three-dimensional Folding of Genomes," at 2:55 p.m. Tuesday, April 12, at the 2011 annual meeting in Washington, D.C.

Mentoring in Academia and Industry

Series Editor: J. Ellis Bell, University of Richmond, Richmond, VA





The series Mentoring in Academica and Industry enriches science teaching and mentoring of both students and faculty. It provides guidelines for improving academic and career building skills.

asbmb member spotlight

Alberts Honored with Vannevar Bush Award

Bruce M. Alberts was named the recipient of the 2010 Vannevar Bush Award, presented by the National Science Board, in recognition of his lifetime contributions to the U.S. in science and technology.

The award honors truly exceptional, lifelong leaders in science and technology who have made substantial contributions to the welfare of the nation through public-service activities in science, technology and public policy. It was established in 1980 in memory of Vannevar Bush, who served as science advisor to President Franklin D. Roosevelt during World War II, helped to establish federal funding for science and engineering as a national priority during peacetime and was behind the creation of the National Science Foundation.

Alberts currently serves as editor-in-chief of the journal Science and as a U.S. science envoy. He also is professor emeritus in the department of biochemistry and biophysics at the University of California, San Francisco.

"We are pleased to recognize Bruce for his dedication to the creativity, openness and tolerance that define science, passion for improving the human condition and transformational and inspirational leadership in science education, international capacity building and the tireless pursuit of a scientific temperament for the world," said Steven Beering, NSB chairman.

PHOTO CREDIT: TOM KOCHEL, AAAS

Katzenellenbogen Receives Portoghese Award

John A. Katzenellenbogen, Swanlund chairman and professor of chemistry at the University of Illinois, recently was selected to receive the inaugural Philip S. Portoghese Medicinal Chemistry Lectureship. The award, named in honor of Phil Portoghese, the long-standing editor-in-chief of the Journal of Medicinal Chemistry, is administered jointly by the editor-in-chief of the journal and the American Chemical Society Division of Medicinal Chemistry.

The lectureship honors the contributions of an individual who has had a major impact on medicinal chemistry research.

Katzenellenbogen's research spans chemistry, biology and medicine and involves analysis of steroid receptor structure and function and use of receptors and their ligands in various biological and biomedical applications. He prepared the first-affinity labels and subtype-specific agents for estrogen receptors, and he has probed the receptor with ligands of diverse structure and chemotype, finding compounds with unusually selective biological activities. He also has developed an extensive series of steroid receptor-based agents for imaging receptor-positive breast and prostate tumors by positron emission tomography and obtained the first PET images of these tumors based on their receptor content.

Catterall Wins Gairdner Award

William A. Catterall, chairman and professor of the department of pharmacology at the University of Washington School of Medicine, was one of five scientists awarded 2010 Canada Gairdner International Awards from the Gairdner Foundation.

The Gairdner Awards are given annually to individuals from a variety of fields for outstanding discoveries or contributions to medical science. According to the Gairdner Foundation, which was established by Toronto stockbroker James Arthur Gairdner in 1957, next to the Nobel Prize in Medicine, the Canada Gairdner Awards are the most prestigious global medical research awards.

Catterall was recognized by the foundation for discovering the voltage-gated sodium-channel and calcium-channel proteins that underlie electrical signaling in the brain. His work also has led to a new understanding of the molecular mechanisms of function and regulation of these ion channel proteins. Catterall's recent work has turned toward understanding diseases caused by impaired function and regulation of voltage-gated ion channels, including epilepsy and periodic paralysis.

Catterall officially will be presented with the 2010 Canada Gairdner International Award in October. Each of the awards come with a $100,000 cash prize.

Jordan Appointed to Komen Council

V. Craig Jordan has been appointed to the Susan G. Komen for the Cure® Scientific Advisory Council. Jordan is the scientific director and vice chairman of the department of oncology at the Lombardi Comprehensive Cancer Center at Georgetown University Medical Center.

According to Komen, appointment to the council is reserved for those who have a distinguished record of leadership and commitment to breast cancer research, as well as innovative contributions to breast cancer advancements. Those who are appointed as council members "will serve as distinguished scholars advising and providing expertise to Susan G. Komen for the Cure in peer review, scientific research, sponsored programs, program development and review and public policy."

Council members serve for renewable, two-year terms during which they are expected to commit approximately 100 to 120 hours each year to council activities. Jordan also will be awarded a $250,000 Komen research grant annually for the duration of his term on the council. The grant must be used to study critical questions in breast cancer.

Jordan is an internationally recognized breast cancer scientist whose research focuses on the response of breast cancer cells to preventive and treatment agents. A pharmacologist, Jordan is recognized by many as the "father" of the anticancer drug tamoxifen.

Sifers Garners Award for Excellence in Education

Richard N. Sifers, an associate professor of pathology and immunology at Baylor College of Medicine, received the Barbara and Corbin J. Robertson, Jr. Presidential Award for Excellence in Education. The honor is Baylor College of Medicine's highest award given to faculty members for their efforts in education.

Sifers has served as a member of more than 40 graduate student committees and has lectured at numerous international symposia and workshops in which scientists, students, clinicians and patients have served as the immediate learners. He also is involved with the Alpha-1 Foundation, serving as a member of its educational materials working group, which develops educational materials for worldwide distribution as a means to educate the public about the cause of numerous conformational diseases.

Sifers' research focuses on dissecting the mechanism of human endoplasmic reticulum mannosidase I and delineating its participation in the etiology of liver disease. His long-term goal is to demonstrate how a core element of the glycoprotein quality control machinery can function as a disease modifier, possible diagnostic marker and potential site for therapeutic intervention.

Gerlt Wins Scott Medal

John A. Gerlt, Gutgsell chairman and professor of biochemistry, chemistry and biophysics at the University of Illinois, Urbana-Champaign, is the winner of the 2010 A. Ian Scott Medal, presented by the American Chemical Society Texas A&M Section and Texas A&M University's department of chemistry. The award recognizes excellence in biological chemistry research. Gerlt will receive a gold medal and bronze replica during an awards ceremony at Texas A&M University in October.

Gerlt's research focuses on the importance of chemistry in the evolution of new enzymatic activities. His work has included pioneering studies of how enzymes, such as mandelate racemase, abstract protons from extremely weak acids to generate carbanion intermediates. Gerlt and co-workers also suggested that electrophilic catalysis and strong hydrogen bonding were key factors in making such difficult reactions proceed at reasonable rates. These studies have led to a better appreciation for the sophisticated tools that enzymes can use to accelerate reactions.

Currently, Gerlt is studying two groups of enzymes that are derived from common ancestors, both of which share the ubiquitous (β/α) eight-barrel fold: the members of the enolase superfamily and the members of the orotidine 5'-monophosphate decarboxylase suprafamily. He also is involved in discovering and characterizing novel enzymes involved in the degradation of lignin in plant biomass.

PHOTO CREDIT: L. BRIAN STAUFFER, UNIVERSITY OF ILLINOIS, URBANA-CHAMPAIGN.

Ginsburg Honored with Medical Research Award

David Ginsburg, the James V. Neel Distinguished University Professor of Internal Medicine and Human Genetics at the University of Michigan Medical School, is the recipient of the Robert J. and Claire Pasarow Foundation 22nd Annual Medical Research Award in Cardiovascular Disease.

The Robert J. and Claire Pasarow Foundation was established by the Pasarows more than 20 years ago to celebrate stellar achievement, creativity and distinction in research in three areas of medicine: cancer, cardiovascular disease and neuropsychiatry.

Ginsburg, who also is a Life Sciences Institute research professor and an investigator at Howard Hughes Medical Institute, studies the components of the blood-clotting system and how disturbances in their function lead to human bleeding and blood-clotting disorders. Specifically, he and his colleagues are looking at the blood-clotting protein von Willebrand factor and how molecular defects in the protein are responsible for many of the less common subtypes of von Willebrand disease. He also studies diseases involving coagulation factor V, a central regulator in the early phases of blood-clot formation, and plasminogen activator inhibitor-1 (PAI1) and PAI2, both of which regulate the fibrinolytic system that breaks down blood clots.

Four ASBMB Members Receive HUPO Awards

The Human Proteome Organization Awards committee recently announced the recipients of the HUPO distinguished awards for 2010, four of whom were American Society for Biochemistry and Molecular Biology members. Richard M. Caprioli will receive the HUPO Distinguished Achievement Award in Proteomic Sciences, John J. M. Bergeron was named the HUPO Discovery Award in Proteomics Sciences recipient, and Michael Dunn and Ralph A. Bradshaw garnered the HUPO Distinguished Service Award.

RICHARD M CAPRIOLI, Stanley Cohen professor of biochemistry and director of the Mass Spectrometry Research Center at the Vanderbilt-Ingram Cancer Center, investigates biological processes involving the synthesis, modification, storage and degradation of peptides and proteins using mass spectrometric methods of analysis to follow molecular events.

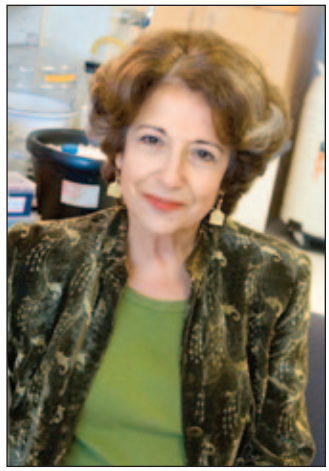
JOHN J. M. BERGERON, a medical scientist in the department of medicine at the McGill University Health Centre Research Institute, uses proteomics to characterize the proteins of the mammalian cell by a strategy known as the CellMap.

MICHAEL DUNN, professor of biomedical proteomics at the University College Dublin Conway Institute of Biomolecular and Biomedical Research, focuses on three major areas of biomedicine: cardiovascular proteomics, transplantation proteomics and neuroproteomics.

RALPH A. BRADSHAW, professor emeritus of physiology and biophysics at the University of California, Irvine, has two major areas of investigation in his laboratory. In the first, polypeptide growth factors and their receptors are being examined with respect to structure and mechanism, whereas the second block of studies addresses the manner in which protein turnover in eukaryotic cells is regulated.

Mina J. Bissell: *Going the Extra Mile… and Dimension*

BY NICK ZAGORSKI



In 1992, Mina J. Bissell found herself in an unusual position. She had just been appointed director of all the life sciences at the Lawrence Berkeley National Lab in California and thus also had been placed in charge of LBNL's genome center, which recently had begun sequencing portions of human DNA for the Human Genome Project.

Having LBNL play a central role in such an ambitious endeavor could be considered an honor, but Bissell was troubled: "I remember even before the genome was completed, almost everyone who was talking about the project was promising that it would simplify science and medicine, cure all diseases and answer all our questions."

"And, I remember telling them over and over again that it was not so simple," she adds.

For one thing, why would her colleagues want to make science simple? "For me, at least, the beauty of science has always been its complexity," she says. "Every question you answer opens up more exciting questions, more riddles to solve. The sequence of the genome has opened up a whole host of other questions."

"And, besides, how would the complete genome solve developmental and cell biology questions? An eye and a nose have the exact same genome in an individual, so, why are they so different? The sequence alone won't answer that."

Fiery, passionate and certainly not afraid to upset the scientific apple cart is a brief, but apt, description of Mina Bissell.

In fact, Bissell, a distinguished scientist at LBNL, where she has been since 1972, has spent her entire career challenging traditional views. Fortunately, another of her qualities is doggedness, which is vital, for the scientific establishment puts a heavy burden of proof on those who wish to challenge tradition. And, in Bissell's arena of cancer research, the prevailing view for more than 30 years has been that the "gene is king," and even single mutations dictate cancer incidence and progression.

Bissell, though, has been working tirelessly to prove that the king needs to share his throne. Using an integrative approach that combines an ingenious 3-D cell-culture system with other molecular biology, imaging and high-throughput methodologies, she has demonstrated that a tissue's architecture and its surrounding microenvironment — such as cell-cell interactions and the extracellular matrix — are just as important in cancer progression as the genetic alterations within.

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Berkeley, Calif., in the 1970s was abuzz with oncogenes. Numerous discoveries during that time, including important work done by Peter Deusberg and G. Steve Martin at Berkeley and Peter Vogt at the University of California, Los Angeles had demonstrated how viruses (Rous sarcoma virus) could use their genetic material to turn normal cells into tumor cells, and Michael Bishop, Harold Varmus and colleagues had shown that even some host genes had inherent potential to promote cancer if mutated. Many scientists believed these discoveries would win Richard Nixon's recently declared war on cancer.

Bissell, however, was a bit more skeptical about the oncogene revolution at that time. In reading some literature about cancer, Bissell had been more intrigued by another, older concept: the Warburg hypothesis, which suggested that altered metabolism could induce cancer.

"Of course, by then, most scientists had discredited the Warburg theory, so no one was really pursuing it," she says, then, adding adamantly, "but I was interested in it."

Bissell notes that the main issue she discovered was that researchers who had measured metabolism and cancer cells often did not regulate various external factors like temperature, cell density and pH, which led to inconsistent results in the literature.

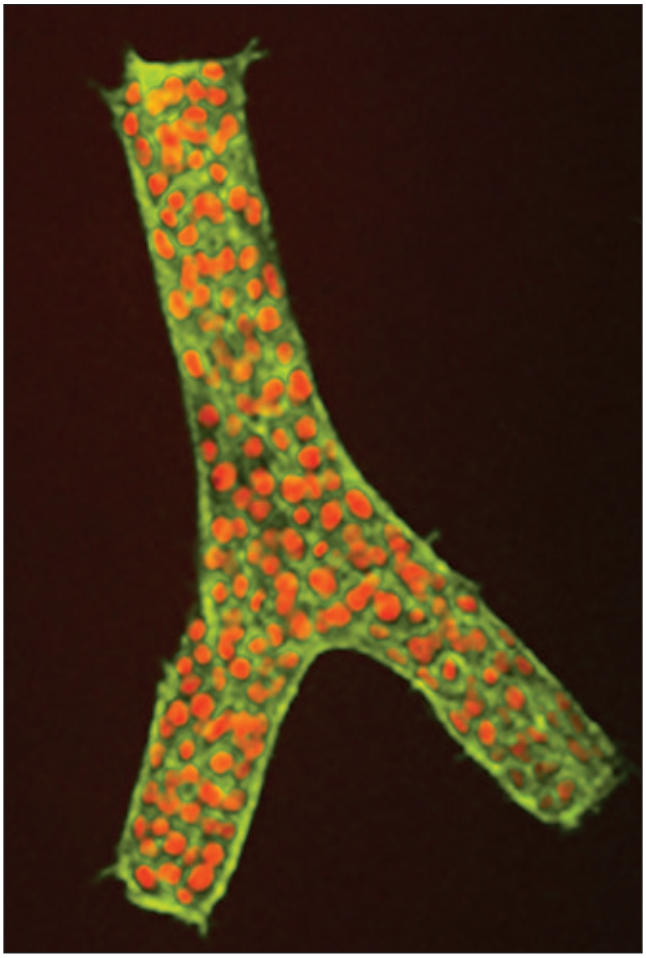
So, together with Al Bassham, a protégé of legendary chemist Melvin Calvin (of Calvin cycle fame), she devised a unique steady-state machine that could keep the environment of cultured cells constant. Then, they adapted some kinetic techniques Calvin and Bassham had employed in studying photosynthesis to animal cells and tracked glucose metabolism in various cell types.

"Everyone thought glucose metabolism was a housekeeping function that should be the same in all cells, but we

found that glucose metabolites had tissue-specific expression patterns," she says proudly. "Furthermore, we found that glycolysis was always higher in cells infected and transformed by RSV once all factors were properly controlled, but the increases were not necessarily due to defects in cellular respiration, which Warburg had believed."

The real intrigue came in further studies in which Bissell manipulated the glucose levels in normal and transformed cells; when she lowered the glucose concentration in RSV-infected cells, they began to appear more normal, whereas increasing the glucose concentration in normal cells could induce them to begin looking transformed.

"These findings were quite exciting to me," she says. "Unfortunately, no one else was particularly interested, because metabolism was the last thing people wanted to hear about at that time; it was old and boring."



In addition to her work uncovering the role of the microenvironment in cancer, Mina J. Bissell has been examining other aspects of its regulation, such as how the ECM, ECM regulatory proteins and tissue geometry influence mammary gland branching and morphogenesis.

Then, one day, near the end of the decade, Bissell happened to attend a most interesting lecture given by Beatrice Mintz of Philadelphia's Fox Chase Cancer Center. In her talk, Mintz discussed studies in which she had integrated mouse cancer cells into developing mouse embryos and shown that, even though the embryos incorporated genetic material from these cancerous cells — which would readily form tumors if injected into adult animals — the mice were born healthy and happy.

The cancer signals had somehow been repressed, which Bissell believed indicated that, much like the metabolic environment, the physical environment of a cell could dictate its predilection for disease.

It was a radical concept — most scientists believed extracellular molecules like collagen merely were inert structural components — and one Bissell could not resist trying to pursue further.

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It might have seemed unusual for a young, still somewhat-unproven researcher to take on such a hefty challenge, but family and friends who knew her during her youth in Iran, before she arrived in the U.S. in 1959 to begin her college studies at Bryn Mawr (having won a prestigious scholarship as Iran's top high school student), probably were not surprised.

Bissell, after all, grew up in a well-to-do academic family in Tehran that had a history of going against the grain. Her father, who came from a long family line of ayatollahs, bucked the tradition of first-born sons attending divinity school and instead became a lawyer, and an agnostic to boot. Yet, this didn't offend her grandfather, who, contrary to the image most Westerners have of these Islamic religious figures, was the most enlightened man Bissell knew.

"I mean, my grandfather's best friend was Tehran synagogue's head rabbi," she says, mentioning a fact that highlights some of the misconceptions Bissell has had to deal with on occasion.

"I've had people comment that they're impressed I've managed to succeed in my career considering I grew up a woman in the Middle East," she says.

"And, I always correct them and say I succeeded precisely because I grew up in the environment I did."

She points out that, prior to the Islamic revolution, Iran featured Muslims, Christians, Jews, Armenians — you name it — all co-existing with very little bias. Likewise, gender discrimination was not a serious issue, at least in large cities. (Even today, despite the changes in government, Bissell notes

Iran is a highly educated country and that women make up an equal percentage of the students in hard sciences, and, at Tehran University, 50 percent of faculty are women.)

"My family always told me that I could become whatever I dreamed of," she says, adding that her father did advise her to stay away from law, because "he knew that fundamental religion was penetrating the legal system, and I might encounter some prejudice against me, which, given my nature, I would fight vigorously and get into more trouble."

Years later, that desire to stand up for her beliefs would be tested in the scientific arena.

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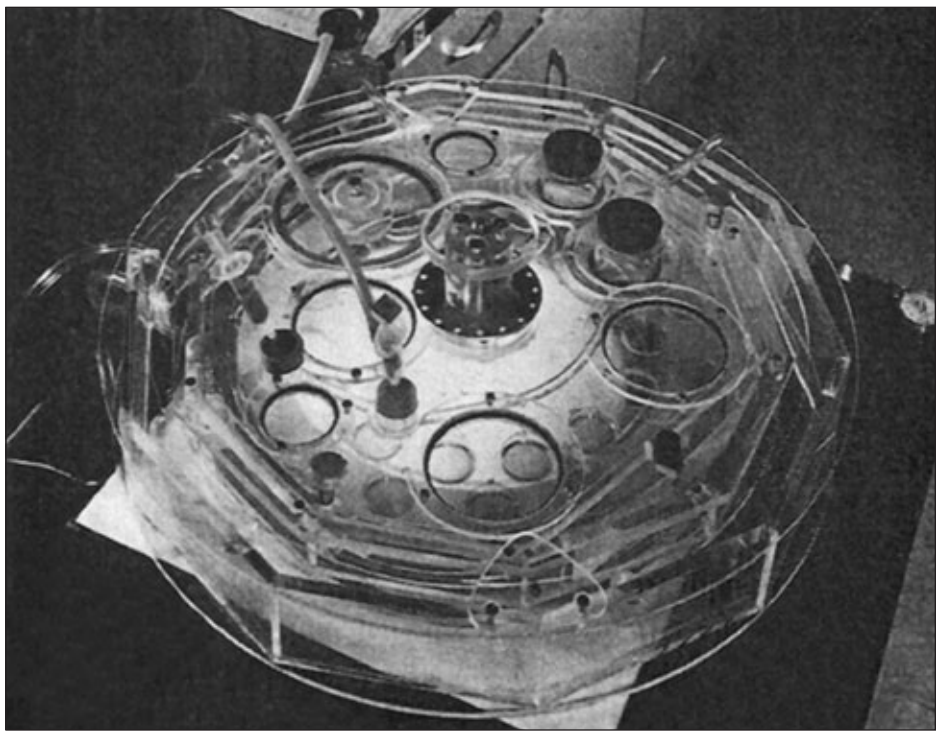

A steady-state apparatus developed by Mina J. Bissell and Al Bassham used to more accurately quantify metabolism in a variety of cell types.

Together with postdoctoral fellow David Dolberg, Bissell continued her studies with oncogenes and changes in the microenvironment by testing whether RSV could transform chicken embryos. It was well-known that if RSV was injected into an adult chicken wing, it formed a tumor; however, when they injected the virus into developing chicken embryos, no tumors formed. But, more intriguingly, if those injected embryo wings were separated into individual cells and put in a dish, they would become cancerous again.

The team looked at another RSV-related fact — that viral administration typically only produced tumors near the site of injection, even though the chickens had viral particles circulating in their blood. However, if they wounded infected chickens at other locations, those sites also could develop tumors, which they determined were not due to metastasis. Subsequently, with another student, Michael Siewke, she demonstrated that a wound-response protein, TGF-β, mediated this postinjury tumor formation.

Now, quite fascinated with how the surrounding tissue architecture might influence these events, Bissell decided to switch to a model more relevant to the human condition. "Fortunately, I had a wonderful postdoc, Joanne Emerman, who had done her thesis on mammary glands, so we decided to focus on that, since the mammary gland undergoes a lot of developmental changes and is frequently associated with cancer. And her help in getting our work underway was quite invaluable."

(Because her own background was primarily bacterial genetics, enzymology and metabolism, Bissell also recognizes two other great postdocs, Rick Schwarz and Glenn Hall, who used their graduate student expertise in collagen and basement membranes, respectively, to mentor her in those areas.)

The key to success, though, would be finding a suitable method to study microenvironment interactions in detail. "Obviously, two-dimensional studies in petri dishes would be limited, but some experiments would be impractical in mouse models as well," she says.

Her solution was to develop an ingenious three-dimensional culture matrix that resembled a natural extracellular matrix and enabled mammary cells to form spatially relevant structures like a real mammary gland, initially in mice (with postdoc Mary Helen Barcellos-Hoff) and then in human breast (with Ole Petersen, a young professor in Denmark). She states that this is, by no means, a perfect system, but Bissell and her lab continually are working on improving their three-dimensional matrices.

Since then, Bissell and her group have been using these three-dimensional models to explore how cells and the surrounding extracellular matrix interact to shape cell behaviors such as polarity, migration and proliferation; it's a concept she has termed a "dynamic reciprocity" in signaling between the extracellular matrix, transmembrane receptors,

the cytoskeleton, the nucleus and the chromatin.

This has led to some real eye-opening discoveries, perhaps best highlighted by a series of studies in the late 1990s, in which Bissell's group demonstrated that antibodies against the β1-integrin receptor lowered EGF signaling and altered the behavior of cancerous breast cells to a more normal phenotype; conversely, adding matrix metalloproteinases to degrade the three-dimensional matrix could induce invasive phenotypes in otherwise nonmalignant breast cells.

And, these eye-opening results would not have been evident in any two-dimensional system.

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One would imagine that, given the remarkable nature of Bissell's early findings, her pioneering studies with three-dimensional mammary models would establish quickly the importance of the ECM in cell physiology.

However, although scientists often like to think of themselves as a progressive lot, in many ways, science — notably basic academic science — is a conservative field. Discoveries are made in steady, incremental steps, whereas funding agencies tend to favor established scientists providing safe, tractable projects.

So, for many years, Bissell struggled with National Institutes of Health funding, picking up grants from other agencies (especially the Office of Biological and Environmental Research at the U.S. Department of Energy) willing to take a risk on an innovative idea, while also failing to get a significant foothold in the cancer community at large. Even now, she notes, most textbooks still mention the ECM purely as a structural component.

"People can be set in their ways sometimes, and science is no different," she notes. "I think this might have been especially true in the early days of the molecular biology era, with the new techniques that broke research down into simple pieces. Either your gel had a band, or it didn't; a cell had a functional copy of a gene, or it didn't. People didn't step back and consider broader possibilities."

Another influencing factor, Bissell believes, was the growing commercialization of science in the 1980s and beyond. "Now, all of a sudden, a lot of good scientists were spinning their discoveries into businesses and had tangible investments in their products. And, if you have a gene that may be crucial in cancer development, you don't want to hear someone else saying all this stuff outside the cell is important."

Particularly because Bissell believed — and showed — that changing the extracellular environment could help prevent the spread of cancer, even by genetically defective cells.

These were frustrating times, but, Bissell states definitively, "I was not raised to be a quitter."

She certainly did not quit when she became pregnant during her first year of graduate studies at Harvard in 1963 — the medical school had only three female students and 200 males, and most everyone assumed she would drop out. And, she wouldn't quit now.

Slowly, with continued determination and persistence, aided by former lab members who helped spread her ideas to other institutes and "a few wonderful colleagues," Bissell's ideas became more accepted.

Indeed, the past few years have seen her receive many honors as a testament to this, such as election to the Institute of Medicine, American Academy of Arts and Sciences and, more recently, both the American Philosophical Society (2007) and National Academy of Sciences (2010). She also has received the Pezcoller Foundation-American Association for Cancer Research International Award for Cancer Research (2007); the Federation of American Societies for Experimental Biology Excellence in Science Award (2008), the American Cancer Society Medal of Honor (2008) and, recently, her own "Mina J. Bissell" Award, which will be presented every two years by the University of Porto in Portugal.

With her newfound recognition, Bissell has been quite busy on the lecture circuit; even though she says she only can accept about one of every four speaking invitations, she still feels like she's continually on the go. Still, she uses that time to relate her story and encourage others, especially young scientists, to follow their own scientific ideas and not get discouraged by setbacks.

"Innovative people always have to prove themselves, so stay with it and don't let the establishment tell you what to do," is one of her mantras, usually followed by a wink and nod to her own recent success.

"Of course, now that my work has been accepted, I guess I'm part of the establishment too, so I guess you shouldn't listen to me either." ∿∿∿

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The Interface between Cell and Molecular Biology and Animal Agriculture

BY RUSSELL V. ANTHONY AND SCOTT L. PRATT

Today, most investigators give little thought to the interface between biochemistry, cell and molecular biology and agriculture — much greater emphasis is placed on the biomedical relevance of research than on its relevance to animal agriculture. This likely is due to the changing demographics of the United States. At the turn of the 20th century, 43.5 percent of the U.S. work force was involved in agriculture, as compared with only 2.4 percent by the end of the century. Yet, advances in cell and molecular biology continue to impact animal agriculture, and livestock species often are valuable models for biomedical research. The following are a few examples of how cell and molecular biology interface with animal agriculture.

Recombinant DNA Technology

Recombinant DNA technology has been used to generate effective vaccines and hormones for the livestock industry. For example, a polypeptide derived from the recombinant pseudo-rabies virus glycoprotein has been used for the generation of a pseudo-rabies vaccine for swine. A recombinant DNA vaccine also currently is marketed for the vaccination of horses against West Nile virus, and additional vaccines for livestock, derived from recombinant DNA technology, are being developed.

Recombinant DNA technology also led to the development and use of recombinant bovine somatotropin (bST; growth hormone) in lactating dairy cows to enhance the efficiency of milk production. Although the use of bST may be viewed as controversial, it still is a "success story" for the interface of molecular biology with animal agriculture.

Furthermore, the successful recombinant generation of several reproductive hormones, such as gonadotropins and gonadotropin-releasing hormone, has enhanced the development and efficiency of assisted reproductive technologies in livestock, including artificial insemination, estrous synchronization, in vitro fertilization and embryo transfer.

Molecular Technology

Molecular technologies have allowed the generation of reagents and diagnostic kits previously unavailable for livestock. This includes reagents for diagnostic enzyme-linked immunosorbent assay kits, as well as reverse transcription-polymerase chain reaction and standard PCR. The latter two have been used for identification of viral and microbe infection (e.g., screening pig semen for porcine reproductive and respiratory syndrome virus), as well as genetic diagnosis of embryonic sex prior to embryo transfer.

Cell Biology Technology

Cell biology is being used to examine sperm membrane compositional changes during capacitation and the acrosome reaction to assess sperm quality and to enhance the cryopreservation of livestock sperm and embryos.

Fluorescence-activated cell sorting was used for the commercialization of "sexed" semen, allowing the dairy industry to obtain greater numbers of female offspring for milk production, and helping the beef industry obtain more male offspring for the efficient production of nutrient-dense meat for human consumption.

Functional Genomics

Although the complete genomic sequences for many livestock species are yet to be completed or released, considerable effort is being directed toward identifying quality trait loci and single nucleotide polymorphisms that can be used to enhance genetic selection. At commercial artificial insemination companies, the use of single nucleotide polymorphism chip analysis of sires is becoming routine.

Genetic sex determination currently is utilized, as well as limited "marker assisted selection" for production traits, such as muscle development and intramuscular fat deposition (i.e., meat quality). With second-generation, solid-state DNA sequencing now available, complete transcriptome analysis of various production efficiency traits is on the horizon.

Transgenesis

The generation of lines of transgenic livestock has not met the expectations initially anticipated, primarily because of low technical efficiency and long generation intervals. It was hoped that transgenic lines could be developed that were either disease-resistant; that produced valuable products (e.g., pharmaceuticals) that could be harvested from milk, blood or eggs in large quantities or that exhibited decreased excretion of compounds detrimental to the environment.

Somatic cell nuclear transfer initially was applied to livestock, and although it has not had the anticipated commercial application, it has provided considerable insight into factors regulating early embryo development. Genetic manipulation of the "donor" cells is more efficient than standard transgenic approaches and has allowed the generation of SCNT-transgenic lines. Some of these are being developed as models for human disease and/or xenotransplantation.

For example, CFTR-null pigs, generated by SCNT, appear to be a better model for human cystic fibrosis than available mouse models, because the *CFTR*-null piglets develop more of the hallmark pathologies associated with cystic fibrosis in humans.

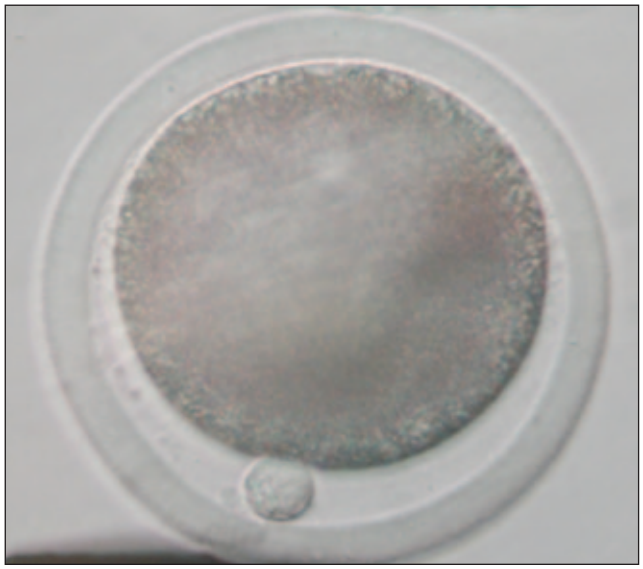
Recently, infection of early-stage embryos or blastocysts with lentiviral constructs, to either overexpress or "knock down" expression of specific genes, have been reported in cattle and sheep and have promise for more efficient genetic manipulation of livestock, at least for research purposes.

Advances in Biomedical Research

This brief synopsis of how cell and molecular biology technologies are interfacing with animal agriculture is not meant to be all-inclusive or exhaustive, but rather to highlight areas that have already or have the potential to impact livestock production. However, a discussion of this "interface" would not be complete without providing examples of how livestock species have helped to advance biomedical research.

For example, many assisted reproduction technologies, such as artificial insemination, cryopreservation of gametes and embryo transfer, initially were developed in livestock species before being applied to humans. There has been, and continues to be, a strong interface between efforts to improve human fertility and similar efforts in animal agriculture.

Another example is the use of livestock, especially sheep, to investigate the physiology of gestation. The pregnant sheep has many attributes that make it a relevant experimental model: It is a long gestational mammal like the human; it often gives rise to a single offspring that has similar organ developmental maturity to the human newborn; and it can



Representation of somatic cell nuclear transfer. Somatic cells are transferred into the perivitelline space of an MII stage-enucleated oocyte, fused and activated, and either cultured or immediately transferred into a recipient.

be manipulated surgically such that chronic instrumentation (vascular catheters, flow probes, etc.) of the fetus allows repetitive sampling on both sides of the placenta under nonanesthetized steady-state conditions. This animal model has provided considerable insight into placental nutrient transfer, fetal-nutrient utilization and the impaired fetal physiology associated with intrauterine growth restriction.

Additionally, swine provide a very relevant model for studying the development of cardiovascular disease, and chickens are being used as a natural model for ovarian cancer.

Clearly, animal agriculture has benefited and continues to benefit from advances made in cell and molecular biology and livestock species have served as valuable and relevant animal models for biomedical research. And, although the percentage of the U.S. work force involved with agriculture continues to decline, agriculture still is an important and required component of everyday life. The interface between cell and molecular biology and agriculture has been robust, and should continue to be, with both scientific disciplines benefiting from each other.

Russell V. Anthony (Russ.Anthony@Colostate.edu) is the Hill professor in the department of biomedical sciences at Colorado State University. Scott L. Pratt (scottp@clemson.edu) is an assistant professor in the department of animal and veterinary science at Clemson University.

The School at Columbia University's Science Expo

BY DANA PE'ER

It all started when Inbar, my beloved 10-year-old daughter, declared in a tone of complete surprise, "What, scientists are *still* discovering new things?" and, with an even bigger shock, "What, *you* discover new things? I thought all you did all day was write e-mails." That is what made me decide to organize a science expo at The School at Columbia University — my daughter's K-8 school.

Planning the Expo

The concept behind the expo was to make kids realize that science is all about inquiry, curiosity and exploration. I made a plea to my colleagues, asking them to come share what they are doing in their labs, what questions they are asking and why they are asking those questions. I was surprised at how easy it was to recruit my colleagues — 38 scientists volunteered, a good number of whom are faculty members at Columbia University.

I wanted the event to be a success, but how does one explain topics such as computational complexity, statistical genetics and epidemiology to children who still are grappling with basic arithmetic operations? I recruited the school's science teachers to come to our aid and paired each scientist with an elementary or middle school teacher, whose expertise was in presenting complex scientific concepts to a young audience. Together, the teams formulated an accessible language and designed engaging hands-on activities that brought the cutting-edge of science to the K-8 classroom.

The Exhibits

Preparations for the event were intense and further intensified by our inherent competitiveness: Put a bunch of scientists together on some task, and we will all try to outdo one another, even if the task is designing the most striking science exhibit for young kids. Activities included looking through microscopes at neurons, bacteria and fruit flies, modeling DNA recombination through cutting and pasting, observing electric fish, constructing models of molecules, games of coordination to test learning of motor skills and many activities in physics, chemistry and engineering.

Helen Causton and I designed an exhibit on how variation in DNA codes for phenotype. This included streaking different yeast strains on Petri dishes, DNA "code-cracking" puzzles and testing who can taste phenylthiocarbamide. I wanted the older kids to understand why genetic association studies are so difficult and used height as an example. We stacked pennies to measure differences in height (the width of each penny being the contribution of a single allele to height) and used interactive software I designed for kids to visualize how effect size and sample size influence our ability to identify a quantitative trait loci in association studies. With proper visuals, the kids could comprehend genetic association even without a knowledge of statistics.

Getting People to Attend

The planning was an enormous amount of work, and we wanted the science expo to be attended schoolwide, by children from Harlem to Wall Street. PR was needed because, sadly, the American public does not share the passion for science that many of us do. The school stepped up to the challenge. Annette Raphel, the head of school, allocated significant funding; the communications liaison and the par-

Expo attendees learned that science is all about inquiry, curiosity and exploration.

ent association led an extensive PR campaign and the music department composed songs about science to sing with the kids. Additionally, the curriculum was adapted mid-year to include a special unit about scientific inquiry. At the end of the unit, students thought up science questions which decorated the walls of the school. These included, "How can space always be there with nothing making it?" and "How are languages formed?"

The Event

On the day of the event, the school was transformed into a six-story, hands-on science museum, with each classroom illustrating different research topics. I was surprised to find a packed house of people, waiting for the opening speeches by Nobel laureate Martin Chalfie and Columbia University Dean of Engineering Feniosky Pena-Mora. Afterwards, attendees were handed a "Passport to Discovery," which distilled scientists' work into one salient question and shared pictures of the scientists from their elementary years. Then, the crowds wandered through the exhibits — each room was crowded and electrifying, as professor after professor explained complex concepts to gaggles of excited school kids. When the expo ended, the biggest challenge was closing — four hours of science had just whetted the crowd's appetite, and security was needed to help clear families out of the building.

Those four hours were both exhausting and exhilarating. We typically had 20 to 30 people at our exhibit at any given time, all spread across the different activities. I most enjoyed one-on-one discussion with the kids, which required flexibility — the little ones shot unexpected questions of all kinds. The parents were just as thrilled and curious as the kids. Some even told me: "I never realized how exciting science was — I always viewed it as something nerdy." The event changed the way many perceive science; and, if it inspired even one child to become a scientist, it was well worth it.

The biggest surprise for my colleagues and myself was just how rewarding the experience was. We found so much gratification from working with this age group, perhaps because the kids were so impressionable and enthusiastic. I have come to realize that the key obstacle to training the next generation of American scientists is the meager pool of talented undergraduates interested in science. Outreach at this young age really can make a difference.

Go to www.asbmb.org/asbmbtoday to hear a companion podcast for this article.

Dana Pe'er (dpeer@biology.columbia.edu) is an assistant professor of biological sciences at Columbia University.

A Transformative Experience

BY ANNETTE RAPHEL

The School at Columbia University is only seven years old, and is faced with the ambitious task of providing pre-high school education of the caliber that has made its university partner so esteemed — without competitive admissions. A lottery-based school, where 50 percent of our students come from Harlem, Morningside Heights and the Upper West Side, and the other half have parents who work at Columbia University, we arguably are one of the most diverse independent schools in New York City. Our students create a robust community, but their parents don't always share experiences, so one of our highest priorities is to bond our community around the intellectual mission of the school. We have offered many opportunities for parent engagement, with varying degrees of success. Dana Pe'er's idea had a ripple effect, first to our faculty, then to Columbia scientists and finally to our children and their parents.

We know that understanding and appreciating science is life changing, both for children whose parents work in academia and for children whose parents have not completed high school. We also know that teaching science from a text does not begin to electrify children in the ways that current scientists talking about real questions and research does. And, we also know that when real scientists share their work with faculty, it enhances the skill sets, perspectives and energy of an already talented group. We had lofty goals for our science exposition, and they were exceeded, leaving us hungry to exploit the potential of our initial relationship with practicing scientists.

The event's success sparked a desire on both sides to continue the collaboration between researcher and science teacher. The science teachers particularly enjoyed the opportunity to expand their knowledge of the latest scientific discoveries through their interaction with the leading researchers across science and engineering.

At the end of the day, we had many more children considering science as a career, our own teachers totally re-energized about the importance of their work and scientists appreciating the complexity of taking sophisticated ideas and demonstrating them to children. This was one of those unforgettable moments in a child's education. It is clear to everyone that science in our school is a priority and the work that our volunteer research scientists did was transformative.

Annette Raphel is the head of the School at Columbia University.

This article describes one of the themes that is part of the ASBMB annual meeting, which will be held April 9–13, 2011, in Washington, D.C.

The Intersection of Chemistry and Biology: Drugs, Disease and Tools for Discovery

BY TAMARA L. HENDRICKSON AND SHANA O. KELLEY

The annual American Society for Biochemistry and Molecular Biology meeting theme "Chemical Biology and Drug Design" will showcase cutting-edge research in areas where chemistry and biology intersect. In four sessions, the molecular mechanisms of disease, the newest approaches to drug discovery for disease treatment and exciting developments in the generation of tools that may shed further light on disease and drug discovery will be highlighted in presentations delivered by leaders in the field.

Tackling Complex Problems in Biology

Each of the speakers in the first session, titled "The Chemical Biologist's Toolbox," are applying sophisticated and elegant chemical methods to tackle complex problems in biology.

Christopher J. Chang (University of California, Berkeley) will present his group's work on the use of cell-permeable fluorescent chemosensors to track reactive oxygen species inside cells in response to environmental triggers, finally providing a means to track radicals in situ. Orthogonal probes also can be used simultaneously to observe the generation of different ROS (e.g. H_2O_2 and HOCl), allowing the interplay of oxidants to be studied.

Sarah Trimpin (Wayne State University) will discuss how her group merges the capabilities of laser and electrospray ionization methods for solvent-free mass spectrometric analyses of tissue samples to allow the study of site-specific physiological processes at the molecular level.

And, finally, Michael L. Gross (Washington University) will present recent progress on the development of mass spectrometric methods to characterize protein complexes and deconvolve the intricate patterns of interactions that guide biological function.

Each of these presentations will highlight promising new tools that will drive the discovery of new phenomena in biological systems.

Hendrickson

Kelley

Peptide Applications

In the second session, "Peptide-based Drug Delivery, Discovery and Biomaterials," a variety of recent advances in the application of peptides as potential drugs and biological probes will be presented.

Alanna Schepartz (Yale University) will present her group's recent discoveries using miniature proteins. Schepartz has reported exciting results highlighting the interplay of cell permeability and efficacy of peptide-based drugs in human cells.

Annelise Barron (Stanford University) will discuss recent progress on the use of peptide mimics for a variety of interesting applications, including the study of the systemic toxicities of host defense peptides in the innate immune system. In her work, the ability to synthetically control peptide structure with extreme precision is important to imparting activities not attainable with natural sequences.

And, lastly, Shana O. Kelley (University of Toronto) will explain her group's work on engineering mitochondrial specificity into cell-permeable peptides, a trait that enables peptide-based probes and drugs to access a different set of targets. These peptides allow site-specific chemistry to be studied within cells, facilitating interesting comparisons between similar processes in different cellular compartments.

High-throughput Methods

The third session, "Novel Approaches to High-throughput Drug Discovery," looks at the diverse array of high-throughput methods that currently are being applied to

drug discovery and the understanding of disease progression.

Michelle Arkin (University of California, San Francisco) will provide an overview of the activities of the Small Molecule Discovery Center at UCSF, where high-throughput screening of small molecules that modulate biochemical or cellular processes is generating interesting leads on novel drug targets and drugs.

Grant K. Walkup (AstraZeneca R&D Boston) will present a new twist on high-throughput screening in which biochemical cascades are used to prioritize isolated hits.

Finally, Tariq M. Rana (Sanford-Burnham Medical Research Institute) will discuss RNA regulatory machines and the interesting results obtained when evaluating these entities as drug targets.

Disease State Applications

The last session, titled "The Chemical Biology of Human Disease," will look at the application of chemical perspectives to the study of disease states.

The first two speakers both will look at the biological role of glycosylphosphatidylinositol anchors. Tamara L. Hendrickson (Wayne State University) will present her work on GPI transamidase, a multisubunit, membrane-bound enzyme. The only subunit of this enzyme that is not directly implicated in tumorigenesis is its active site. Peter H. Seeberger (Max Planck Institute) will discuss important advances in using GPI anchors as targets for malaria vaccine development.

And finally, Jeff Kelly (The Scripps Research Institute) will address the modulation of protein homeostasis (the combination of protein synthesis, folding and breakdown) as a novel approach to treat both loss- and gain-of-function misfolding diseases.

In addition to the invited speakers whose works are highlighted above, 12 short talks will be selected from abstract submissions.

Tamara L. Hendrickson (tamara.hendrickson@chem.wayne.edu) is an associate professor in the department of chemistry at Wayne State University. Shana O. Kelley (shana.kelley@utoronto.ca) is a professor and the director of the division of biomolecular sciences and a faculty of pharmacy, medicine, and biochemistry at the University of Toronto.

Chemical Biology and Drug Discovery

Session: The Chemical Biologist's Toolbox

Molecular Imaging Approaches to Understanding Chemistry in the Brain, *Christopher J. Chang, University of California, Berkeley*

Laserspray Ionization— A New Method for Protein Analysis Directly from Tissue at Atmospheric Pressure with Ultra-High Mass Resolution and Electron Transfer Dissociation Sequencing, *Sarah Trimpin, Wayne State University*

Mass Spectrometry and Structural Proteomics: Mapping Proteins with H/D Exchange and OH Radical Reactions, *Michael L. Gross, Washington University*

Session: Peptide-based Drug Delivery, Drug Discovery and Biomaterials

Cell-permeable Miniature Proteins, *Alanna Schepartz, Yale University*

Systemic Toxicities of the Host Defense Peptides of the Innate Immune System, *Annelise Barron, Stanford University*

Mitochondrial Drug Delivery Using Peptide Carriers, *Shana O. Kelley, University of Toronto*

Session: Novel Approaches to High-throughput Drug Discovery

Screening Technologies for Unusual and Challenging Targets, *Michelle Arkin, University of California, San Francisco*

Completing the Screen: Biochemical Cascades to Prioritize HTS Output, *Grant K. Walkup, AstraZeneca R&D Boston*

RNA-regulatory Machines and Development of New Therapeutics, *Tariq M. Rana, Sanford-Burnham Medical Research Institute*

Session: The Chemical Biology of Human Disease

The Role of GPI Transamidase Noncatalytic Subunits in Tumorigenesis, *Tamara L. Hendrickson, Wayne State University*

Using Synthetic GPI Glycans to Explore the Mechanism of Malaria Infection and Create an Antitoxin Vaccine, *Peter H. Seeberger, Max Planck Institute*

Adapting Proteostasis to Ameliorate Loss- and Gain-of-function Misfolding Diseases, *Jeffrey W. Kelly, The Scripps Research Institute*

2011 ANNUAL MEETING DATES TO REMEMBER:
Abstract Submission Deadline: November 8, 2010
Travel Award Application Deadline: November 10, 2010

This article describes one of the themes that is part of the ASBMB annual meeting, which will be held April 9–13, 2011, in Washington, D.C.

RNA: The Continuing Frontier

BY TINA M. HENKIN AND STUART MAXWELL

Research in RNA biology and biochemistry continues at a rapid pace. New tools, including rapid genome sequencing coupled with deep sequencing of all transcripts, have led to the identification of new RNA species and unexpected RNA populations that define novel RNA functions.

The importance of noncoding RNAs for regulating gene expression in both eukaryotic and bacterial organisms is readily apparent. Equally important has been the identification of RNA-binding proteins that establish myriad ribonucleoprotein (RNP) complexes important for RNA maturation and RNA function. We still are scratching the surface of RNA biology and biochemistry and therefore should anticipate future surprises and novel functions. It was a challenging task to decide on just four topics for presentation and discussion for the RNA theme of this meeting. With that in mind, we have selected areas that are progressing rapidly and yielding exciting new results.

Regulating Bacterial Gene Expression

The first session, titled "RNA-based Gene Regulation in Bacteria," will examine the regulation of bacterial gene expression by small noncoding RNAs and RNA motifs. Susan Gottesman (National Institutes of Health) will discuss how small RNAs and associated proteins regulate different networks in Escherichia coli. Kenneth Keiler (Pennsylvania State University) will explore how the bacterial tmRNA affects the cell cycle and developmental process in Caulobacter crescentus. And, finally, Tina M. Henkin (Ohio State University) will reveal how specific RNA motifs, termed "riboswitches," found in specific mRNAs directly bind specific ligands to regulate the cognate metabolic pathways.

Editing and Modification

The speakers in the "RNA Editing and Nucleotide Modification" session will explore how post-transcriptional nucleotide modification and editing mechanisms alter nucleotide identity to affect both RNA structure and function. Eric M. Phizicky (University of Rochester Medical Center) will discuss how modified nucleotides can serve as quality control points in yeast tRNA maturation. Kazuko Nishikura (Wistar Institute) will describe how A-to-I editing of endogenous miRNAs regulates viral infection of mammalian cells. And Stuart Maxwell (North Carolina State University) will discuss how evolving box C/D RNP core protein binding capabilities have facilitated evolving RNP function.

Henkin

Maxwell

Transport and Localization

The next session, titled "RNA/RNP Transport and Localization," will explore nuclear-cytoplasmic transport of RNAs/RNPs as well as RNA localization, both of which are critical for RNA maturation and regulation of RNA function. Arlen W. Johnson (University of Texas at Austin) will discuss how genetic and biochemical analyses have defined specific transport proteins critical for the nuclear-cytoplasmic transport of the yeast ribosome subunits. Anita T. Hopper (Ohio State University) will describe how yeast genetics coupled with biochemical and cell biology approaches are dissecting the process of tRNA transport to insure RNA quality control as well as regulate function. And Robert H. Singer (Albert Einstein College of Medicine) will report on in situ hybridization and high-resolution digital imaging approaches that allow direct visualization of RNA transport and localization of specific RNAs within individual cells.

Regulation by Small RNAs

In the final session, titled "Small RNA Regulation of Eukaryotic Gene Expression," we will explore how small RNAs regulate complex processes of cell differentiation and gene regulation in eukaryotes. Scott Hammond (University of North Carolina at Chapel Hill) will talk about his miRNA work as it relates to oncogenes and human disease. Amy Pasquinelli (University of California, San Diego) will discuss how she has coupled Caenorhabditis elegans genetics with molecular and biochemical techniques to define miRNA-targeted mRNAs that control

cellular differentiation pathways. And John L. Rinn (Beth Israel Deaconess Medical Center and Harvard Medical School) will look at large intergenic non-coding RNAs.

Finally, three additional short talks will be selected from submitted abstracts for each session to allow presentation of recent exciting results.

Tina M. Henkin (henkin.3@osu.edu) is the Robert W. and Estelle S. Bingham professor of biological sciences and chairwoman of the microbiology department at Ohio State University. Stuart Maxwell (stu_maxwell@ncsu.edu) is a professor of biochemistry at North Carolina State University.

RNA

Session: RNA-based Gene Regulation in Bacteria

Linking Regulatory Networks via sRNAs, *Susan Gottesman, National Institutes of Health*

Regulation of Caulobacter Development by Trans-translation, *Kenneth Keiler, Pennsylvania State University*

Regulation of Gene Expression by Riboswitch RNAs, *Tina M. Henkin, Ohio State University*

Session: RNA Editing and Nucleotide Modification

tRNA Quality Control Mechanisms Mediated by Modification, *Eric M. Phizicky, University of Rochester Medical Center*

A-to-I Editing of miRNAs Controls Viral Latency, *Kazuko Nishikura, Wistar Institute*

Structure and Evolution of the Box C/D RNPs, *Stuart Maxwell, North Carolina State University*

Session: RNA/RNP Transport and Localization

Nuclear Export and Maturation of Ribosomes, *Arlen W. Johnson, University of Texas at Austin*

tRNA Subcellular Dynamics, *Anita T. Hopper, Ohio State University*

Watching Single mRNAs in Living Cells, *Robert H. Singer, Albert Einstein College of Medicine*

Session: Small RNA Regulation of Eukaryotic Gene Expression

Micro RNAs in Disease and Development, *Scott Hammond, University of North Carolina at Chapel Hill*

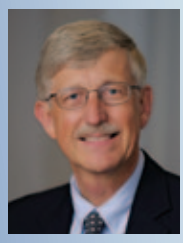
Pinning Down MicroRNA Targets in Animals, *Amy Pasquinelli, University of California, San Diego*

Large Intergenic Noncoding RNAs (lincRNAs): From Chromatin to Stem Cells and Cancer, *John L. Rinn, Beth Israel Deaconess Medical Center and Harvard Medical School*

2011

ASBMB Annual Meeting

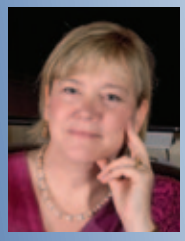
Plenary Lecture Schedule



Francis S. Collins
National Institutes of Health
"NIH and the Biomedical Research Community: Opportunities and Concerns"
APRIL 11, 6:30PM
Sponsored by the ASBMB Public Affairs Advisory Committee

Chi Van Dang
Johns Hopkins University School of Medicine
"Back to the Future: Cancer Genes and Metabolic Pathways"
APRIL 10, 2:55PM

Michael M. Gottesman
National Institutes of Health
"What Have We Learned about Multidrug Resistance in Cancer?"
APRIL 12, 9:03AM



Leona Samson
Massachusetts Institute of Technology
"The Pros and Cons of DNA Repair"
APRIL 10, 8:30AM

More program information available at www.asbmb.org/meeting2011

This article describes one of the themes that is part of the ASBMB annual meeting, which will be held April 9–13, 2011, in Washington, D.C.

Examining Obesity

BY CRAIG E. CAMERON AND C. P. DAVID TU

Obesity is a major public health concern. It is caused by high calorie intake and low levels of physical exercise. If Americans continue their current lifestyles, 43 percent of adults may be obese in 10 years. The extra weight increases the risk of diabetes, heart disease and many types of cancer. Obese individuals incur 30 percent more in health care expenses than their normal-weight peers. The cost of obesity may represent as much as 21 percent of health care spending by 2018. The Centers for Disease Control and Prevention reported that the number of Americans from the ages of 18 to 34 who are considered obese has jumped from 6 percent in 1987 to 23 percent in 2010. A whopping 35 percent of Americans ages 17 to 24 are unqualified for the military because of physical and medical issues. Thus, obesity causes not only work force productivity problems but also homeland security issues. The prevalence of obesity also has increased significantly in global populations. According to a 2005 estimate by the World Health Organization, at least 400 million adults were obese worldwide. The organization projected that this number would nearly double by 2015.[1]

Obesity is the result of an imbalance between energy intake and energy use. This excess energy is stored as fat when the glycogen storage has been saturated. Excessive fat can cause major changes in gene expression, enzyme function, regulatory schemes, hormone patterns and metabolism in different tissues and organs, which, in turn, can lead to the development of various diseases.

The diversity of human genomes (gene-gene interactions) and cultures (gene-environment interactions) contributes to racial and ethnic differences in the regulation of body weight and the subsequent development of obesity due to further energy imbalance. Because adipose tissue and adipokines play a central role in body weight control, we need to understand the signaling pathways that link excessive energy storage to the development of disease.

The American Society for Biochemistry and Molecular Biology Minority Affairs Committee has organized an obesity theme titled "Molecular Mechanisms, Treatment and Disparities of Obesity" for the 2011 annual meeting.

Cameron

Tu

System Physiology Modeling

In a session titled "Frontiers in Obesity Research," speakers will focus on system physiology modeling of human metabolism, brown adipose tissue and the biochemistry of addiction. Kevin D. Hall (National Institutes of Health) will discuss system physiology modeling of human metabolism and body weight change. Aaron M. Cypess (Joslin Diabetes Center) will talk about functionally active brown adipose tissues in adult humans and their relationship to age, body mass index and other variables. Nora D. Volkow (National Institutes of Health) will discuss the biochemistry of addiction and its conceptual link to our understanding of obesity.

Treatment, Prevention and Complications

In another session, titled "Treatment, Prevention, and Complications of Obesity," C. P. David Tu (Pennsylvania State University) will talk about a mechanism of garlic's action and show that dietary garlic supplement prevents the development of or alleviates obesity and diabetes in four mouse models. E. Dale Abel (University of Utah School of Medicine) will discuss cardiac complications of obesity in the context of mitochondrial oxidative stress and insulin signaling pathways in the heart. Jose R. Fernandez (University of Alabama at Birmingham) will talk about different approaches in obesity prevention in light of genetic influences that contribute to racial differences in obesity and diabetes.

Enzymes and Hormones

In a final session titled "Enzymes, Hormones and Obesity," James M. Ntambi (University of Wisconsin-Madison) will address the cellular and physiological roles of stearoyl-CoA desaturases in energy metabolism from the perspectives of tissue-specific and isoform-specific expressions of this gene family and in the context of preventing obesity and

insulin resistance. Naima Moustaid-Moussa (University of Tennessee) will talk about the complex interactions among the adipose rennin-angiotensin system in relation to hypertension and obesity. And Rexford S. Ahima (University of Pennsylvania School of Medicine) will address the adipokine regulation of energy and glucose homeostasis in the context of central regulation of body weight and energy balance.

Craig E. Cameron (cec9@psu.edu) is the Paul Berg professor of biochemistry and molecular biology at the Pennsylvania State University. C. P. David Tu (unh@psu.edu) is a professor of biochemistry and molecular biology at the Pennsylvania State University.

FOOTNOTE

1. Statistics in this paragraph were taken from an article by Nanci Hellmich that appeared in USA Today, titled "Rising Obesity Will Cost U.S. Health Care $344 Billion a Year."

Molecular Mechanisms, Treatment and Disparities of Obesity

Sponsored by the ASBMB MAC

Session: Frontiers in Obesity Research

System Physiology Modeling of Human Metabolism and Body Weight Change, *Kevin D. Hall, National Institutes of Health*

Brown Adipose Tissue: Quantification and Therapeutic Potential, *Aaron M. Cypess, Joslin Diabetes Center*

The Biochemistry of Addiction, *Nora D. Volkow, National Institutes of Health*

Session: Treatment, Prevention and Complications of Obesity

Dietary Garlic Prevents Development of or Alleviates Obesity and Diabetes in Mice, *C. P. David Tu, Pennsylvania State University*

Cardiac Complications of Obesity, *E. Dale Abel, University of Utah School of Medicine*

Should We Have a One-size Fits All Approach in Obesity Prevention?, *Jose R. Fernandez, University of Alabama at Birmingham*

Session: Enzymes, Hormones and Obesity

Role of Stearoyl-CoA Desaturase in Energy Metabolism, *James M. Ntambi, University of Wisconsin*

The Adipose Renin-angiotensin System, Obesity and Insulin Resistance: Dissecting the Complex Interactions, *Naima Moustaid-Moussa, University of Tennessee*

Adipokin Regulation of Energy and Glucose Homeostasis, *Rexford S. Ahima, University of Pennsylvania School of Medicine*

2011 ASBMB Annual Meeting

JOIN US AT THE ANNUAL MEETING TO EXPLORE

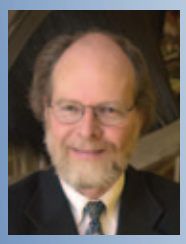
"Scientific Credibility and the Politicization of Science"

Sponsored by the ASBMB Public Affairs Advisory Committee

Scientists often have been viewed as objective purveyors of truth, but, as scientific issues dominate political discourse, both sides of prominent political debates claim to have "science" on their side. Whether the issue is global climate change, stem-cell research, energy policy or evolution education, politics is charged with "scientific" information.

Questions that speakers will address include: How does the use of science for political purposes affect the credibility of science? How does the political climate for science affect the public's trust in science and its findings? How can scientists communicate more effectively, promote accurate scientific information and reclaim their credibility?

Elizabeth H. Blackburn
2009 Nobel laureate in Physiology or Medicine
University of California San Francisco



James J. McCarthy
Alexander Agassiz professor of biological oceanography, Harvard University, Chairman of the Board: Union of Concerned Scientists and Co-chairman of the 2007 Nobel Peace Prize-awarded Intergovernmental Panel on Climate Change

Michael Specter
The New Yorker and author of "Denialism: How Irrational Thinking Hinders Scientific Progress, Harms the Planet, and Threatens Our Lives"

More information available at www.asbmb.org/meeting2011

UAN

ASBMB Undergraduate Affiliate Network

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- $20 for each additional student
- *New chapter faculty receives one year of ASBMB membership free*

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- Free online and print subscription to *A-Today*
- Membership to ASBMB

UAN BONUS BENEFITS

- Travel Awards to ASBMB Annual Meeting in Washington, D.C., April 9-13, 2011
- Undergraduate research awards and K12 outreach awards
- Funding support for undergraduate research symposia
- Membership to Chi Omega Lambda the National Honor Society of ASBMB
- Receive special consideration for competitive undergraduate travel awards and faculty travel awards to Annual Meeting

WWW.ASBMB.ORG/UAN

Renew/Apply!

A report from the Education and Professional Development Committee.

ASBMB Kicks off Regional Meeting Series

Student-organized career symposium hopes to be first of many society-sponsored events

BY NICK ZAGORSKI

As American Society for Biochemistry and Molecular Biology President Suzanne Pfeffer noted in her inaugural column in the July issue of ASBMB Today, one of her top goals for the society was to do more to address the needs of ASBMB's youngest members (and potential members), namely graduate students and postdoctoral researchers. And, just recently, ASBMB showcased one of its major efforts in this initiative by hosting a graduate-student research and career symposium in Chicago, Ill., this past August.

This special one-day event, held at Northwestern University Medical School, was the first of what will hopefully be many regional meetings dedicated to students and postdocs. Although these meetings will feature research talks and poster presentations, their primary goal is to help young scientists advance in their careers by providing panels that address topics such as career options, applying for grants and balancing work and family.

Pfeffer got the ball rolling for this special symposium with help from Benjamin Glick, her former lab mate at Stanford University and current professor at the University of Chicago. However, she notes the event would not have been possible without the three student organizers who volunteered their time to put it together: Darja Pollpeter of Northwestern University, David Courson of the University of Chicago and David Taussig of the University of Illinois at Chicago.

Student meeting organizers Darja Pollpeter, David Courson and David Taussig.

"They deserve tremendous recognition for all their hard work," she says, "especially considering this meeting was a true pilot project by ASBMB."

"I definitely didn't know what to expect going in, but it was a fun time putting the meeting together, and it gave me valuable experience for the future," notes Pollpeter, a fifth-year graduate student who also is president of her program's student organization.

Courson and Taussig agree with the assessment and also note that the whole process, which involved setting up the meeting location and

continued on page 31

Ac-cent-tchu-ate the Positive[1]

Introducing Students to Research

BY PETER J. KENNELLY

You've Got to Accentuate the Positive[1]

Investigators who welcome students into their laboratories to experience "real-life" research for the first time perform an extremely valuable service that requires a major commitment of time and effort. Unfortunately, after years of training to become self-reliant molecular explorers toughened by the realities of pressurized competition for grants, jobs, tenure, publications and recognition, research mentors sometimes forget that they, too, were novices, enthusiastic but devoid of research skills and experience.

With time and distance, it becomes increasingly difficult to remember just how lost we felt upon venturing into the unfamiliar world of our first "real" research laboratory; how intimidating we found that groaning, squealing, steam-belching monster called the autoclave; how sheepish we felt when we asked what "subculture" meant and how we broke into a cold sweat the first time we were permitted to fly solo on some expensive piece of equipment. We tend to forget just how little we initially understood about the rewards and frustrations of working at the bench and how thin was the foundation of confidence and self-assurance that buttressed our youthful eagerness.

When welcoming students into a research laboratory for the first time, it is important that care is taken to demonstrate to students early on that, yes, they can do this, and steps are taken to build a foundation of self-confidence that will help them cope with the inevitable vicissitudes of authentic research.

Eliminate the Negative[1]

Upon entering the laboratory, the new student leaves behind an orderly world of regular and predictable schedules and neat and tidy metrics. Gone are the homework, quizzes, exams, points, curves and grades used not only to assess progress but, for many students, to define success itself. No matter how assiduously a mentor may try to explain the nature of authentic research, students may feel insecure and uncertain upon entering an environment devoid of the familiar landmarks previously relied upon to direct their efforts and identify their destinations. Gone, too, is the assuring, black-and-white reality wherein every answer can be determined unambiguously to be either correct or incorrect. And, how is this determination made? By referring to some higher authority, such as a textbook or an expert, extrinsic to the students themselves.

Students, even at the graduate level, inculcated in the "undergraduate mindset" enter the research lab programmed to believe that any experiment designed by an expert such as their research mentor should "work." By this, I mean that it will operate as intended on the first try and yield results consistent with the hypothesis that inspired it: the nearest equivalent to an extrinsically derived "right" answer. Students trapped in this mindset interpret any outcome that deviates from what is anticipated as a failure on their part, for to accept otherwise is to reject the concept of an ultimate higher authority, with all the comfort and security it provides.

Latch onto the Affirmative[1]

When investigators immediately plunge new, unprepared undergraduate or graduate students into a novel, authentic research project, they oftentimes place the students' enthusiasm for science and research at risk. The seeds of discouragement frequently lie in elements so simple that they fly under the trouble-shooting radar.

Sometimes, students end up metaphorically banging their heads against the wall because a laboratory's tried-and-true expression vector proves unsuitable to generate some new recombinant protein. Because the vector "should" work, students may be set off on a frustrating set of trials in which they vary growth conditions, inducer concentration and induction times to no avail.

Similarly, a research group long-accustomed to working with His-tagged proteins may be slow to suspect that the fusion domain is responsible for the lack of catalytic activity in the new trainee's recombinant enzyme preparation. The mentor is faced with two unknowns, an unproven research student and a novel target. Under these circumstances, it is possible that a trainee may be performing flawlessly, yet never realizes it.

Don't Mess with Mister In-between[1]

Students, as well as research projects, are wonderfully diverse. Hence, there is no single universal prescription for how to conduct a student's initiation into the world of authentic research. However, I would argue that, when in

doubt, it is advisable to start new trainees out on something that is not just likely to work, but whose feasibility has been demonstrated by a preliminary experiment or two in your own laboratory. This may take the form of some small introductory project or training activity, or a long-term product for which the first couple of operations have undergone some preliminary testing to establish their feasibility.

The benefits of rigging the game to produce early success are several-fold. It provides students with some positive feedback, particularly the affirmation that they are capable of performing laboratory research. Second, it affords the mentor an opportunity to evaluate a new student's abilities free from the potentially confounding factor of an untested system. The concomitant sowing of the seeds of mutual trust will serve both student and mentor well, as the project progresses and challenges are encountered.

Many of you reading this column, as well as its author, first imagined that we might have what it takes to become a research scientist as a consequence of an undergraduate research or summer internship experience. Opening the eyes of students to their full potential is one of the most rewarding things we can do to fulfill our role of advisers and educators and honor those key people who made such a critical contribution to our own lives.

Peter J. Kennelly (pjkennel@vt.edu) is a professor and head of the department of biochemistry at Virginia Polytechnic Institute and State University. He also is chairman of the ASBMB Education and Professional Development Committee.

FOOTNOTE

1. Excerpted from the lyrics of the song "Ac-cent-tchu-ate the Positive (Mister In-between)" by Johnny Mercer and Harold Arlen.

ASBMB Kicks off Regional Meeting Series *continued from page 29*

schedule (the Northwestern medical campus offered a centralized location and good transit options) as well as handling the all-important task of inviting the speakers, was not extremely time-consuming and encourage students at other schools to help organize similar events if opportunities arise.

And, the hard work paid off. Despite the uncertainties that come with any new endeavor (for example, how and how much to advertise) and the fact that the event was scheduled for a summer Saturday, more than 100 people attended, most of whom were graduate students or postdocs at universities across the greater Chicago metropolitan area.

The symposium included a pair of career panels in the morning, featuring seven professionals in various disciplines of biological sciences, such as educators, science writers, patent lawyers and administrators. These panels were followed by a catered lunch, which gave attendees the opportunity to mingle with career panel presenters and collect additional information. The afternoon was dedicated to research, and featured six short scientific talks by students, as well as more than 20 poster presentations, while the event finally closed with a special topics panel that discussed issues based on responses to a survey given by attendees prior to the meeting.

"Overall the symposium was definitely well-received, particularly the career panels, which I think were the most successful part of the day," Pollpeter says.

"If we could change anything it might be to space the career panels out over the whole day, since we did notice a lower turnout for the afternoon science sessions." adds Taussig. "But that's a good learning experience."

As expected, the symposium also provided great networking opportunities. "I saw a lot of business cards being handed out," says Courson, who managed to pick up a few contacts himself and got some useful information to boot.

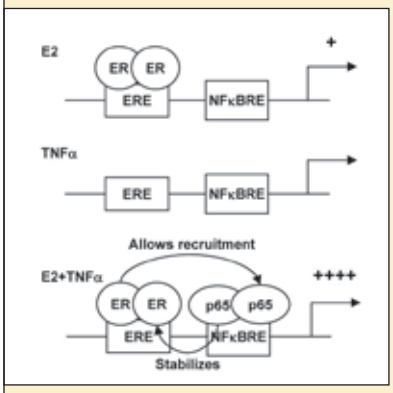
"Even though my wife and I are both planning to do postdocs, she is potentially interested in science writing," Courson says. "She couldn't attend, so I took in some sessions on her behalf and learned a lot about how to pursue a career writing about science."

Pfeffer, who assisted the student organizers through regular conference calls and also attended the event, was quite pleased with the symposium overall and hopes that it can show what students can accomplish given the opportunity. And, she also is confident that this symposium in the Windy City will be just the first of many regional career meetings devoted to some of our youngest and brightest scientists.

Nick Zagorski (nzagorski@asbmb.org) is a science writer at ASBMB.

Inflammatory Cooperation

Estrogen receptor (ER) and NFκB are key transcription factors that regulate breast cancer cell proliferation and survival. While most studies have focused on how these factors influence each others' transcriptional activity, this article describes a novel mechanism by which ER and NFκB work together to regulate expression of the multidrug transporter ABCG2, which is known to be involved in breast cancer drug resistance. The authors found that under proinflammatory conditions, these two transcription factors are cooperatively recruited to the promoter region of the ABCG2 gene at adjacent sites.



Proposed model for potentiation of E2-regulated ABCG2 expression during inflammation.

ER allows the NFκB family member p65 to access a latent NFκB response element located near the estrogen response element (ERE) in the gene promoter; in turn, this p65 recruitment is required to stabilize ER occupancy at the functional ERE. Once present together on the ABCG2 promoter, ER and p65 act synergistically to potentiate mRNA and subsequent protein expression. This study has important implications for patients with ER-positive breast tumors, as it reveals a mechanism whereby inflammation enhances the expression of an ER target gene, which, in turn, can exacerbate breast tumor progression by promoting drug resistance.

Proinflammatory Cytokines Enhance Estrogen-dependent Expression of the Multidrug Transporter Gene ABCG2 through Estrogen Receptor and NFκB Cooperativity at Adjacent Response Elements

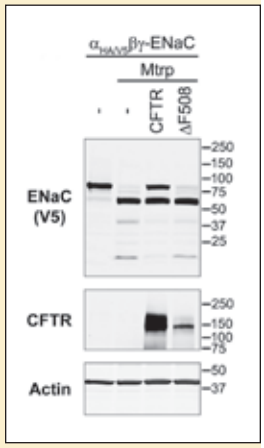
Madhumita Pradhan, Leslie A. Bembinster, Sarah C. Baumgarten and Jonna Frasor

J. Biol. Chem., published online Aug. 12, 2010

jbc

Proteolysis Protection of CFTR

Mutations in the cystic fibrosis transmembrane conductance regulator that prevent its proper folding and trafficking to the cell membrane are the cause of cystic fibrosis, which is characterized by poorly hydrated airway surfaces and difficulty breathing due to defective chloride secretion. In addition to defective Cl^- export, CF airway cells also undergo excessive Na^+ absorption, which exacerbates these conditions. However, the molecular link between missing CFTR and increased Na^+ absorption has remained elusive; evidence implicates hyperactivity of the epithelial Na^+ channel, though some suggest that such findings merely are electrophysiological or expression-related artifacts. In this study, the authors confirm that ENaC and CFTR physically interact and also show that wild-type CFTR protects ENaC from proteolytic cleavage and stimulation of open probability; in contrast, the common CF mutant ΔF508 failed to protect ENaC from proteolytic cleavage and stimulation. The authors followed up these observations in Xenopus oocytes with studies in human-airway epithelia, finding that ENaC associates with the anti-CFTR immune precipitate in healthy cells, whereas in CF cultures, the proportion of full-length ENaC protein was reduced consistently. This study provides solid evidence for a potential mechanism for CFTR-dependent down-regulation of Na^+ absorption, which may help resolve the outstanding debate.



Wild-type, but not ΔF508 CFTR, inhibits the proteolysis of ENaC by matriptase.

The Cystic Fibrosis Transmembrane Conductance Regulator Impedes Proteolytic Stimulation of the Epithelial Na+ Channel

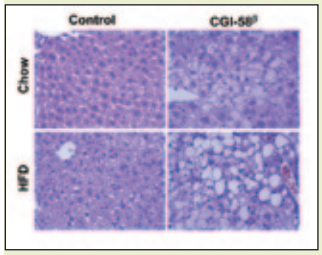
Martina Gentzsch, Hong Dang, Yan Dang, Agustin Garcia-Caballero, Hamsa Suchindran, Richard C. Boucher and M. Jackson Stutts

J. Biol. Chem., published online Aug. 13, 2010

jbc

Better Livers through CGI

Mutations in CGI-58 (comparative gene identification-58, also known as Abhd5) lead to Chanarin-Dorfman syndrome, characterized by abnormal accumulation of triglycerides, nonalcoholic fatty liver disease and dry, scaly skin. It's still unclear how CGI-58 functions to prevent CDS, and CGI-58 knockout mice are neonatal lethal, which hinders integrated lipid and energy metabolism studies. In this article, the researchers circumvented this limitation by using antisense oligonucleotides to inhibit CGI-58 expression in adult mice by up to 95 percent. In chow-fed mice, ASO-mediated depletion of CGI-58 did not affect weight gain, plasma TG or plasma glucose, though it did raise hepatic TG levels ~4-fold. In contrast, in high fat diet-fed mice, CGI-58 depletion protected against diet-induced obesity, even as the hepatic levels of TG, phosphatidylglycerol, diacylglycerols and ceramides all were elevated; these hepatic lipid alterations were associated with significant decreases in hepatic TG-associated enzyme activity and secretion, and reduced plasma concentrations of ketones, nonesterified fatty acids and insulin. In addition, HFD-fed and ASO-treated mice were more glucose-tolerant and insulin-sensitive. Collectively, this study demonstrates a critical role for CGI-58 in maintaining hepatic TG and glycerophospholipid homeostasis and has unmasked an unexpected link between CGI-58 and HFD-induced obesity and insulin resistance.



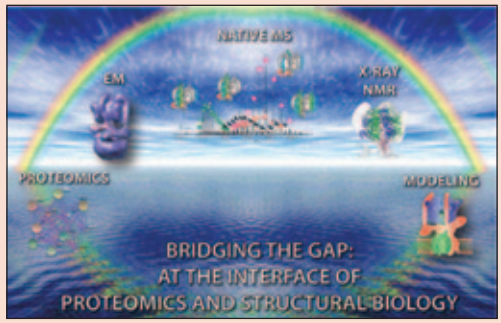
CGI-58 inhibition results in hepatic steatosis in both chow-fed and high fat diet-fed mice.

CGI-58 Knockdown in Mice Causes Hepatic Steatosis, but Prevents Diet-induced Obesity and Glucose Intolerance

J. Mark Brown, Jenna L. Betters, Caleb Lord, Yinyan Ma, Xianlin Han, Kui Yang, Heather M. Alger, John Melchior, Janet Sawyer, Ramesh Shah, Martha D. Wilson, Xiuli Liu, Mark J. Graham, Richard Lee, Rosanne Crooke, Gerald I. Shulman, Bingzhong Xue, Hang Shi and Liqing Yu

J. Lipid Res., published online Aug. 27, 2010

MCP Explores Proteomics and Protein Interactions



This August, Molecular and Cellular Proteomics featured a special issue highlighting the recent progress made at the interface of two exciting research areas: interaction proteomics and structural biology. The general view has emerged that most biological processes involve regulated cooperation between multiple protein partners, and such molecular interactions can be studied from the top-down or bottom-up; large-scale proteomic studies have provided an important catalog of potential protein interaction networks, while in-depth structural and functional characterization of individual proteins and complexes reveals the mechanistic details of the interactions. The special issue features both original research articles and reviews that discuss several emerging technologies, such as combining electron and/or atomic force microscopy with mass spectrometry, which may help bridge the gap between these two approaches and thus paint a more complete picture of the molecular organization of a cell. The papers feature collaborative efforts between scientists of diverse backgrounds using computational, conventional structural biological, and mass spectrometry-based approaches to uncover unique details on the constituency, conformation and assembly dynamics of several large protein assemblies, including the proteasome, ribosome, spliceosome, nuclear pore complex and even whole viruses.

Bridging the Gap: At the Interface of Proteomics and Structural Biology

Mol. Cell. Proteomics, August 2010

Going Beyond Your Limits
A Career in Biomarker Discovery

BY SHERI WILCOX

I was only 2 years old, but I remember it very well. My older sister Laurie and I were playing in our basement with some friends when Laurie inexplicably passed out. The next two years were filled with trips to hospitals in Atlanta, and, eventually to St. Jude Research Hospital as my sister fought her battle with Wilms tumor, a solid tumor of the kidney that is the fourth most common type of cancer in children. She was six and I was four when she died. That was the spark that started my passion for making a difference in the fight against cancer. Since then, I've lost many relatives, including both of my parents, to cancer. Today, the cure rate for Wilms tumor is 85 to 90 percent, and there are effective treatments available for other cancers as well. The problem is that you can't treat cancer as successfully if you don't find it in its earliest stages. That's why early diagnosis of cancer and other diseases is now my passion.

My career path to this point has been in part by design and part fortuitous. I always have been fascinated by science. I loved going to the Fernbank Science Center in Atlanta with my mother when I was a little girl. Once I got to college, I might as well have declared chemistry as my major even before I took my first class. I started doing research in analytical chemistry during my sophomore year and then moved into a biophysical chemistry lab as a junior.

An Interdisciplinary Education

During my senior year, I learned about a multidisciplinary graduate program at The Scripps Research Institute called "Macromolecular and Cellular Structure and Chemistry." (Now, it's simply called "Chemical and Biological Sciences.") The intent was, and still is, to train scientists across chemistry and biology fields to contribute productively in a very collaborative environment. The emphasis was on having a broad foundation so you could really evaluate the quality of scientific research even if it wasn't in your own field.

I decided that was the direction in which I needed to be going, even through I had not taken any biology classes in college. I'm still not sure how, but I was accepted into the program at Scripps, and I began my graduate career. The program's seminar-style classes exposed me to many aspects of structural and molecular biology. I joined David Goodin's lab for my thesis research. We focused on cytochrome *c* peroxidase, probing structure/function relationships with site-directed mutagenesis, enzymatic activity measurements, EPR spectroscopy and X-ray crystallography. The breadth of what I learned both in class and in the lab at Scripps built my confidence and showed me that I am never limited to what I've already learned. The belief that I always can learn new fields and take on roles in new areas has propelled me to where I am today.

Controlling My Destiny

As I finished up my doctoral research, I decided to make my first heretical move and do a postdoctoral fellowship in industry. I accepted a position in proteomics at what was then Pharmacia and Upjohn in Kalamazoo, Mich. After two years, it was time to get a real job. I started interviewing with contacts I'd made at confer-

Sheri Wilcox received her bachelor's degree in chemistry from Vanderbilt University in 1993 and her doctorate in macromolecular and cellular structure and chemistry from The Scripps Research Institute in 1999. She conducted her postdoctoral research in the protein science unit at Pharmacia and Upjohn in Kalamazoo, Mich. Wilcox joined SomaLogic as a scientist in 2001. She is now an associate director at SomaLogic. Her group is responsible for performing the selections and qualifying the aptamers for SomaLogic's biomarker discovery array.

ences and searching for jobs through traditional means.

Then, my husband and I had a revolutionary thought — we wanted to be in control of our destiny and decide where to live rather than just letting the advertised job openings dictate our path. We chose Colorado. It's not exactly a booming biotechnology community like the San Francisco Bay Area or Boston, but it's not too shabby either.

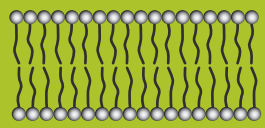
Now, it was time for heretical act number two. I started cold-calling every biotech company in Colorado. I discovered that most people are quite willing to talk about what they are trying to do at their company, especially when they are passionate about it. After I described my research experience at Pharmacia, several people suggested I contact Larry Gold and talk to him about his newest company, SomaLogic. Larry was gracious and accepted my call. We decided I would host him to talk about the SomaLogic technology at Pharmacia, and he would arrange for me to interview at SomaLogic. The agreement worked well, and, within a few months, we moved to Colorado. I started out at SomaLogic knowing shamefully little about aptamers. Now, nearly 10 years later, I direct the company's aptamer discovery group.

A Perfect Fit

I really could not have asked for a more perfect fit for what I wanted to do with my life. SomaLogic's mission is to find protein signatures associated with disease. These protein signatures can be a hallmark of disease before symptoms are even evident. Signatures also can be used to identify patients who will or won't respond to a particular therapy. The proteins are measured using a novel class of aptamers called SOMAmers (slow off-rate modified aptamers). We now have developed SOMAmers that recognize 1,000 human proteins, and we use them to measure protein levels out of a single 15-µL biological sample in a high-throughput manner. We can measure many hundreds of proteins in many hundreds of samples to do biomarker discovery for diagnostics and assist throughout the drug development process.

In the future, I hope no one has to watch his or her parents go to the doctor with vague symptoms for months without getting an accurate diagnosis. Instead, patients should be able to take a simple blood test that helps doctors know when follow-up testing is warranted long before there are rampant metastases.

I'm really glad I didn't let "requirements" keep me from applying to positions that drew my interest. I love what my company is doing, and I think our approach is the best way to make it really work. I never would have had the opportunity to be a part of what I believe will be a major tool for personalized medicine in the future if I had limited myself to what made "sense." If you're smart, have good critical judgment and feel strongly about where you want to make a difference, nothing should stop you.



Phosphatidic Acid: From Biophysics to Physiology!

BY EDGAR E. KOOIJMAN

Apart from phosphoinositides, phosphatidic acid (PtdOH) is arguably one of the most important glycerophospholipids found in biomembranes. It is the glycero-phospholipid precursor (1) and has been implicated in processes from membrane dynamics to signaling (2, 3). However, little was known regarding the specific regulation of proteins by PtdPOH, despite its extremely simple chemical structure.

Several years ago, while working on elucidating the role of PtdOH in membrane dynamics, we initiated a biophysical study into the charge carried by the phosphomonoester headgroup of PtdOH (4). At the time, we were interested merely in the degree of ionization, as this likely was to affect the molecular shape of PtdOH. However, we found that lyso-PtdOH carried more charge than PtdOH at constant pH in a phosphatidylcholine matrix, despite identical phosphomonoester headgroups. Furthermore, phosphatidylethanolamine increased the overall charge of both PtdOH and LPtdOH. A breakthrough in our understanding came from experiments with a LPtdOH compound lacking the free hydroxyl group in the backbone of LPtdOH. This so-called dehydroxy-LPtdOH behaved identically to PtdOH, implicating the hydroxyl in the difference in ionization behavior. This also indicated that the effect of PtdEth likely was due to its primary amine compared with the quaternary amine of phosphatidylcholine. Further studies with model membrane-spanning α-helical peptides eventually led us to introduce the electrostatic/hydrogen bond switch to describe the ionization and protein interaction mechanism of PtdOH (5).

The model describes the effect of hydrogen bonds on the degree of ionization of PtdOH. Upon losing its "first" proton, the remaining proton becomes more tightly bound, not only by covalent interactions, but also by the electrostatic charge of the phosphate. Interestingly, hydrogen bonds formed with the phosphate of PtdOH destabilize (most likely through a competition for electrons) the "second" proton, facilitating its removal. The further deprotonation leads not only to an increased negative charge but also creates an additional H-bond acceptor. We thus proposed that proteins recognize and interact with PtdOH based on the novel mechanism. This electrostatic/hydrogen bond switch model not only describes the ionization properties of PtdOH, but of every phosphomonoester moiety. Recent work on other lipids, such as cer-1-p and polyphosphoinositides, confirmed the model.

The implications of the model are numerous. It predicts a role for PtdOH at basic sites (at the headgroup/acyl-chain interface) of transmembrane proteins (6) and predicts pH-dependent binding of peripheral membrane proteins. Indeed, the latter property recently was confirmed by Chris Loewen and co-workers (7). They showed that Opi1 in yeast binds PtdOH at the endoplasmic reticulum in a pH-dependent manner in vivo, as predicted by the electrostatic/hydrogen bond switch. More importantly, they showed that the binding of PtdOH by Opi1 is regulated by the metabolic state of yeast and that PtdOH thus ties metabolism to membrane biogenesis. The pH-dependent interaction of Opi1, and potentially other proteins, likely is a subtle function of the number and position (structure) of basic residues in the binding domain, as well as local lipid composition in the membrane. The exciting work by Loewen and co-workers raises intriguing questions as to which other proteins are regulated in this fashion and how other lipids, such as cer-1-p and the PIPs, might exploit this property of their phosphomonoester headgroup.

Edgar E. Kooijman (ekooijma@kent.edu) is an assistant professor in the biological sciences department at Kent State University.

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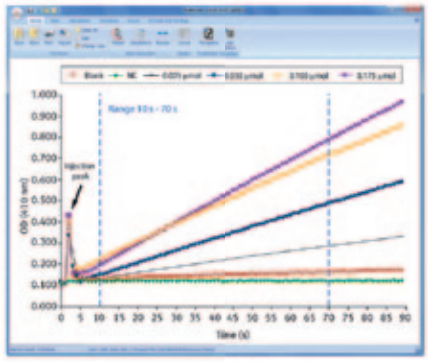

Overlay plot of esterase catalysed pNPA reactions at different concentrations.

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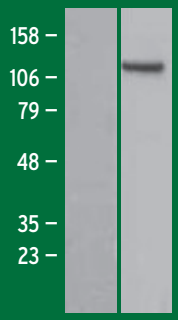

HEK293 were transfected with L) empty vector R) TrueORF for Myc/DDK-tagged hTERT(Cat# RC217436). The lysates were analyzed using anti-DDK antibody to show over-expression of hTERT. *DDK is the same as FLAG.

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