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contents

APRIL 2008

ON THE COVER:
Uncovering the multi-faceted role of the atypical neurotransmitter nitric oxide is just one way that Solomon Snyder has made people re-think the way they think. 26

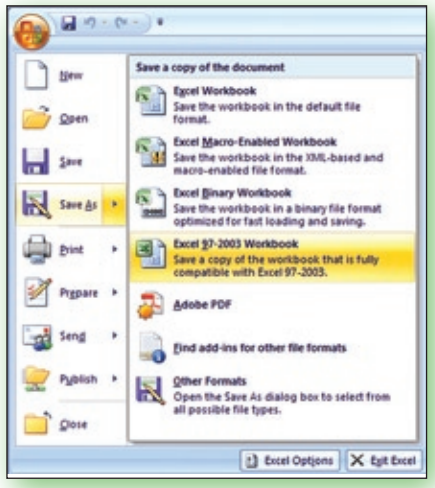
society news

special interest

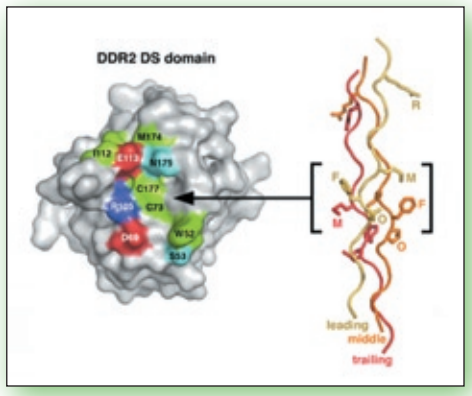
science focus

departments

resources



A look at Excel 2007. 16



Collagen's "Disco" Domain. 24

podcast summary

Download the March ASBMB AudioPhiles *JBC* News Podcast and hear about Kensal van Holde, Distinguished Emeritus Professor at Oregon State University, and how he and his colleagues came to discover and characterize the nucleosome as the basic unit of chromatin structure.

This and other podcasts are available at: www.asbmb.org/media

ASBMB today

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from the **editor**

Two Important Changes and a Reminder for Authors of ASBMB Publications

The following editorial is from ASBMB Director of Publications Nancy Rodnan. The editorial also appears on the ASBMB Web site (www.asbmb.org) and on our individual journal web sites (www.jbc.org, www.jlr.org, www.mcponline.org).

1. The NIH Mandate for Article Deposits in PubMed Central

As of April 7, 2008, the final redacted versions of all research articles resulting from partial or complete support from NIH must be deposited immediately in the NIH repository, PubMed Central. PubMed Central will not release articles to readers for 12 months. Whereas compliance to this NIH mandate is the responsibility of the authors, ASBMB will automatically deposit articles accepted to the *Journal of Biological Chemistry*, the *Journal of Lipid Research*, and *Molecular and Cellular Proteomics* on behalf of authors as a service.

During submission of a manuscript for review, authors will be required to indicate whether or not the work resulted from NIH funding. If NIH funding is involved, and the paper is ultimately accepted for publication, the final, redacted version will automatically and immediately be sent to the NIH on behalf of the authors. This will completely satisfy the NIH mandate and authors need do nothing else.

This service will be free for ASBMB members and will cost $50 for non-members. The $50 fee covers the cost to the publisher to tag and upload high resolution figures and supply supplemental data from our vendors to PubMed Central.

2. Author's Choice Publication Option

ASBMB is initiating a new submission option for authors that have requested to pay an additional fee to have the final redacted version of an article released immediately to readers without any subscription barriers. For a few authors this is a condition of funding.

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The Author Choice option will cost ASBMB members $1,500 above the usual publication charges. Non-members will be charged $2,000. This fee is a portion of the cost to publish an edited article. This option too is selected at submission.

ASBMB continues to be at the forefront of developments that enhance our mission of service to authors, readers and the scientific community.

Reminder:

Authors are reminded that all manuscripts accepted by ASBMB publications appear as Papers in Press (PIPs) immediately upon acceptance and that these remain freely accessible on the journal website at all times following the initial posting. Neither transfer to PubMed Central or opting for immediate release (Author's Choice) affects PIPs.

letters to the editor

NIH Grant Review

***To the Editor*:**

Having read the discussion of NIH grant review procedures in recent issues of ASBMB, both in the letters and editorials, I'd like to add my two cents. (Full disclosure: this is slightly more than the value of my current NIH funding.) I'll touch on three areas with suggestions that I haven't seen in previous writings on this issue.

New investigator funding

There is general agreement on the value of making strong efforts to fund new investigators. I would recommend that grants from new investigators continue to be assessed by study sections together with those from established investigators, but be funded at a different percentile. This would allow the new PIs to see where they stand relative to their future competitors, but to catch a break on funding.

Productivity

Typically productivity, gauged by number and quality of publications, is assessed and remarked on by study sections as part of their overall evaluation. However, criteria for productivity are vague in the sense that it appears not to matter how much funding was available to support these publications. The result is that study sections (based on my own experience serving on study sections and reports from colleagues) are often wowed by an investigator who publishes, for example, six papers per year over the last 5 years and are much less impressed by one who has 1-2 papers per year—even if the former is supported by 3-4 grants and the latter by only 1 grant. This problem is exacerbated by PIs who do not explicitly cite which grants support individual publications, or who habitually cite multiple grants, and by reviewers who do not check this.

Someone remarked after the success of the movie "Titanic" that if his grandmother were given $200 million, she could make a great movie, too. Although it is probably fair to say that most of our grandmothers could not publish many papers even with 3-4 grants, there is no doubt that more money should equate to greater productivity (in quantity, quality, or both). Furthermore, the efficiency with which a PI has used the funds they have would seem a fair indicator of the likelihood of their future productivity. I would therefore propose that study sections, when considering productivity, explicitly include consideration of the PI's previous level of support (the number and size of grants).

Innovation

One woman's (or man's) innovation is another's same old same old. I strongly suspect that this category, on which comment is required in reviews of NIH grant applications, shows the widest disparity in individual reviewer assessments among categories commented on by a wide margin. The requirement to address innovation also often forces PIs into narrative contortions in their applications, searching for innovation when good science ought to be the driving force. I would propose that this category be abandoned, as it can be subsumed in the overall assessment, and if truly innovative approaches are proposed, this will not be missed by reviewers.

Along the same lines, grants that do indeed propose high risk/high payoff research ought to be reviewed by more than the standard two reviewers and one reader. I would suggest inviting applicants to self-identify grant applications that are truly innovative (transformative, perhaps, in the current labeling scheme) and obtaining 5 to 6 reviews on these applications. Reviews would be required from the additional reviewers only if they agreed that the proposal was indeed remarkably innovative. This would help to level out the disparity in opinion often encountered in this type of assessment and would likely apply to less than 5% of submissions. This approach might help in allowing informed voices to support projects like Mario Cappechi's famously discouraged proposal to develop targeted integration into mammalian cells; the present system asks only two principal reviewers to make this assessment, greatly increasing the odds that such proposals will be rejected out of hand.

Randall H. Morse
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Tell Us What You Think We appreciate receiving letters that are suitable for publication regarding issues of importance or comment on articles appearing in *ASBMB Today*. Letters should be sent to the editor at the address found in the masthead. Letters must be signed and must contain the writer's addresss and telephone number. *The editor reserves the right to edit all letters for clarity and length. Opinions expressed in letters do not necessarily reflect ASBMB policy.*

Centers Versus Individuals—Funding Choices at NIH

BY HEIDI HAMM

In this space I frequently write about the move at NIH in recent years away from small, investigator-initiated science toward what I would call "big science," or science focused around programs and centers rather than individuals.

This trend has shown itself most apparently in recent years with the gradual decline in the number of investigator-initiated grants and the increase in the number of research grants awarded in response to Program Announcements. This in turn demonstrates that NIH is beginning to support more staff-driven research ideas rather than those generated by individual investigators as it has done so successfully in the past.

Other manifestations of the trend away from investigator-initiated research include the development and funding of the Clinical and Translational Science Awards (CTSA). These mega-grants have effectively soaked up most of the money that the National Center for Research Resources (NCRR) has had in recent years to support smaller unsolicited investigator-initiated grants. Although NCRR is currently taking steps to slow the growth of CTSAs to salvage at least some of its other small grant programs, the long term trend is very clear—more and more of NCRR's funds will go toward these large grants.

Another piece of the puzzle fell into place in early March when ASBMB staff took a look at NIH numbers for funding of centers *versus* research project grants (RPG). Unfortunately, the data indicate a similar pattern.

Center grants, according to NIH, are awarded on behalf of program directors and groups of collaborating investigators. They support long term, multidisciplinary programs of research and development, mostly located at academic institutions. NIH data indicate that growth in centers funding has increased 20% since the doubling of the NIH budget was completed in 2003. Over the same time period (2003-2008), funding for NIH research project grants increased only 13%. Table 1 shows the change.

These data indicate that funding for research centers is growing at twice the rate of NIH as a whole, and although RPG funding is also increasing faster than the overall agency budget, centers remain the component with the most growth since the doubling ended.

The situation is even worse when inflation is taken into account. Inflation at NIH is calculated annually according to the Biomedical Research and Development Price Index (BRDPI, commonly referred to as "bird pie"). BRDPI is usually a point or two above the general inflation rate, and in recent years has been in the range of about 3.5% annually, or about 21% overall in the period 2003-2008.

Thus, because of inflation, NIH as a whole has lost about 12% of the purchasing power it enjoyed in 2003, even though its budget in the same period has gone up

TABLE 1

Growth in Funding for Research Centers and RPGs, 2003-2008 (Dollars in Billions)

YEAR	CENTER FUNDING	RPG FUNDING	NIH TOTAL
2003	2.46	13.70	27.06
2004	2.55	14.50	27.88
2005	2.70	14.89	28.49
2006	2.77	14.75	28.46
2007	2.93	15.62	29.13
2008	2.94	15.54	29.46
2009 (request)	2.96	15.52	29.46
TOTAL Increase:	+$0.5B/20%	+$1.8B/13%	+$2.4B/9%

Source: NIH, AAAS, FASEB.

over $2 billion. Furthermore, despite the evidence that NIH has been trying to insulate RPG funding at least partially from the effects of inflation, it is center funding and not RPG funding that has kept up with inflation since 2003. NIH's priorities are thus clear—it has chosen in a period of declining funding (when BRDPI is taken into account) to shift more of its resources to funding centers and away from RPGs.

Of course, RPG funding still takes the lion's share of NIH's dollars each year—usually 51-52% of the total budget. But, the amount of RPG funding that is investigator-initiated continues to decrease as well. R01 grants were 80-83% of RPG in '96-98; in 2007, they are 60%. Unsolicited R01s were 64-67% of RPG in '96-'98; in 2007, they are 50%.

And it was only in 2007 that center funding accounted for as much as 10% of the NIH budget. It is also important to point out that the foregoing discussion should not be taken to imply that center funding is wasted or supports "bad" science; in fact, these funds are directed by Institutes toward promising disease and therapeutic areas that Congress is eager to fund.

Nevertheless, NIH has built its world-class reputation for innovative research through the very mechanism—the investigator-initiated research project grant--that has been eroding in importance in NIH's portfolio. The issue of how NIH manages its money has not been debated widely within the community; rather, NIH seems to be going ahead with its plans to fund science through centers and other "big science" mechanisms like the CTSA program—at the expense of individual investigators—with little if any pressure not to do so.

I continue to believe that this serious change in how NIH conducts its business needs to be discussed much more thoroughly in the community before NIH proceeds too much further down this road. Are any of you as concerned about this as I am? I would like to hear from you on these issues—but more importantly, NIH needs to hear from you as well.

HOWARD HUGHES MEDICAL INSTITUTE

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HOWARD HUGHES MEDICAL INSTITUTE

NIH Holds Best Practices Workshop

BY ANGELA HVITVED

What are the best programs and policies for sustaining women in biomedical research careers? How can institutions implement effective strategies for recruiting and retaining women at all points of their careers? These questions were the focus of a recently convened conference at the NIH, "Women in Biomedical Research: Best Practices for Sustaining Career Success." Speakers from academia, industry, and government shared their ideas and experiences in a day-long session of panels and seminars with the purpose of summarizing actions needed to sustain the careers of women in academic biomedical research. The conference was sponsored and organized by the Working Group on Women in Biomedical Careers, National Center for Research Resources, and Office of Research on Women's Health at the NIH.

The morning opened with a session on the demographics of the biomedical research workforce and data on women with Ph.D.s in biomedical science. Debra Niemeyer, a colonel in the United States Air Force and Deputy Assistant Surgeon General, Modernization Directorate, presented a military perspective of the issues and solutions. A panel with representatives from Deloitte & Touche and Ernst & Young LLP provided an overview of programs these companies have initiated, some as early as the mid-1990s. Although it is conventional wisdom that the private sector is ahead of academia in recognizing and addressing the needs of professional women, many in the audience were surprised to hear details of the flexible scheduling, career development groups, and back up child care services. A key point during the follow up discussion was that many companies consider these programs important aspects of work force development and good business practice, and not solely an equity issue.

The afternoon sessions focused on initiatives underway at universities and the NIH. Judith Bond, Professor at Pennsylvania State College of Medicine and ASBMB past-president, chaired a panel on models from academia featuring innovative practices at universities. Barry Klein from the University of California, Davis, discussed initiatives in place at that institution, many of which were developed in response to restrictions imposed by Proposition 209 in 1996. Programs were profiled at several institutions throughout the day, including Cornell and Morehouse medical schools, the University of Wisconsin-Madison, Idaho State University, and the University of California, San Francisco.

The NIH panel featured proposals and initiatives in both the extramural and intramural programs to identify and address the career needs of female researchers. Raynard Kington, Deputy Director of the NIH, brought up the importance of building an evidence base for policy development and implementation and emphasized the need for rigorous collection and analysis of data regarding the effectiveness of career development programs. Many participants agreed that more should be done to ensure that programs are meeting real needs, and rigorous methods for determining success need to be developed. One point of apparent consensus was that proposals must take into account the wishes of the specific group they are designed to serve, and better methods for evaluation are necessary. To this end, a Request for Applications (RFA) is currently under development for proposals to determine efficacy and desired outcomes and examine causal relationships between programs and career success.

At the end of the day the floor was opened for ten minutes of discussion on "action items" to help chart the course for future work by a standing committee charged with reviewing progress on these items. Several expressed hope that the day's discussion would lead to the development of specific actions, although it was somewhat unclear as to how it would proceed.

More information as well as a videocast of the conference can be found at http://womeninscience.nih.gov.

Angela Hvitved received her bachelor's degrees in biochemistry and philosophy from Iowa State University and her Ph.D. in biochemistry from Rice University. She is currently the ASBMB science policy fellow and can be reached at ahvitved@asbmb.org.

Congressional Attention Turns Again to Visa Issues for Foreign Scientists

BY CARRIE D. WOLINETZ

Although the visa issues that plagued foreign scientists traveling to the U.S. have improved considerably in the years since the terrorist attacks of 2001, there has been some recent attention to scientists and visas on Capitol Hill. The House Committee on Science & Technology, Subcommittee on Research and Science Education, held a hearing in early February on "Visas for Foreign Scholars and Students." The stated purpose of the hearing was to "review the status of visas and other policies governing the entry into the U.S. of foreign students and scholars." Witnesses included Harvey Fineberg of the IOM, Allen Goodman of the Institute for International Education, Cathryn Cotten of Duke University's International Office, and Tony Edson of the Department of State.

Generally, the tone of the hearing was in favor of attracting foreign scholars and students to the U.S. and working on visa policies that would 1) make it easy for scholars to study or conduct research here, and 2) relieve the perception that the U.S. is unwelcoming or that our visa process is insurmountable.

Both Edson and Goodman presented data showing that many of the earlier problems with the visa system had been mitigated and that foreign student enrollment in the U.S. is on the rise. In particular, the recent decision by the State Department to waive in person consular issues for renewal applicants that meet certain conditions (*i.e.* same kind of visa, fingerprints on file, etc.) was praised by all the other witnesses.

There seemed to be consensus around several major policy issues that need to be addressed:

- **A system needs to be developed to reissue visas domestically, so visitors do not have to worry about getting delayed trying to get a return visa to re-enter the U.S.**
- **Nonimmigrant status denials (i.e. 214(b) clause), there was a call for greater transparency about visa denials and a statutory change so that the default position is not to try to discourage foreign scholars from staying.**
- **A removal of the 2-year ban for returning to the U.S. for participants in the Exchange Visitor's Program.**

Other issues discussed included revising the classified Technology Alert List, the complications that the ongoing immigration debate brought to this issue, and increased training of consular officials. Unfortunately, although the State Department official seemed open and sympathetic to exploring these ideas, the Department of Homeland Security (DHS) plays a significant role in many of these policy issues, and DHS officials were unable to attend the hearing. However, Chairman Brian Baird (D-WA) suggested the result of the hearing would be a behind-the-scenes integrated effort involving the committee, State Department, DHS, and perhaps the witnesses to begin to work toward solutions for these issues.

Meanwhile, many of these recommendations are incorporated into a bill introduced by Senators Bingaman (D-NM) and Coleman (R-MN).

Although some of the provisions go beyond the scope of FASEB's interests and deal with immigration concerns, business travelers, etc., there are a number of provisions consistent with our previous visa policy recommendations from 2004 and 2005. These include:

- **Improving the Visas MANTIS clearances for scientists, including a periodic review of the Technology Alert List**
- **Expanding the portability and duration of some visa clearance times and reducing processing time**
- **Easing the transition from student status to H1-B (employment) visa status**
- **Creating an expedited review for "trusted travelers"**
- **Allowing renewal of select nonimmigrant visas without having to depart the U.S.**
- **Enhancing consular resources and training**
- **Modifying the nonimmigration intent criteria (*i.e.* 214(b), the clause through which many scientists and students are denied visas).**

Carrie D. Wolinetz is Director of Scientific Affairs and Public Relations for the Office of Public Affairs at the Federation of American Societies for Experimental Biology (FASEB). She can be reached at cwolinetz@faseb.org.

Hearings and Letters and Meetings, Oh My!

'09 Budget, Appropriations Fights Begin in Earnest

Action aimed at increasing the 2009 budgets for National Institutes of Health, National Sciences Foundation, and other science agencies began in earnest within days of the release of the Bush administration's final budget proposal on February 4 (covered in March in *ASBMB Today*). Whereas congressional leaders declared the President's budget "dead on arrival," the President is still a force to be reckoned with as he has sufficient support in Congress to sustain his veto if he chooses to use it—and he has indicated he will do so if Congress approves appropriations bills larger than he has called for.

Because of this threat, it is highly likely that only one or two spending bills will make it to the president's desk before Election Day. The rest of the federal government will be funded under a continuing resolution that will probably stay in effect until well after a new administration takes office, perhaps as late as March 2009. Congressional leaders believe that regardless of who gets elected to the presidency, the new president will be more likely to support spending increases in key domestic programs, including scientific research, than President Bush.

Thus, the science community and its allies in Congress have launched a number of efforts to get spending boosted in the other appropriations bills that will be passed but not sent to the White House until President Bush has left office.

NIH—Opportunities Lost

The House Appropriations subcommittee that funds NIH held a hearing in mid-February called "Opportunities Lost and Cost to Society: The Social and Economic Burden of Disease, Injuries, and Disability" in which several public health specialists discussed how failing to fund medical research as a budget-cutting strategy actually ends up costing more money in the long run when one factors in costs associated with hospitalization, lost income and productivity, treatment, and suffering.

More directly, since 2003, the NIH budget has shrunk 14% because of flat funding and the effects of inflation. This of course affects the amount and quality of scientific work being done. Laboratories are being closed; scientists are spending more time writing grant applications, the average age of a scientist getting his first grant continues to increase and 8 of 10 applications are not funded in any case; and overseas investment in biomedical research continues to increase (thus increasing pressure on the U.S. research system as it tries to retain the "best and the brightest".

These problems are all covered in more detail in a publication called "Within Our Grasp—or Slipping Away?", prepared by a coalition of major research universities. The report notes areas where biomedical progress has been made but where further progress is seriously threatened by funding cutbacks. These include saving and improving memory; targeted therapies for cancer; outwitting resurgent and new infectious diseases; tackling the twin epidemics of obesity and diabetes; developing new tools for bioterrorism preparedness; and repairing spinal cord damage.

House Appropriations Chair Dave Obey (D-WI) took the opportunity on February 27 to lecture HHS Secretary Mike Leavitt on the importance of investing in biomedical research. He said that future savings in health care costs will be significantly more than what was invested in research and diseases that are almost always more expensive to treat than prevent. Leavitt agreed prevention was always desirable but replied that the inefficiencies of our health care system, particularly Medicaid, are pulling money away that could fund other programs such as the NIH.

The tart-tongued Obey replied that the Administration's "tax cuts for millionaires" and spending on the war in Iraq at the expense of medical research imply a difference in priorities and the problem therefore is not just a reflection of increased costs of health care. He noted that the Appropriations Committee would not accept these kinds of cuts. He also expressed the hope that there would be some compromise this year on spending rather than a repeat of last year's vetoes.

Letters in Transit

At least two Congressionally authored letters regarding NIH are circulating. The first was sent on February 28 to the leaders of the House Budget Committee, calling for an increase at NIH at least equal to biomedical inflation, which is about 3.5%. This letter was signed by a bipartisan group of six congressmen led by Rep. Ed Markey (D-MA) and Chris Shays (R-CT). Markey and Shays also began circulat-

ing a "dear colleague" letter on March 4 seeking an increase of at least 6.5% for NIH in 2009. This letter was going to go to the House Appropriations Committee. The 6.5% figure was derived from biomedical inflation plus 3%, the minimum needed to ensure that NIH funding increases enough to support some new research. This letter matches a request prepared by a coalition of science and education groups (ASBMB participates in most of them), to the House and Senate Budget committee leadership, calling for a 6.5% increase at NIH.

FASEB President Bob Palazzo noted that "Although President Bush has given lip-service to supporting the search for treatment for diseases like cancer, Alzheimer, and pandemic influenza, this budget again reveals his failure to uphold that commitment. This is an injustice to the patients and their families suffering from conditions for which research funded by NIH is their only hope."

Boosting NSF Funding Also a Focus

On another front, the Administration would like to give the NSF a healthy increase this year, in the overall range of 13%, from just over $6 billion to more than $6.8 billion. However, the America COMPETES Act, signed into law with great fanfare last August, calls for the NSF to be funded in 2009 at a level of more than $7.3 billion. This is the funding level that a group of congressmen, headed by Rep. Vern Ehlers (R-MI) and Rush Holt (D-NJ), is urging in a "dear colleague" letter circulating in the House.

As the letter notes: "A renewed commitment to core basic research and educational programs at NSF is essential to meet the enormous promise of scientific innovation, to better train future scientists, engineers, and technicians, and to promote the success of multidisciplinary initiatives….We now need to make substantial investments in the physical sciences and engineering. NSF is the core agency for these endeavors."

Unfortunately, the administration request, although good for scientific research as a whole, would fund biological research at NSF at about half the rate of physical sciences and engineering research, the focus of the COMPETES Act. Thus, the biological sciences community is working to get report language included in the NSF funding bill this year that would require NSF to fund the different types of research at NSF more or less equally. Similar language was included in the report last year.

Schachman Award Presented—ASBMB officials and staff met with Rep. Michael N. Castle (R-DE) on February 26 to present him the Howard K. Schachman Public Service Award. *From L to R: Angela Hvitved, ASBMB Science Policy Fellow; Peter Farnham, Director of Public Affairs; Robert Wells, member, Public Affairs Advisory Committee; Rep. Castle; ASBMB President Heidi Hamm; PAAC member William Merrick.*

Veterans Affairs Research

ASBMB also participates in a group called the Friends of the VA, and has signed onto the FOVA request for an increase in VA Medical and Prosthetics Research (the VA's research program) of $75 million, putting the program at a total funding level of $555 million. In addition, FOVA has called for an additional $45 million to improve VA research facilities.

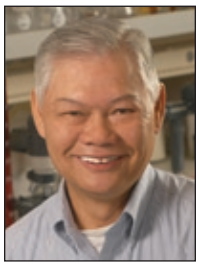
Increase Public Health Spending

Finally, more than 440 organizations (including ASBMB) signed a letter prepared by the Coalition for Health Funding to increase spending on public health programs, including NIH, by $5.3 billion in the 2009 budget resolution currently being considered in Congress. This is considered the amount that would restore funding to public health programs cut over the past several years, restore lost purchasing power that flat-funding has eroded, and provide investments that begin to meet health challenges facing the nation in the areas of biomedical research; disease prevention and health promotion; access to safety net health care services; health professions' education; mental health and substance abuse; health services research; health care for indigenous populations, and food and drug safety.

Peter Farnham CAE is public affairs officer of the Society, a position he has held since 1985. He can be reached at pfarnham@asbmb.org.

asbmb member spotlight

Chan Honored with Thomas Willis Award



Pak H. Chan, Professor of Neurology and Neurosurgery at Stanford University School of Medicine, was given the American Stroke Association's highest honor this past February—the Thomas Willis Award. Chan delivered the Willis Lecture and received his award at the International Stroke Conference.

Chan, who is also the James R. Doty Professor in Neurosurgery and Neurosciences and Professor by courtesy, and vice chair and director of research in the Department of Neurosurgery at Stanford, has pioneered research in stroke and central nervous system injury research. He was the first investigator to use transgenic animals to study oxidative mechanisms in neuronal death and survival. His current research interests focus on oxidative signaling in cell death/survival mechanisms in stroke and central nervous system injuries and how to translate this basic knowledge into clinical therapies.

The Willis Award, which recognizes "major contributions to the understanding of stroke over a sustained period," honors pioneer physician Thomas Willis, who is credited with providing the first detailed descriptions of the brain stem, cerebellum, and ventricles along with hypotheses on their function.

Schachman to Receive Carl Brändén Award

Howard Schachman, Professor of the Graduate School Division of Biochemistry and Molecular Biology at the University of California, Berkeley, has been selected to receive the Protein Society's 2008 Carl Brändén Award. The award, sponsored by Rigaku Corporation, is given to an outstanding protein scientist who has also made exceptional contributions in the areas of education and/or service to the science. The award will be presented to Schachman during the Protein Society's 21st Annual Symposium in July.

Schachman is being honored for his major contributions to protein science and for his exceptional contribution to both service and education. He has pioneered research on the ultracentrifuge and proteins such as aspartate transcarbamylase, and has trained more than 150 students and postdoctoral fellows in his laboratory. Schachman has served as President of both ASBMB and FASEB, and as the NIH Ombudsman in the Basic Sciences. Through his articles, speeches, and testimony before committees of the United States Congress and government agencies, Schachman also has made crucial contributions toward the formulation of policies aimed at preserving academic freedom and fostering the responsible conduct of research.

Rees Granted Dorothy Crowfoot Hodgkin Award

Douglas Rees, Professor of Chemistry at the California Institute of Technology and Investigator of the Howard Hughes Medical Institute, will receive the Protein Society's 2008 Dorothy Crowfoot Hodgkin Award, sponsored by Genentech. The award is given for exceptional contributions in protein science, which profoundly influence our understanding of biology.

The award recognizes Rees' fundamental contributions to the understanding of the structural biology of metalloproteins and membrane proteins, most notably by his analyses of the nitrogenase molybdenum-iron (MoFe-) protein that established the unprecedented structure of the FeMo-cofactor providing the active site for biological nitrogen fixation. Rees' work has also resulted in the first structure determination of a physiologically gated ion channel, the mechanosensitive channel of large conductance (MscL) from *Mycobacterium tuberculosis* and the first structure determination of an intact and fully ordered member of the widespread family of ABC transporters, the Escherichia coli importer BtuCD for vitamin B_{12}.

Stroud to Be Given Hans Neurath Award

Robert Stroud, Professor of Biochemistry & Biophysics and Professor of Pharmaceutical Chemistry at the University of California, San Francisco, will be awarded the Protein Society's 2008 Hans Neurath Award this July. The award, sponsored by the Hans Neurath Foundation, recognizes an individual who has made a recent contribution of unusual merit to basic research in the field of protein science, including but not restricted to the chemistry, design, folding, structure, or biological function of proteins.

The award will be presented to Stroud at the Protein Society's 21st Annual Symposium. He is being recognized for his significant contributions to the understanding of structure-function relationships in enzymes and membrane proteins. Stroud's work has focused on the molecular levels of cellular signaling and communication across cell membranes as well as the macromolecular encoding of specificity and affinity at protein/protein and protein/ligand interfaces. He has determined the high resolution three-dimensional structures of numerous proteins of different classes and used these structures to define biological, biochemical, and cellular function as templates for drug design. His seminal contribution of defining the mechanism of zymogen activation by demonstrating structurally that the catalytic site becomes rearranged is now taught in any undergraduate biochemistry course.

Hood Accepts Pittcon Heritage Award

Leroy Hood was awarded the seventh annual Pittcon Heritage Award this past March. The award, jointly sponsored by the Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy (Pittcon) and the Chemical Heritage Foundation (CHF), recognizes outstanding individuals whose entrepreneurial careers have shaped the instrumentation community, inspired achievement, promoted public understanding of the modern instrumentation sciences, and highlighted the role of analytical chemistry in world economies.

"Award-winning researcher, gifted entrepreneur, and brilliant innovator, Leroy Hood pioneered the techniques that made the rapid pace of the Human Genome Project possible," said Thomas Tritton, President and CEO of CHF. "Without his contributions, the sequencing of the human genome could have taken years or even decades longer."

Hood's research has focused on fundamental biology and on bringing engineering to biology through development of the five instruments that constitute the technological foundation for modern molecular biology and genomics: the DNA and protein sequencers and synthesizers and the ink-jet oligonucleotide synthesizer.

In 1992 Hood became founder and chairman of the Department of Molecular Biotechnology at the University of Washington, and in 2000 he co-founded the Institute for Systems Biology, a nonprofit research institute established to pioneer systems approaches to biology and medicine.

IN MEMORIAM:

Sidney F. Velick

Sidney F. Velick died at the age of 94 this past December in Salt Lake City after a combined struggle with pneumonia and a stroke. He was widely recognized for his research in protein biophysics, particularly enzyme structure and mechanisms, and was also an advocate for mental health issues and a supporter of classical music.

Velick was born in Detroit in 1913, attended Detroit City College, and earned his doctorate in biological chemistry from the University of Michigan in 1938. After postdoctoral research at The Johns Hopkins University and Yale, he joined the faculty at Washington University in St. Louis. In 1964 he moved to Utah after accepting a position as chairman of the Department of Biochemistry at the University of Utah School of Medicine. He led the department until his retirement in 1978.

Among his honors, Velick received a Distinguished Research Award from the University of Utah in 1976 and was elected to the National Academy of Sciences in 1981.

Stubbe Honored with Award in Chemical Sciences and Emil Thomas Kaiser Award

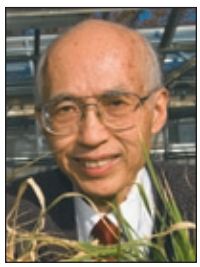
JoAnne Stubbe, Novartis Professor, Departments of Chemistry and Biology, Massachusetts Institute of Technology, has been honored with the Emil Thomas Kaiser Award, sponsored by the Protein Society, and the National Academy of Sciences Award in Chemical Sciences.

The Emil Thomas Kaiser Award recognizes a recent, highly significant contribution in applying chemistry to the study of proteins. In Stubbe's case, her outstanding contributions to the understanding of the involvement of cell enzymes in the production and breakdown of DNA are recognized.

The National Academy of Sciences Award in Chemical Sciences is awarded annually for innovative research in the chemical sciences that contributes to the better understanding of the natural sciences and to the benefit of humanity. Stubbe received this award "for landmark work on the mechanisms and regulation of ribonucleotide reductases, a compelling demonstration of the power of chemical investigations to solve problems in biology."

IN MEMORIAM:

Ray Wu

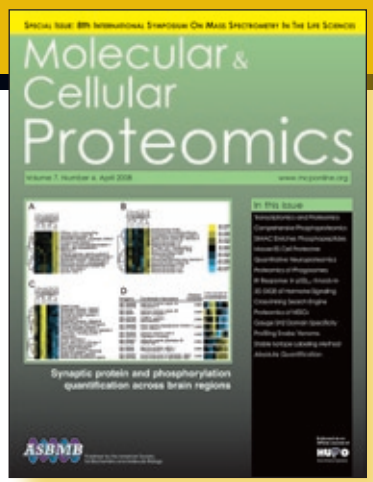


Geneticist and genetic engineering pioneer Ray Wu died on February 10 of cardiac arrest. He was 79.

In 1970, Wu developed a new location-specific primer-extension technique that became the first method of sequencing DNA. In the following decade, Frederick Sanger adapted the approach for faster sequencing, and received the Nobel Prize in Chemistry for the work in 1980.

Wu's lab also devised other approaches that were used to analyze genetic sequences and to construct vectors for cloning genes. Wu used his novel genetic engineering techniques to insert foreign genes into rice; the idea was to improve yields of cereal crops in the developing world. A technique he developed in 2002 for producing high-yield rice resistant to environmental factors such as drought, salinity, and insect attack is now being developed for commercial use.

Wu was born in China in 1928 and came to the United States when he was 20 years old. In 1966, he joined the biochemistry and molecular biology faculty of Cornell University. In the 1980s, he founded and ran an initiative that brought more than 400 top Chinese students in biochemistry and molecular biology to train in the United States. Throughout his career, he served on several Chinese, Taiwanese, and international advisory councils on genetic engineering and biotechnology.



The Mass (Spectrum) Effect

April issue of MCP *has a special section devoted to mass spectrometry meeting*

BY NICK ZAGORSKI

This month, *Molecular and Cellular Proteomics* will feature a special issue highlighting some of the research presented at the 8th International Symposium on Mass Spectrometry in the Health and Life Sciences, held this past August in San Francisco. This Symposium focused on mass spectrometry applications in proteomics, describing how recent advances in mass spectrometry technology and methodology have expanded our current knowledge about the vast protein networks inside cells and how they are regulated.

Historically a tool designed for chemical applications, mass spectrometry's role in the biological arena has been steadily growing. And with the power to separate and analyze large samples on the order of several thousand molecules, this technology has found a perfect home in the field of proteomics, which traditionally has relied on two-dimensional gels to separate out protein mixtures. In addition, mass spectrometry can readily distinguish various chemical signatures, making it especially well suited for identifying post-translational protein modifications like phosphorylation.

"As scientists uncover more data, they're going to ask ever more sophisticated questions, and require ever more sophisticated equipment," says *MCP* co-editor Ralph Bradshaw. "That's the reason that over the past decade the use of mass spectrometry in proteomics has grown to the point where we can now consider it a core technology. At the same time I believe our journal has become the key depository for mass spectrometry-based proteomics papers. So, with this special issue, we can now showcase this convergence."

Of course, considering the large number of protocols and uses for mass spectrometry, Bradshaw notes it would be impossible to encompass the whole breadth of applications this technology offers in just a single issue, but he thinks that the 10 articles selected at least capture the "flavor" of how mass spectrometry can aid and advance proteomics. "These are great studies, and some of them are really at the cutting edge of research," he says.

Contributed from authors around the world, the articles highlighted in the special April issue on mass spectrometry research and include:

- **A global analysis of how acetylation modulates the function of the tumor suppressor p53 in response to radiation.**
- **A quantitative analysis of protein expression and phosphorylation status in the synapses of four different brain regions.**
- **The development of a new strategy to rapidly separate out mono- and multiphosphorylated proteins from complex samples.**
- **An examination of the large collection of microarray-specific statistical tools that can be applied to shotgun proteomics datasets.**
- **The development of a user-friendly search engine to detect cross-linked peptides from digests of large protein conjugates.**

This special feature will also help raise the awareness on the upcoming 9th International Symposium, to be held in the summer of 2009 (never too soon to start thinking about it), so the meeting can continue to grow in attendance and stature. Previous meetings had packaged together many of the important papers in a book, but in an age where the number of themed meetings continues to rise, combined with the prominence of the internet, special issues provide a more useful outlet for dissemination of knowledge. A planned upcoming issue highlighting clinical proteomics work and the 2009 mass spectrometry issue, which Bradshaw hopes can be a full-sized issue that comes out right after the meeting.

"ASBMB has taken a strong role in opening up the field of proteomics to society members and researchers in general," Bradshaw says. "The journal [*MCP*] has been highly successful; we've added parts of the national meeting specially devoted to proteomics, and established symposia in the field like this one on mass spectrometry. This is just another component of building to the future and achieving our goal."

Nick Zagorski, Ph.D., a graduate of Johns Hopkins and Cornell Universities, is a science writer for ASBMB. He can be reached at nzagorski@asbmb.org.

ASBMB Evaluates Undergraduate Education

In November 2006, the American Society for Biochemistry and Molecular Biology received a $75,000 grant from the Teagle Foundation to evaluate the biochemistry and molecular biology major and to consider how our discipline supports the broad goals of a liberal education. As a result, ASBMB convened a working group headed by Adele Wolfson of Wellesley College.

Since 1992, ASBMB has supported a recommended curriculum for the bachelor's degree in Biochemistry and Molecular Biology. This curriculum can be found at http://www.faseb.org/asbmb/epd/Curriculum.html. The working group recently sent a survey to chairs and instructors of departments offering an undergraduate major in biochemistry or molecular biology to assess how the ASBMB recommended curriculum is being received and implemented in different types of institutions.

Some of the preliminary data from the survey have been analyzed and have provided the working group with some useful information. For example:

- **Only about half of the institutions surveyed explicitly follow ASBMB's recommended curriculum. However, most departments do include the elements of the recommended curriculum.**
- **Most skills are introduced in introductory courses and built upon in subsequent courses, but the primary literature is rarely introduced until upper level courses.**
- **Similarly, open-ended research projects are present mainly in advanced courses.**
- **Traditional pedagogies predominate, with lecture format emphasized in at least 80% of classes at all levels.**

The initial survey did not ask about research experiences. Interview and other qualitative data indicate that students gain many of their skills and much of their knowledge from such undergraduate research. As a result, the Teagle working group has decided to conduct an additional survey addressing issues such as the skills taught in the context of a research experience, the level or year at which students do scientific research, and how the institutions define the success of their programs and gradu-

continued on page 14

ASBMB Education Survey

To take part in this survey you can either fill it out on line by accessing it from the ASBMB Website (www.ASBMB.org) or you can answer the questions below and email your responses to Adele Wolfson at awolfson@wellesley.edu or:

Adele Wolfson
Wellesley College, Office of the Dean of the College
106 Central Street, Wellesley, MA 02481

1. Please indicate your type of institution and degree offered.
2. Which of the following skills does your department/program teach in the context of a research experience?
   a. Understanding of the fundamentals of chemistry and biology and the key principles of biochemistry and molecular biology.
   b. Awareness of the major issues at the forefront of the discipline.
   c. Ability to assess primary papers critically.
   d. Good "quantitative" skills such as the ability to accurately and reproducibly prepare reagents for experiments.
   e. Ability to dissect a problem into its key features.
   f. Ability to design experiments and understand the limitations of the experimental approach.
   g. Ability to interpret experimental data and identify consistent and inconsistent components.
   h. Ability to design follow-up experiments.
   i. Ability to work safely and effectively in a laboratory.
   j. Awareness of the available resources and how to use them.
   k. Ability to use computers as information and research tools.
   l. Ability to collaborate with other researchers.
   m. Ability to use oral, written, and visual presentations to present their work to both a science literate and a science nonliterate audience.
   n. Ability to think in an integrated manner and look at problems from different perspectives.
   o. Awareness of the ethical issues in the molecular life sciences.
3. Does your department/program teach ethics in the context of scientific research?
4. At what year/level do your molecular biology/biochemistry undergraduate students typically do scientific research?
5. Does your institution supply money for undergraduate research?
6. Does your institution offer teaching credit for supervision of undergraduate research?
7. Does your institution offer a general education course in biochemistry/molecular biology that you consider to be an excellent model? If so, please send syllabus to awolfson@wellesley.edu.
8. How does your institution define the success of your programs and graduates?
9. If you would like to be involved in further discussion and implementation of any new recommendations, please indicate your email address.

continued from page 13

ates. You can access this survey on the ASBMB Website (www.asbmb.org). The questions can also be found in the sidebar accompanying this article.

As for all undergraduate majors, biochemistry and molecular biology may lead to graduate school, to employment in the discipline, or to other career paths. Departments are faced with the problem of designing a major that is appropriate for all of these students. The working group is considering ways in which advising or different degrees (B.A. *versus* B.S.) may help students select the best program for them.

The working group is also interested in hearing from faculty who teach general education courses with a biochemistry/molecular biology theme. They will issue a White Paper in the fall of 2008 and will publicize its findings and recommendations to the Society during the 08/09 academic year.

New Staff Members at ASBMB

Over the past several months, ASBMB has seen the addition of two new staff members. Nick Zagorski joined ASBMB in November 2007 as the society's new Science Writer and Mary Li-Min Chang was hired this past February as the new Managing Editor of the *Journal of Lipid Research*.

Nick Zagorski

Zagorski's main role will be to assist in the public relations efforts for the society's three journals as well as in the production of *ASBMB Today*.

Before coming to ASBMB, Zagorski served as an assistant director of basic science research communications at Johns Hopkins Medicine, where he handled media relations duties for the Institute of Basic Biomedical Sciences and also contributed his writing skills to Hopkins newsletters and the medical magazine. Prior to that, Nick worked as a science writer for *Proceedings of the National Academy of Sciences*, writing research article highlights and member profiles for the journal.

Nick received his B.A. in Biology from Johns Hopkins and Ph.D. in Molecular Biology and Genetics from Cornell University, where he studied heavy metal bioremediation in bacteria. He later conducted a brief postdoc at the Cornell School of Veterinary Medicine, examining virulence factors in the pathogen *Listeria monocytogenes*, before deciding to leave research and pursue a career in science writing. In 2003, he returned to Johns Hopkins and completed his master's degree in science writing.

Mary Li-Min Chang

Prior to joining ASBMB, Chang worked at Aspen Systems Corporation (now part of Lockheed Martin Corporation), supporting the National Library of Medicine—Clinical Information Services. She served as editorial lead for clinical trial protocol abstractions published on *ClinicalTrials.gov* for the National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute for Arthritis and Musculoskeletal and Skin Diseases (NIAMS). She also oversaw publication of drug records and fact sheets and a redesign of the AIDS*info* Web site (an HHS-sponsored project with federally approved information on HIV/AIDS clinical research, treatment, and prevention, and medical practice guidelines). Chang became a certified Editor of the Life Sciences (ELS) with the Board of Editors in the Life Sciences in 2006.

Chang received her B.A. in Biology, with a specialization in cell and molecular biology and genetics, from the University of Maryland, College Park, in 2001. That fall, she began her Ph.D. studies at Maryland in the Department of Cell Biology and Molecular Genetics, studying apoptosis in *Drosophila*.

As Chang told *ASBMB Today*, "*JLR*'s research papers are based on the hard work, many long hours conducting experiments, creativity, and innovation of scientists, and they advance the fields of biochemistry and biomedical research. I am thrilled to be involved with the publication of this scientific journal." In addition to her duties as Managing Editor of *JLR*, Chang will be providing *ASBMB Today* with articles on *JLR*'s special features, implementing Bench Press for *JLR*, assisting in the redesign of ASBMB's Journal Web sites, and helping to promote ASBMB publications.

Retrospective: Joshua Lederberg (1925-2008)

Nobel Laureate Joshua Lederberg, often referred to as one of the founders of molecular biology, died on February 2, 2008, at age 82.

Lederberg was born in Montclair, New Jersey, in 1925 and was raised in New York City. He enrolled at Columbia University where he met Francis J. Ryan, who introduced him to the red bread mold, *Neurospora*. Lederberg received his bachelor's degree in 1944 and began working toward an M.D. at Columbia University's College of Physicians and Surgeons. Although medical students were not encouraged to do research, Lederberg continued to do experiments under Ryan's supervision, investigating the genetics of bacteria.

PHOTO: STANFORD UNIVERSITY NEWS SERVICE.

In 1946, Lederberg took a leave of absence from medical school to carry out experiments on *Escherichia coli* in collaboration with Edward L. Tatum at Yale University. He demonstrated that certain strains of bacteria undergo a sexual stage during which they mate and exchange genes. At the time, scientists believed that bacteria reproduced asexually, so Lederberg's discovery of bacterial recombination was a radical one. He and Tatum were also able to map the *E. coli* chromosome, showing the locations of several of its genes. With Tatum's support Lederberg submitted this research as his doctoral thesis and received his Ph.D. from Yale in 1947.

Rather than go back to medical school, Lederberg decided to accept the offer of an assistant professorship in genetics at the University of Wisconsin at Madison. There, he continued to study bacterial genetics and produced a steady stream of techniques and results that became the basis of genetic engineering in the 1970s. His most important discoveries at the time were that of transduction, the transfer of genetic fragments from one cell to another by a virus, and of the extra-chromosomal genetic particles called plasmids.

In 1957, Lederberg helped found and became chairman of a new Department of Medical Genetics at the University of Wisconsin. One year later, he accepted an offer to become the first chairman of the newly established Department of Genetics at Stanford University's School of Medicine. Later that year, he was awarded the 1958 Nobel Prize in Physiology or Medicine, along with Tatum and George W. Beadle.

Lederberg returned to New York City in 1978 as President of Rockefeller University. He became University Professor Emeritus and Raymond and Beverly Sackler Foundation Scholar in 1990.

Not only recognized for his research accomplishments, Lederberg was also heavily involved in advancing reforms by influencing public policy and advised a total of nine White House administrations. He was also a consultant to NASA on the Viking space missions to Mars and played a role in engineering experimental devices used to determine the possibility of life on the red planet.

Lederberg was also instrumental in expanding the role of computers in scientific research. Along with Edward A. Feigenbaum and Carl Djerassi, Lederberg devised DENDRAL (for Dendritic Algorithm), a computer program that could elucidate the structure of unknown organic compounds taken from known groups of such compounds, such as the alkaloids and the steroids.

From 1966 to 1971, Lederberg wrote a weekly column for The Washington Post, commenting on science education, scientists' role in society, and topics such as population control, intelligence testing, and regulating recombinant DNA technology.[1]

FOOTNOTE:

1. For more information on Joshua Lederberg see the National Library of Medicine's Joshua Lederberg Papers at http://profiles.nlm.nih.gov/BB/.

EXCEL 2007... Friend or Foe?

This article is the second in a series on publishing your research in the *Journal of Biological Chemistry*. The series will address a variety of issues that authors may have when writing and submitting articles to the *JBC*. The articles will be written by Cadmus Professional Communications, a Cenveo Company, who are responsible for the editing, production, and printing of *JBC* articles.

In continuation of our *Office 2007…Friend or Foe?* series from the March issue, we now examine the new and (dare we say) "improved" Excel 2007. Open Excel 2007, and you will see a completely new interface. If you felt comfortable with older versions of Excel, be prepared to spend some time becoming acquainted with Excel 2007. Almost all of the features you came to know and love are there, but getting at them is completely different.

The Office Button

As part of Microsoft's Office suite of applications, Excel 2007 has the Office button in the upper left corner of the screen (Figure 1). Remember the File menu in Excel? Well, click on this large Office button to find many of the same commands: New, Open, Print, Save, Save As, and Close. But you'll also find some new commands: Convert, Prepare, and Publish. In basic terms, the new Office button is a pumped up expansion of the old File menu in previous versions of Excel. You'll want to use Convert to save to Microsoft's open XML standard; notice that the extension for these converted files will end with .xlsx. Prepare will finalize or encrypt your spreadsheet. Want to publish your spreadsheet to an intranet? If so, use the Publish feature in the new Excel, which allows you to save your workbook to a document management server.

The Ribbon Ties It Up

Just as in Word 2007, the main difference in the interface of Excel is the Ribbon. The Ribbon has seven tabs: Home, Insert, Page Layout, Formulas, Data, Review, and View. You can also add the Developer as the eighth tab. Within each tab are groups, and within each group are command buttons. Again, this is similar to the Ribbon in Word 2007. Learning where your favorite commands are located within each tab or group will take some time. The commands are context-sensitive,

Fig. 1. The Office button and its commands.

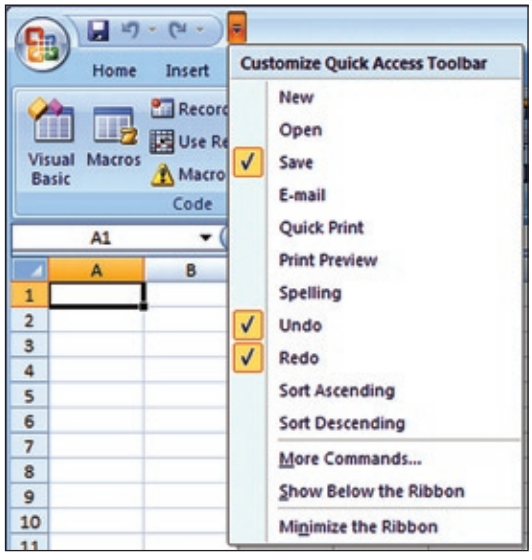


Fig. 2. The Quick Access Toolbar.

and your choices may change depending on what you are working on in the screen area. One complaint about the Ribbon is the amount of screen real estate it takes up. If, after working with Excel 2007, however, you decide that you really don't like the Ribbon, you can remove it by clicking the Down Arrow to the right of the Quick Access Toolbar button and choosing Minimize the Ribbon. You can always click Ctrl-F1 to make it reappear.

The Quick Access Toolbar

Just to the right of the Office button at the top of the screen is the Quick Access Toolbar, containing icons for Save, Redo, and (our personal favorite) Undo. There is also a chart-like icon, which allows you a choice of chart types and applies that type to your chart on the screen. You can customize the Quick Access Toolbar by clicking on the hard-to-see Down Arrow on the toolbar to see command options that then can be added to your toolbar (Figure 2). It is highly recommended, for your time and sanity, that you include the commands you use most often on your Quick Access Toolbar.

The Good Ol' Days

If you're a fan of keyboard shortcuts, you'll be happy to know that most of your old favorites work in Excel 2007 as they did in earlier versions of Excel. Alt key combinations work with the Ribbon too. Alt H brings you the Home tab on the Ribbon, and Alt P takes you to the Page Layout tab. And, if you use Macros, you'll need to create your macros using the Developer tab in Excel 2007.

Charting the Difference

More cells, more rows, more columns, and more colors augment the data that can be charted in the new Excel. Data sorting has been developed to 64 levels. Sorting can also be done by color or icon. Color choices are greatly expanded in Excel 2007 as are the number of columns (more than 16,000 columns are available as compared with 256 in earlier versions). A new feature that is sure to please some users and visually enhance charts is the Data Bar. The Data Bar (Figure 3) uses background color to add context to data, and the length of the color bar corresponds to the value within the cell. Icons are another way to add value to the data in a chart visually. Remember, however, that these charts will be converted to be saved as .tif or .eps figures in your manuscript submission and published as graphic images in your article on line and in print. Styles and themes allow a user to have a consistent palette and to look at all of the tables and charts. Although this might be useful for a branded look for a company or department publication, it is not likely that authors from different academic institutions will find this helpful in submitting manuscripts for publication in ASBMB journals because these figures will be converted to match the specific journal style.

Are You Compatible?

Sharing documents with colleagues can be of concern with Excel 2007 as it is with Word 2007. Excel 2007 has four new XML-based file formats as follows: .xlsx for standard worksheets, .xlsm for those with macros, and .xltx and .xltm for templates. You can check to see if the features you've used in your Excel 2007 document will be easily read and accessed by earlier versions of Excel by saving your document as an earlier version of Excel. Unless you are sure that your collaborators are using Excel 2007, it may be best to save your document in Excel 2003 just to be safe. Users of Excel 2003 can download a patch to allow them to access and read Excel 2007 documents. Please see: http://www.microsoft.com/downloads/details for instructions to download the free patch.

Want more information on the Office 2007 suite? Then stayed tuned as we continue this series by exploring PowerPoint 2007 in the May issue of *ASBMB Today*.

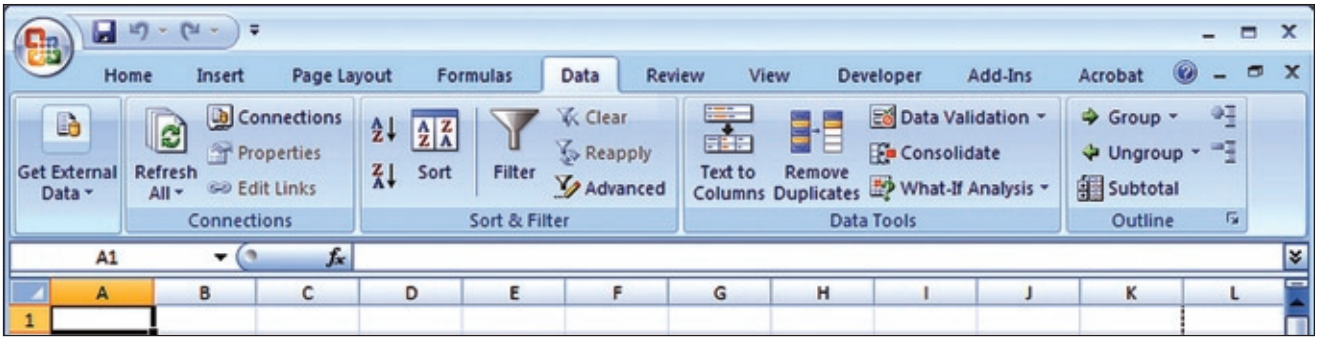


Fig. 3. The Data Bar.

Undergraduates from Historically Under-represented Groups—How Do We Capture Them?

BY TAKITA FELDER SUMTER

Despite the strides made in diversifying the sciences, many would agree that there still exists a leaky pipeline through which many aspiring scientists from under-represented groups fail to matriculate to the Ph.D. and subsequently to the professoriate. What is the missing link? It seems that we've identified several important experiences and characteristics that are essential to the success, but clearly there are additional elements to be identified. So the question becomes how can we nurture the interests of young minority scholars who enter undergraduate programs to a degree that increases their likelihood of pursuing graduate studies? What skills do these scholars need to acquire to become effective educators and mentors? More importantly, how can the lessons learned from efforts to diversify the sciences be applied to strengthen our appreciation of other areas of diversity (*i.e.* female faculty mentorship, international affairs, etc.) in academics? To adequately begin to address these issues, it's important that we approach undergraduate education with nontraditional approaches to our teaching, mentoring, and research programs.

Demonstrating Relevance

In our teaching we must spawn interest in the sciences early on by demonstrating relevance throughout the curriculum. Many would argue that they currently do so by adding a few interesting tidbits in their general chemistry and biology courses. Unfortunately, these courses are crowned the gatekeeper courses that deter students from continuing their pursuit of the sciences. Does this mean that our demonstration of relevance is ineffective? This is still to be determined. However, there are many examples where faculty at various institutions have released themselves from what some refer to as "tyranny of the textbook" and embraced the freedom to discuss thematic topics of relevance while introducing a little chemistry or biology along the way. This approach has even prompted the American Chemical Society to publish a textbook with this idea in mind. In fact, I've spoken with several faculties who've tried this approach, and although they'll admit that the teaching preparation for this method is extremely burdensome, they too are so excited about the subject matter that they find a renewed interest in teaching the introductory courses.

Increasing Student Interest

My colleague and I recently tried this approach in my own classroom as a means of increasing student interest in chemistry and preparing them for early entry into undergraduate research and were quite pleased. We developed a second semester general chemistry course that used biological models to study essential topics in general chemistry. Students taking this course had successfully completed first semester general chemistry and introductory biology and were required to purchase a supplemental biochemistry text. The course provided students with the interdisciplinary insights vital to beginning research in their sophomore year. The students learned the essential principals of electronegativity and condensation reactions during their study of the chemical properties of phospholipids, carbohydrates, amino acids, and nucleotides while also learning how to evaluate the importance of intermolecular forces involved in protein interactions and maintaining protein structure. When studying chemical reaction kinetics, we used the Michaelis-Menten model and Lineweaver-Burk plots and compared them with

> *"It's important that we approach undergraduate education with nontraditional approaches to our teaching, mentoring, and research programs."*

traditional chemical reactions. Students used cyclooxygenase and opioids as case studies for understanding kinetics and receptor binding while also learning about various organic function groups that can be added to proteins as a means of modifying their activity. General chemistry is typically a major barrier to the retention of minority science majors in molecular biology and biochemistry, and we've seen improved success of these students in classroom settings.

Downsides

But what are the downsides? Opponents to this approach argue that many students will likely focus on the topics of interest and fail to fully appreciate the chemistry or biology involved. This may be true in some cases; however, I would argue that the exposure and the innate drive resulting from increased interest will keep students learning all aspects of the discipline. In fact, I believe that minority students in particular are those whose interest feeds off of relevance. Why should I learn this and how does it relate to everyday life? When this is readily apparent, it's likely that the students will understand how these subjects fuel more commonly pursued careers like medicine and pharmacy and will at least consider chemistry and biology as options.

Early Exposure

Another nontraditional approach to curriculum enhancement has been early exposure to organic chemistry. To this end, a few institutions have a three semester sequence that combines general and organic chemistry, and others have offered organic chemistry to first semester science majors. These approaches argue that Lewis structures, bonding, polarity, hybridization, acid-base equilibrium, and thermodynamics are the only topics from general chemistry required to learn organic chemistry. As a result, several approaches have been explored to prepare students for this course. The benefits of this type of course to maintaining the pool of future scientists are quite clear. First, a student interested in biology would understand the chemistry that drives the molecular and cellular processes being studied in introductory courses. Second, this creates room for greater emphasis on quantitative skills in biology courses as a means to demonstrate the interrelated nature of biology and chemistry. By appreciating the interdisciplinary nature early, we as educators will be in a better position to teach the analytical thinking that is needed in graduate and postdoctoral training. These and other models not mentioned here place special emphasis on creating a classroom environment that supports various academic interests and learning styles. Regardless of the approach, sparking the interests of minority students is a key asset to their pursuit of careers in the life sciences and in academics.

Lab Experiences

Outside of the classroom, students should be exposed to meaningful laboratory experiences both through advanced labs and undergraduate research. In advanced labs, many have replaced the historical experiments in which students follow detailed procedures to completed isolated experiments with those in which student have an opportunity to develop protocols and conduct continuous in-depth studies to answer hypothesis-driven questions. These experiences are designed to foster curiosity, critical thinking, and first-hand appreciation of the scientific method.

Another advantage of this approach is the repetitive presentation of basic concepts and techniques essential to a career in biochemistry or molecular biology. In addition, when these skills are cemented by a significant research experience, students are sure to learn, rather than memorize material, and are consequently better prepared for graduate programs.

Continued Committment

In summary, it is essential that the academic community continue their commitment to exploring nonconventional methods of educating undergraduates and mentoring our future scientific community. In particular, we must ensure that we obligate ourselves to assessing the effects of our efforts in improving the interest and retention of students from under-represented groups in life science disciplines. Novel approaches to education, like the need to diversify the sciences, not only benefits minorities but also encourages increased originality and creativity as it relates to scientific discovery.

Takita Sumter is an Assistant Professor of Chemistry at Winthrop University where she studies the function of high mobility group A proteins in chromatin remodeling and transformation. She received her B.S. in Chemistry and Ph.D. in Biochemistry from the University of South Carolina in Columbia, SC, and completed her postdoctoral fellowship in molecular oncology at Johns Hopkins School of Medicine in the Department of Hematology. She currently serves on the Minority Affairs and Undergraduate Affiliates Network Committees for ASBMB. She can be reached at sumtert@winthrop.edu.

Working with High School Students and Teachers

BY LISA GENTILE

Faculty Who Make a Difference—Part I

This month we are pleased to present the first of two articles that highlight the activities of two young faculty members who make a real difference in their teaching and research environment and illustrate the type of activities that can have an impact on students choosing to go into science. Both faculty members have been honored by the National Science Foundation, receiving 5-year CAREER grants. This first article is written by Lisa Gentile, an Associate Professor at the University of Richmond, who works with high school students and their teachers from various high schools in the Richmond, Virginia area.

When I wrote my National Science Foundation (NSF) grant, I wanted the educational section to reflect my passion for being involved in the K-12 community. Having a middle school-aged daughter interested in math and science, I have had a few years to observe the excitement that "doing experiments" generates as well as the challenges of finding the time, equipment, funding, and expertise to incorporate laboratory science into the early curriculum. Knowing that it was high school lab science that got me hooked on chemistry, I decided to make that my focus.

The grant that NSF generously funded allows me and my undergraduate research group to work with two high school teachers and two high school students each summer, with an option for a 1- or 2-year experience. The program is now in its 3rd year, and thus far three high school chemistry/biology teachers (two opting for a 2-year experience) and eight junior or senior high school students (four opting for a 2-year experience) have done full-time research in my lab. This summer, in addition to the high school students and teachers that will be working in my lab, others will be working in the labs of two of my colleagues. I have tried to work with a mix of students, some of whom had a great lab science background and simply needed more experience than they could get in school, and some of whom have had almost no lab science background and wanted to be introduced to experimentation. Although it is difficult to measure success, of the seniors that have graduated, all have gone to college with at least an interest in the sciences.

I am a biophysical chemist interested in, among other things, regulation of ionotropic glutamate receptors (iGluRs) from a structural perspective. One of the things I strive to do is to give my students the background necessary to be involved in my research in a meaningful way. What has worked the best for me is to relate the research to what high school students know from their introductory science classes. In this respect, having both high school students and their teachers in my group has been a significant advantage. For example, in discussing secondary and tertiary structures of proteins, a discussion of hydrogen bonding and ΔG rings a familiar bell.

During this full-time summer research experience, days start off with a group meeting to refocus on overall project goals, the results of yesterday's experiments, and the next step. We then move into the lab where I help the students and teachers accomplish the day's goals. The projects I've found that work the best are self-contained ones. For example, a student or teacher might clone tryptophan to phenylalanine mutants of one of the iGluR family members, overexpress the resultant mutant proteins, purify them, and characterize their binding. In this way, they are part of what some of the undergraduates in the lab are working on, but they can also take ownership of their own piece of the story.

During the course of the summer, I also organize many community building activities so the high school group feels integrated into my undergraduate group. Past activities have included hiking, mountain climbing/camping, weekly softball games, weekly Friday lunches out, professional baseball games, and white water rafting trips. At the end of the summer, some of the high school students and teachers have opted to make posters of their research to hang in the science classroom at their high school, others have worked on a poster to present at an on-campus fall undergraduate research symposium, and others have co-authored a poster at a regional fall American Chemical Society meeting.

Although I have fully enjoyed this interaction with the high school students and teachers with whom I have worked, there have been some benefits I had not envisioned when starting this project. These benefits seem to go hand in hand with the enthusiasm of the teacher with

The Gentile Group whitewater rafting during the summer.

The Gentile Group outside of Gottwald Center for the Sciences, University of Richmond.

whom I have been working. For example, some teachers have employed undergraduates in my research group as tutors for students struggling in their high school chemistry classes. This year, one of the undergraduates in my research lab, who will be working with Teach for America next year, is spending two afternoons a week helping one of the high school teachers. She is working in the high school with lab safety (revising and editing current protocols), lab equipment (demonstrating proper techniques and usages), general lab (the design of 2-3 new general chemistry labs), lab reports (helping students write each section of a lab report), and tutoring. This has been a really nice example of a win-win situation that has come from the partnership I have with this high school teacher. Not only does the teacher get some assistance, but the student, not particularly interested in lab research, gains experience that will help her in the future. Also this year, one of the teachers that participated in the program is talking with local/regional faculty that we bring in for our weekly departmental seminar series. In this way she is able to disseminate information about the faculty's research to interested high school students. Additionally, this year a high school junior whose teacher worked in my laboratory is spending Friday afternoons in my lab working on projects with three of my undergraduates. She will be in the lab full time this summer.

Although there are many benefits to a program such as this, it does require a significant amount of resources. For example, the program takes up most of my time during the summer because I have to train the students and teachers (in an undergraduate lab there are no postdoctoral fellows or graduate students to do the training). I also need extra lab space to appropriately house the high school students and teachers (this can be a challenge especially at primarily undergraduate schools where research lab space may be limited). And finally, in order for the program to work, I need to find high school teachers willing to give up a majority of their summer break to participate in a full-time research experience.

Vicarious Science: *Managing a Grant Portfolio at the National Institutes of Health*

BY TRACY L. RANKIN

During my 1st day as a program officer for the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), I thought I was going to suffocate from the silence. Unlike the lab environment, where there was always a conversation going on, some centrifuge running, or freezer humming, this office was deadly quiet. "Holy smokes," I thought, "I'm going to need a white-noise machine just to get through the day…and lots of caffeine."

That was 6 years ago, and I never did get that white noise machine. And I have managed to keep it to de-caffeinated coffee. I did adapt to the serene office environment, and I am now so busy on a day-to-day basis that I rarely notice how quiet my surroundings are. In fact, there are days when I actually relish the silence. When I was active in the lab, I had no idea what would keep a person occupied within the confines of an office. Now I know.

I manage a portfolio of grants within the Reproductive Sciences Branch of the NICHD. All the grant applications that have anything to do with male reproductive health are generally assigned to my oversight. In essence, I work for the American taxpayer and ensure research dollars are spent for the furtherance of public health—in my particular case for the advancement of basic and clinical science aimed at alleviating male reproductive diseases and disorders. On a practical basis, this means shepherding applications (and applicants) through the grants submission process, interpreting review critiques for the applicants, advising applicants on revisions, and monitoring progress on funded applications. I currently have about 100 or so active research grants in my portfolio, as well as the grants for the Specialized Cooperative Centers Program in Infertility and Reproduction program (SCCPIR). They represent about $40 million dollars in research funding. Each submission round, I am usually assigned between 30 and 40 new and revised applications that I am responsible for tracking through the review process and post-review funding or resubmission. I spend my days primarily on e-mail and on the phone, advising prospective applicants on constructing their grant application, the specifics of the submission process, how to address reviewer's comments, and informing them of funding decisions with respect to their applications. Additionally, I participate in trans-

Rankin

Tracy L. Rankin joined the Reproductive Sciences Branch (RSB) of the Eunice Kennedy Shriver National Institute of Child Health and Human Development in the fall of 2001, and serves as the Director for the Male Reproductive Health Program. She received her undergraduate degree in Biology from the University of Virginia and her Ph.D. in Cell Biology from Vanderbilt University. Rankin held post-doctoral positions at Tufts University, the Worcester Foundation for Biomedical Research, and at the NIH before joining the RSB. Her research background includes epididymal sperm maturation, spermatogenesis, fertilization, and the structure and function of the mammalian zona pellucida.

National Institutes of Health (NIH) committees tasked with developing or implementing new grants policy or programs.

But that's just the "nuts and bolts" of the job. The fun part is having the bird's eye view of the science and being able to develop new initiatives to address areas of science that are under-represented or need a stimulus within my research portfolio. I also get to interact with some of the brightest people in the country and am privy to new developments well before they hit the press. My greatest job satisfaction comes from helping young people get their start, watching them successfully navigate through their first grant submission, and sharing in their excitement when they get that first grant. It is almost like a teacher/student relationship.

So, how did I end up here from a "traditional" Ph.D. experience? Well, it basically came down to a physics problem: two people on different career paths unable to successfully occupy the same space, also known as the "two-career" problem. When it came time to apply for jobs, I kept an open mind and didn't discount any possibilities. I focused on academic appointments but didn't exclude applying for so-called "alternative" opportunities. My Ph.D. mentor brought the program job at the NICHD to my attention during one of our phone conversations. She suggested it might be a very good fit for my abilities and background, given that the job was in reproductive sciences and therefore reflected my scientific expertise. So, I sent in an application, all the while continuing to apply and interview for assistant professorships across the country.

I got offers—and they were in good places with lots of potential. However, they weren't in cities that would afford good career choices for my spouse, who was in another profession and optimally needed to stay on the East Coast. Just as I was about to despair, I received the call from NICHD for an interview. When the job was offered, I faced that fork in the road. I knew it would be nearly impossible to return to an academic track after leaving that environment. I no longer would be in the trenches of the scientific process. But despite the fact that "doing" science was what attracted me to the profession, I had to consider quality of life issues. Moving away from a large East Coast city would translate into long overseas trips for my spouse while I stayed and cared for our young son and simultaneously tried to get a research program up and running. I was confident in my abilities, but in the end, the cost-benefit analysis didn't make sense on a family level. So, here I am—I came to the fork in the road and I took it.

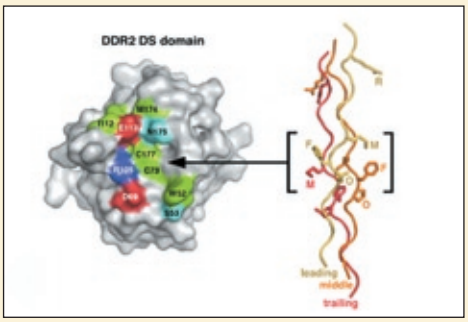
> **"I faced that fork in the road. I knew it would be nearly impossible to return to an academic track after leaving that environment."**

One of the more difficult aspects of the transition from bench to office (aside from the aforementioned quiet) was moving from being an expert on one particular aspect of reproductive science to having to be knowledgeable in very many aspects. I liken it to going from considering the stomata on the leaf on the tree to considering the entire rainforest. I not only had to maintain my working knowledge of the molecular mechanisms of fertilization but also get up to speed on hormone-replacement therapy in men and the conduct and monitoring of clinical research—areas way outside my comfort zone. In one sense, it is very exciting—I'm never at a loss for conversation at cocktail parties—but in another sense it is very frustrating, because I miss having the time to really dig in deep to a scientific problem and consider experiments to solve it. But 6 years into my position, I've reconciled with this issue. I really enjoy what I do, and I take great pride in seeing my portfolio expand and the science move forward. Is every day fun? Well, of course not. I work in a very large, sometimes unwieldy, bureaucracy. There are a lot of policies and regulations to enforce, and sometimes the problem-solving process is not intuitive. But the system does work—sometimes not in a linear fashion and sometimes not quickly, but research dollars do get to our brightest scientists and progress does ensue. We see it every week in the scientific journals. And I, along with my colleagues here at the NIH and other funding agencies, am a big part of it—helping to grease the wheels and keep the engine running.

So, while I may now hold a pen instead of a pipetman, I'm still a scientist—putting that Ph.D. to good work. In my office. Quietly.

Collagen's "Disco" Domain

The two discoidin domain receptors (DDR1 and DDR2) are unique members of the receptor tyrosine kinase family in that they are activated by collagen and not small diffusible proteins. In this *JBC* paper, the authors define for the first time collagen-binding sequence motifs that recognize DDR2. Their comprehensive analysis of collagen II revealed three high affinity binding sites, each of which contains a GFO triplet (O is hydroxyproline). The motif that bound with highest affinity was also conserved on collagens I and III and interestingly overlapped with collagen III-binding site for von Willebrand factor. Using truncated peptides and alanine substitutions, Konitsiotis and colleagues found that the minimal binding sequence for this motif was GVMGFO, with the critical Met and Phe residues properly positioned in close proximity in the triple helical collagen structure. These peptides were sufficient to activate DDR2 signaling, indicating that DDR2 activation does not require the presence of higher order fibrillar collagen.



Molecular structures of the DDR2 collagen-binding DS domain and corresponding collagen II-binding site.

Characterization of High Affinity Binding Motifs for the Discoidin Domain Receptor DDR2 in Collagen

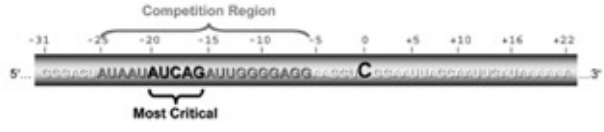
Antonios D. Konitsiotis, Nicolas Raynal, Dominique Bihan, Erhard Hohenester, Richard W. Farndale, and Birgit Leitinger

J. Biol. Chem. 2008 **283**, 6861–6868

jbc

Sharing Your Editor

Post-transcriptional cytosine-to-uracil editing is required for the proper processing of plant organellar RNA. In this paper the authors apply *in vitro* RNA editing in maize extracts to provide the first robust data for trans-factor sharing in a plant other than tobacco, demonstrating that transcripts encompassing two editing sites, ZM-rpoB C467 and ZMrps14 C80, can compete for



Sequence of maize RNA transcript rpoB highlighting the competitive trans-factor binding region upstream of the C467-editing site.

editing activity despite limited sequence similarity. The element they compete for is a single five-nucleotide sequence spanning the region from –20 to –16 relative to the edited C; this region also overlaps a 5' *cis*-element required for editing efficiency. These results indicate that the RNA sequences mediating both editing efficiency and cross-competition are highly similar and that a common trans-factor protein is involved in their editing. Such trans-factor sharing likely facilitates the editing of the large number of different C targets present in plant organelles (30–40 in chloroplasts and over 400 in mitochondria).

Cross-competition in Editing of Chloroplast RNA Transcripts *in Vitro Implicates Sharing of Trans-factors between Different C Targets*

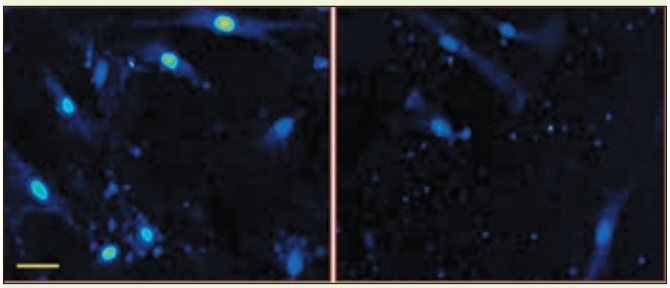
Wade P. Heller, Michael L. Hayes, and Maureen R. Hanson

J. Biol. Chem. 2008 **283**, 7314–7319

jbc

Regulating Cell Death

The sphingolipid ceramide is found in the lipid bilayer of cells, where for years it was thought to serve a purely structural role. However, it is now known that the lipid can also be released from the cell membrane to act as an important second messenger that stimulates apoptosis and growth arrest. In this *JLR* paper, the authors investigated whether or not ceramide exerts its effects on growth by regulating the transport of proteins into and out of the nucleus. They discovered that adding ceramide to smooth muscle cells inhibited the import of proteins into the nucleus via a pathway involving the activation of cytosolic p38 mitogen-activated protein kinase (MAPK). The authors also found that adding ceramide to the cells reduced cell counts and decreased markers of cellular proliferation. However, by adding a p38 MAPK inhibitor they were able to reverse the inhibitory actions of ceramide. Together, these data demonstrate, for the first time, the sphingolipid regulation of nuclear import that defines and expands the adaptive capacity of the nucleocytoplasmic transport machinery.



Treating vascular smooth muscle cells with ceramide causes a decrease in nuclear import.

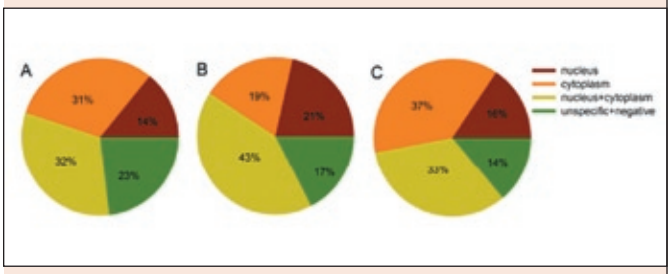
Ceramide Regulation of Nuclear Protein Import

Randolph S. Faustino, Paul Cheung, Melanie N. Richard, Elena Dibrov, Annette L. Kneesch, Justin F. Deniset, Mirna N. Chahine, Kaitlin Lee, David Blackwood, and Grant N. Pierce

J Lipid Res. 2008 **49**, 654-662

Subcellular Protein Localization

Knowing the specific locations of proteins in cells can provide important insights into their function as well as the functions of other proteins with which they interact. One way to determine a protein's location is to tag it with a specific antibody, then add a probe that specifically binds to the antibody, and use a microscope to establish the location of the probe in the cell. The authors of this *MCP* paper used this technique to determine the locations of 466 proteins in three human cell lines. They generated approximately 3000 images and were able to determine the subcellular locations of more than 80% of the proteins they looked at. This is the first large scale antibody-based study to localize proteins into subcellular compartments using antibodies and confocal microscopy, and the results suggest that this approach might be a valuable tool in conjunction with predictive models for protein localization.



Distribution of proteins for the three cell lines analyzed.

Toward a Confocal Subcellular Atlas of the Human Proteome

Laurent Barbe, Emma Lundberg, Per Oksvold, Anna Stenius, Erland Lewin, Erik Björling, Anna Asplund, Fredrik Ponten, Hjalmar Brismar, Mathias Uhlen, and Helene Andersson-Svahn

Mol. Cell. Proteomics 2008 **7**, 499-508

Solomon Snyder: Second Messengers and Signaling Cascades in the Brain

BY NICK ZAGORSKI

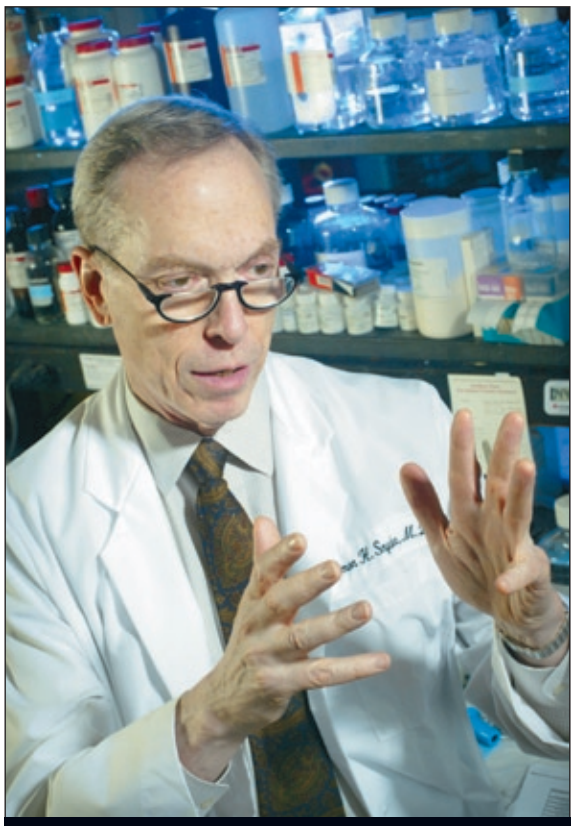
The Solomon H. Snyder Department of Neuroscience at Johns Hopkins may bear his name, but to refer to Dr. Snyder simply as a neuroscientist is akin to calling the brain a massive tangle of nerves inside our skull. To even call him a "scientist" may be misleading; Snyder is a bit of a Renaissance man, equal parts musical virtuoso, analytical genius, and insightful philosopher.

With the aid of these qualities (even the music as you will see below), Snyder has conducted nearly a half-century of research that includes breakthroughs into how nerve signals get transmitted, the mechanisms underlying narcotic action, and the surprising role of gaseous second messengers. His studies have reshaped how we look at chemical signaling in the brain and elsewhere as well as provided invaluable information for the development of new pharmaceuticals.

As is his nature, Snyder puts a more humble spin on things. "I never thought of myself as a scientist," he says, "I'm just a psychiatrist who happens to do some research."

Just One of the Guys

Because individuals are, in part, a product of their genes, then Snyder, born the second of five children in Washington, D.C., the day after Christmas 1938, had the genetic makeup to succeed in science. His father, one of the first employees of the National Security Agency (NSA), helped direct the U.S. code-breaking efforts during World War II and subsequently transitioned to one of the earliest computer programmers; his mother was a decided entrepreneur who made a tidy sum winning radio contests and delving into the post-war housing boom. That combination of analytical insight and free-spirited creativity, Snyder says, has undoubtedly served him well.



Snyder

Not that young Snyder planned a career in science–far from it, in fact. He grew up digesting philosophy books and expressing his creative side through music. On his 9th birthday, he received a mandolin from his grandfather, a gift that introduced him to the melodies of stringed instruments, and a few years later he took up classical guitar, which particularly and immediately enamored him. He was soon playing public recitals to great acclaim; by the time high school graduation and that first "big decision" neared, Snyder seriously considered becoming a professional musician.

However, the "security conscious" aura that permeated the 1950s–steady, well paying jobs and a good family life were the norm–as well as the desire to be "just like the other guys" steered Snyder to a more conventional path. "And being, as my mother said, "A nice Jewish boy," I followed a lot of my friends who wanted to become doctors." So, Snyder proceeded to enter nearby Georgetown College in 1955 and Georgetown Medical School 3 years later (he actually enrolled in medical school without completing his undergraduate studies, as was allowed back then). "I decided early on that I would choose psychiatry as

my field," he says. "It was definitely a fuzzy kind of thinking, but I believed psychiatry was the closest match to being a philosopher."

The Road to Independence

Snyder continued playing guitar while in college, and also helped out at his guitar instructor's music store on weekends. On one such Saturday, a young man came in asking about lessons. He balked upon hearing the rates, at which point Snyder offered to personally teach him for a lower rate. The two became fast friends, and Snyder learned that his student, Donald Brown, was fulfilling his military obligation as a research associate at the NIH (specifically National Institute of Mental Health (NIMH)). This same Donald Brown would later gain scientific fame for uncovering ribosomal gene amplification in *Xenopus* frog eggs and eventually becoming the father of molecular embryology.

"Right before I was ready to begin medical school, Brown told me he needed a technician in his lab that summer and inquired whether I might be interested," recalls Snyder. "And though I still had no real interest in lab work, I thought it might be fun to learn about some of the science behind medicine." It would also be a nice change of pace from Snyder's previous summer internships–arranged by his father–programming computers at the NSA, so he readily agreed.

Brown's research objective involved detailing the metabolism of the essential amino acid histidine. "The rationale behind this work in a mental health lab was that Brown's lab director, Seymour Kety, was fascinated by the presence of abnormal amino acid metabolites in schizophrenics," Snyder says, "so each research associate had to pick his favorite amino acid and thoroughly study it." Much of Snyder's first summer of research thus entailed passing urine through affinity columns to fractionate different metabolites, and it involved a lot of staring as the fractions *slooowly* dropped into test tubes.

Still, Snyder had a great experience; "I absolutely loved it and was eager to come back." He would get a bit of a surprise his second summer, however, as Brown had finished his military obligation and departed for France to train with the renowned Jacques Monod. "Brown had discovered a new metabolic pathway wherein histidine was converted to glutamic acid," says Snyder. "First, an enzyme called histidase pulls off the amino group, creating urocanic acid, which then gets converted to glutamic acid through an unstable intermediate known as imidazolone propionic acid. Before leaving for Paris, Brown laid out a research strategy and importuned, "You, Sol Snyder, will identify, characterize, and purify this intermediate."

The project was laborious, encompassing two summers and some elective time during the school year, and included many false starts and dead ends, but with the help of colleagues in nearby labs–who also happened to be his guitar students–Snyder managed to uncover the enzyme catalyzing this key intermediate step: imidazolone propionic acid hydrolase. Then, with a trusty typewriter and a whole bunch of carbon copies, he wrote up the paper detailing his results all by himself. "And that paper was accepted, with no revisions, in the *JBC*. That's still one of my proudest moments."

Although he caught the research bug, Snyder still envisioned becoming a psychiatrist upon graduating from medical school.

Avoiding One War…

Although he caught the research bug, Snyder still envisioned becoming a psychiatrist upon graduating from medical school. His first order of business, though, was "dodging" the doctor draft. "In those days the military was grabbing up every male medical student for service in Korea or other less-than-ideal locales," he explains. One of the more favorable alternatives entailed joining the NIH for a 2-year military appointment as a physician-scientist, just as Donald Brown had done. Snyder hoped to pursue that option, as it would also count toward his psychiatry residency, but discovered that all the Research Associate positions were filled, as they were allocated by a match program.

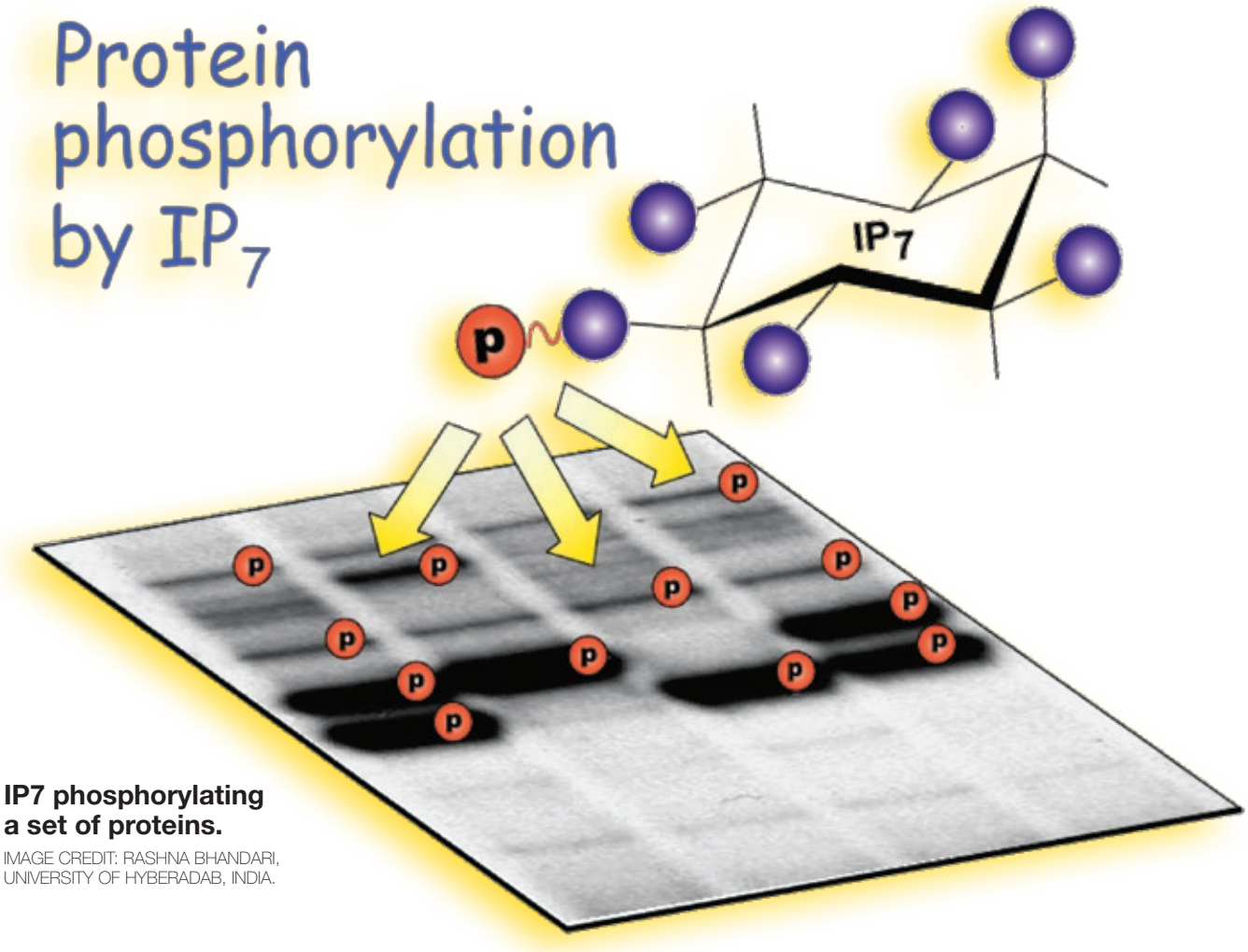
"But then I found hope with Julius Axelrod, whose lab was literally right across the hall from where I had been

working," says Snyder. It turned out that Axelrod's match had just cancelled, creating space. "When I asked him about joining he noted that every other applicant seemed to come from Harvard or Yale, but he knew me and thought that I would do okay." That fortunate cancellation turned out to be one of the most important events in Snyder's life, fittingly with another occurring right around the same time: his marriage to Elaine Borko one week after he graduated medical school.

Axelrod, renowned for his studies on the physiology of the catecholamine hormones epinephrine, norepineprhine, and dopamine, liked to tailor his mentee's projects to their strengths and thus suggested Snyder begin by examining the uptake of the neurotransmitter histamine, a histidine derivative. Later, he switched over to a more exciting area of research with the pineal gland and its hormones melatonin and serotonin. Snyder developed a sensitive technique to assay serotonin in rat pineal glands by fluorescent techniques, which he used to characterize the diurnal rhythm of serotonin production and its contribution to the biological clock.

The 2 years Snyder spent with Axelrod were an amazing experience and definitively gave Snyder the "research bug" (although he still hoped to continue his clinical studies). But in 1965, it was time to move on; and since Snyder and his wife were experiencing their own biological clock activity and hoping to start a family, hopefully he could find a position paying better than the (back then) usual "starvation wage" for a hospital resident. Initially, Snyder had a verbal agreement for a well paying research residency at Stanford's psychiatry department, but it unfortunately fell through at the last minute. He did receive an offer from Johns Hopkins, although only for a conventional (and low paying) residency position.

With Axelrod's assistance, Snyder managed to secure an interview with Case Western Reserve in Cleveland and, having impressed them, received a generous offer to become an assistant professor of pharmacology and run a lab part-time while concurrently completing his psychiatry residency. "And I was all set to go, but when I called Hopkins to decline, Joel Elkes, head of psychiatry, told me he knew about my offer and was prepared to



IP7 phosphorylating a set of proteins.

IMAGE CREDIT: RASHNA BHANDARI, UNIVERSITY OF HYBERADAB, INDIA.

counter." Snyder would spend his 1st year as a psychiatry resident, and then get promoted to assistant professor of pharmacology full-time. So, on July 1, 1965, Snyder arrived in Baltimore.

…Tackling Another

"The first directive I set for myself when I started my lab at Hopkins was to do something different from my research associate projects," Snyder says. "Partially, I did not want to compete with Julie, who had been such an inspiration to me, but I also realized if I just continued with his NIH work, then no matter what I discovered I wouldn't feel I 'discovered' anything." Snyder therefore moved away from the pineal gland and into the stomach.

At the NIH, Snyder worked on an independent project demonstrating that increased gastric acidity resulted from an increased production of histidine decarboxylase, the histamine-synthesizing enzyme. "And in those days before molecular biology, inducible enzymes, which express in specific situations and have short half-lives, were an exciting topic," he says, "so I decided to look at the dynamics of histidine decarboxylase in the stomach." His efforts revealed that histamine was the key mediator of stomach acid release, and not the hormone gastrin as believed previously. Together with his first post-doc, Diane Russell, he uncovered another mystery of amine metabolism, demonstrating that ornithine decarboxylase experienced tremendous turnover in regenerating liver. In addition to clocking in the most rapidly inducible enzyme at that time (the half-life was only 10 minutes), this study was crucial in establishing the role of the polyamine ornithine metabolites in tissue growth and cancer.

Unfortunately, the field of polyamine metabolism never really caught fire, so Snyder began branching out to catecholamines. He and student Joe Coyle stumbled on a method to identify catecholamine transporters in reconstituted nerve endings, or synaptosomes, a technique that enabled his lab to begin years of fruitful research thoroughly quantifying the uptake of catecholamine hormones and drugs that mimicked their actions, like the then-popular amphetamines.

Unfortunately, the field of polyamine metabolism never really caught fire, so Snyder began branching out to catecholamines.

By 1970, however, another narcotic–heroin–was emerging as the drug of choice. Its alarming rise prompted President Nixon to declare "War on Heroin" and appoint a Drug Czar with the authority to dispense billions of dollars to help fight this war. "Nixon's appointee happened to be my old friend Jerry Jaffe, a psychiatry professor at the University of Chicago," Snyder says, "and he called me for advice. I let him know it would be great if he could divert some of that money to basic drug research and not just use it all looking for better ways to detect drugs at the airport." He and Arnie Mandell, psychiatry head at the University of California San Diego (UCSD), then hatched an idea to create national Drug Abuse Research Centers. "And, wouldn't you know it," notes Snyder, "Hopkins and UCSD were among the first recipients."

Receptors Revealed

In writing up his NIH Drug Center application, Snyder drew up some ideas for more catecholamine studies, with which he was familiar, but also put in a novel proposal to find out how opiate drugs like heroin act. "Pharmacologists studying opiates would feed drugs to animals then analyze their liver or brain for chemical changes," he says. "Okay, so heroin activates glucose oxidase...great, who cares. That doesn't explain their mechanism of action." Some of the literature speculated that opiates dissolve through cell membranes, but because some opiate drugs worked at unbelievably low doses, Snyder believed the drugs operated through receptors.

Receptor biology was still a new science in those days, and only a handful had actually been identified. Fortunately, Snyder's lab was adjacent to Pedro Cuatrecasas, who had just come to Hopkins from NIH, where he identified the insulin receptor by mixing radioactive insulin with cells and using a powerful vacuum-linked filter to flush out nonspecific binding. And one day, Snyder perused through the latest issue of *Science* and saw a paper titled "Nerve Growth Factor Sequence Resembles Proinsulin." The gears in his head began turning, and he went next door to discuss strategy.

After learning the basics of the vacuum manifold, Snyder and post-doc Shailesh Banerjee successfully identified nerve growth factor receptors in nerve cells. With the proof of principle in place, Snyder splurged for

some radioactive naloxone (an opiate antagonist used to treat heroin overdose) and in 1973, along with graduate student Candace Pert, discovered the opiate receptor.

Soon, Snyder's lab had turned their vacuum binding assays into a technical art form and could run hundreds of samples a day. Over the next several years the floodgates opened, and Snyder helped identify and characterize enkephalins, the natural ligands for opiate receptors, as well as the receptors for other neurotransmitters such as glycine, γ-aminobutyric acid, acetylcholine, serotonin, and dopamine… to name just a few.

In 1978, Snyder won the prestigious Albert Lasker Award for his groundbreaking receptor studies, and followed that up with election to the American Academy of Arts & Sciences in 1979 and the National Academy of Sciences in 1980. His rising stardom certainly did not go unnoticed, and in 1980 Joshua Lederberg, the newly appointed president of Rockefeller University in New York, began an aggressive wooing of Snyder. "It was a great offer, and I was all ready to leave," he says. "But just like before, Hopkins came back with an extraordinary counter-offer to initiate a department of neuroscience." The department began modestly, a three man affair with Snyder, former student Joe Coyle, and colleague Mike Kuhar. Before long, however, it became the largest basic science department at Johns Hopkins.

Out of Focus: Side Effects May Vary

Although institutes strive to bring top researchers within their halls, they shouldn't overlook other critical positions like, say, patent lawyers. Among his early work with NOS enzymes, Snyder discovered that, in addition to the brain, nNOS was highly localized in penile nerves. Collaborating with Hopkins urologist Arthur Burnett, Snyder demonstrated NOS inhibitors could abolish penile erection, a high impact study that appeared in *Science*. "Well, Pfizer had been working on sildenafil, an artery-relaxing drug to treat angina," says Snyder. This drug inhibited phosphodiesterase-5, which would elevate cyclic GMP and relax smooth muscle. Unfortunately, the clinical trials were a bust and even elicited unwanted erections as a side effect. "So, Pfizer buried the project, that is until they read our paper and decided to retry it for erectile dysfunction." Years later, Snyder could only sit and chuckle during the press conference launching Viagra. "Hopkins had naturally filed for patent protection after our discovery, but forgot to mention cyclic GMP.

It's a Gas

As the 1980s wound to a close, Snyder was ready for a new challenge. "I read a magnificent *Nature* paper by Salvador Moncada identifying nitric oxide (NO) as responsible for relaxing smooth muscle," he says, "and I quickly recalled another paper that suggested NO formation in the brain." In smooth muscle, NO stimulated guanylyl cyclase to form cGMP; cGMP was also especially prominent in the cerebellum, where it was stimulated by the neurotransmitter glutamate. This raised the tantalizing possibility that one of the brain's most important chemicals acted through a gaseous intermediate.

Snyder discussed his idea with his student David Bredt –"one of the smartest kids I ever had"–and they decided to uncover NO's biological role in the brain. One initial hurdle was how to measure the production of a colorless, odorless gas. "But we knew NO was synthesized from the amino acid arginine, and David realized that when a nitrogen was extracted from arginine to make NO, the resulting product was citrulline, which was less positively charged." Bredt designed a tiny ion exchange column and filled it with brain extracts; in response to glutamate, citrulline production rose instantly and fell off the column.

The next step was to purify the NO-synthesizing enzyme (NOS), which many other groups had failed to do. Once again, Bredt displayed his keen insight and reasoned that previous purification attempts might have been dissociating a required cofactor. Based on hints in the literature implicating calcium might be involved in NO synthesis, Bredt added calmodulin to his purified extracts and restored enzyme activity to one of his tubes.

"And then it made perfect sense," says Snyder. "Because NO is a gas, it can't be stored in vesicles, so each nerve impulse would have to generate fresh amounts and thus require a dynamic enzyme. And glutamate receptors are ion channels; when they turn on, calcium flows into the nerve cell, activating calmodulin and NOS." In short order Bredt purified NOS from brain extracts, and cloned its gene, which led to the discovery that there were in fact three separate isoforms of NOS: a neuronal form, an endothelial form, and an inducible form.

Not much later, Snyder's lab showed that NO may be unusual as a neurotransmitter, but it is not unique. Carbon monoxide (CO) is also formed in tissues, a by-product of heme oxygenase (HO), which degrades the heme groups in aging red blood cells. But in addition to high amounts of HO in the spleen, another isoform of HO is concentrated in the brain. His student Ajay Verma showed that this neuronal HO localizes to similar regions in the brain as neuronal NOS and can also activate guanylyl cyclase through CO, suggesting these two gases might act as co-transmitters. As an added bonus, the other product formed by HO's breakdown of heme, bilirubin,

acts as an antioxidant to protect neurons from stress.

Discovering the antioxidant properties of bilirubin spurred Snyder into yet another new direction examining signaling systems involved in protecting or killing cells. One candidate that intrigued him right away was the glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase (GAPDH); studies had reported that anti-sense RNA, which inhibited GAPDH expression, could block neurotoxicity induced by drugs. "This seemed odd, because GAPDH makes up about 1% of a cell's protein content and anti-sense RNA would only marginally dent its production." Snyder and his post-doc Akira Sawa ran their own anti-sense tests and noticed that in the presence of toxic drugs a small percentage of GAPDH translocated to the nucleus, and antisense prevented this nuclear translocation.

But because GAPDH lacks a nuclear localization signal, it shouldn't be able to enter the nucleus in the first place. "And here, our old friend inducible NOS comes into play," Snyder says. "Just like a heat shock protein, iNOS turns on in response to stress, such as the massive glutamate release that occurs during a stroke, and nitrosylates (adds an NO group to cysteine) GAPDH." The nitrosylation removed GAPDH's catalytic activity but allowed it to bind to a protein called Siah, which transports it to the nucleus. Once inside the nucleus, GAPDH then activates p300, which in turn activates p53, the well known tumor suppressor that can kill cells.

The Secret of His Success

A popular question for those discussing Sol Snyder is: How does he do it? This can refer to his ability to continually produce diverse, exciting research findings while simultaneously conducting his departmental affairs, working on journal editorial boards, consulting for biotech companies, performing community service, and being a doting grandfather. His service includes being on the boards of both Hopkins' Peabody Conservatory and the Baltimore Symphony Orchestra, allowing him to continue to share his passion of music with the community (and he still does strum those guitar strings when time permits).

Snyder and mentor Julius Axelrod during the ceremony for Snyder's Bristol-Myers Squibb Award for Distinguished Achievement in Neuroscience Research in 1996.

Although Snyder isn't quite sure how he accomplishes all that–he insists he has a hard time multitasking–he can address a second aspect to "How does he do it?" Namely, how he has managed to create such a diverse and ever-evolving research portfolio. For example, fresh off his NO and CO work, Snyder has ventured into new types of atypical signaling molecules like unnatural "D" isomers of amino acids and higher order inositol phosphates (IP) such as IP7 and IP8 (inositol only has six oxygens, too, so these are molecules where phosphates have phosphates on them).

"I've always kept an open mind about work," he says, "and never resigned myself to one area simply because I was familiar with it. That was a mantra I learned from Julius; explore the science you find fun. Back in the day, I would just leaf through journal contents–*JBC* was always my favorite–and if something caught my eye and I understood at least a few words in the abstract, I would consider following up on it. I still do it today, although I scan the table of contents on my computer instead."

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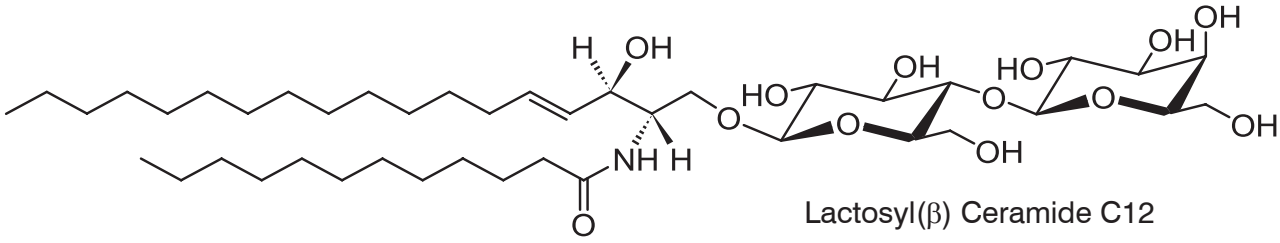

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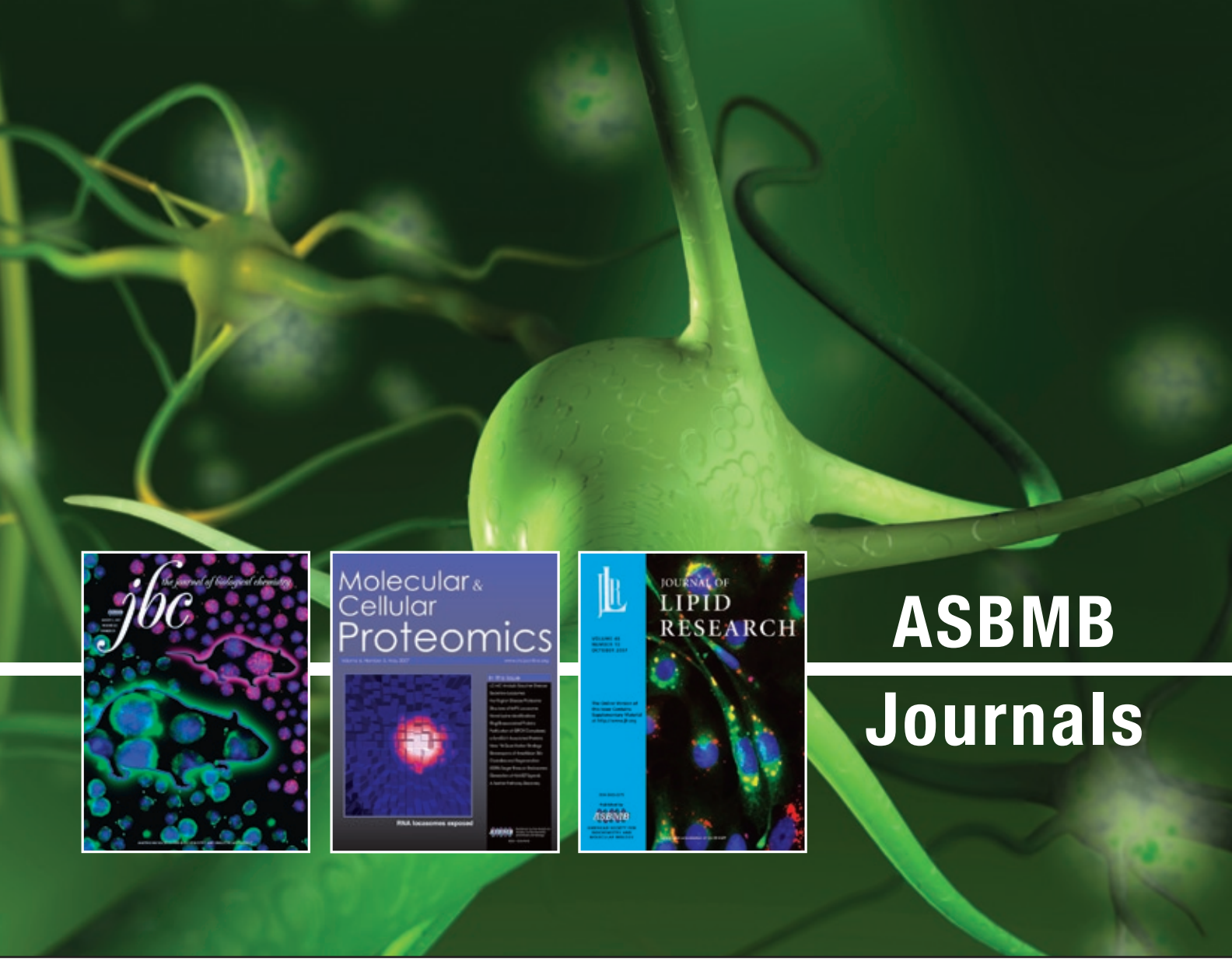

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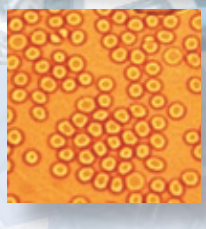
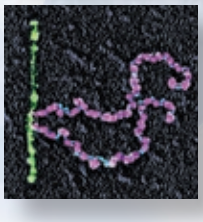
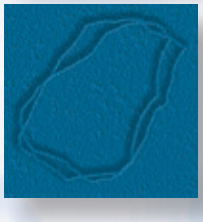
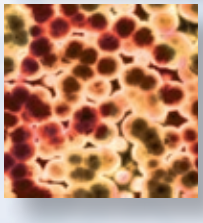
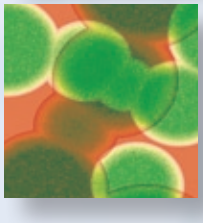
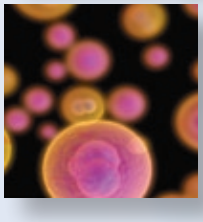
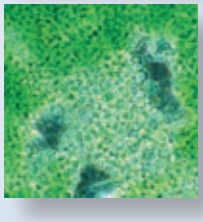
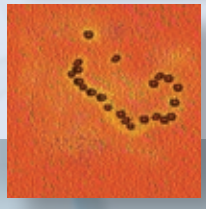


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