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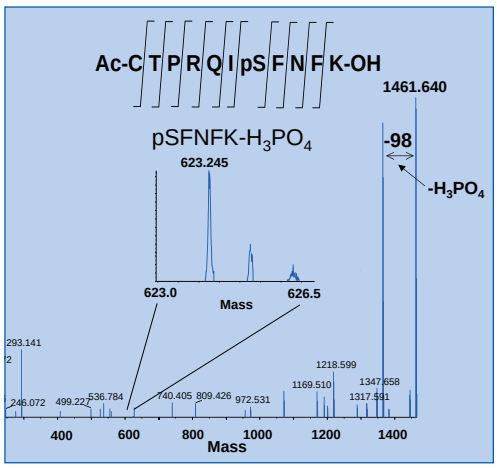

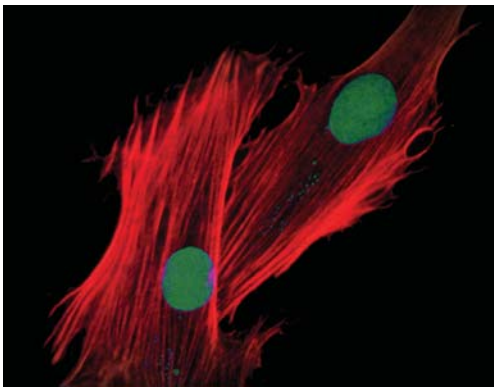

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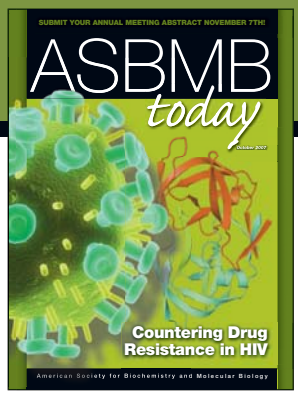

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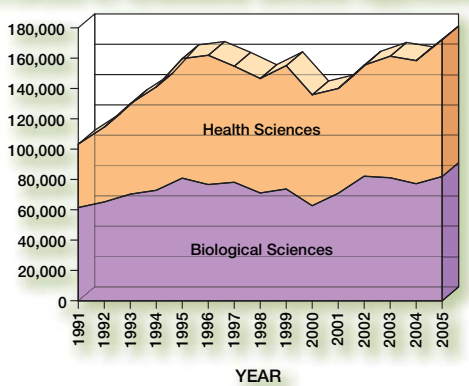

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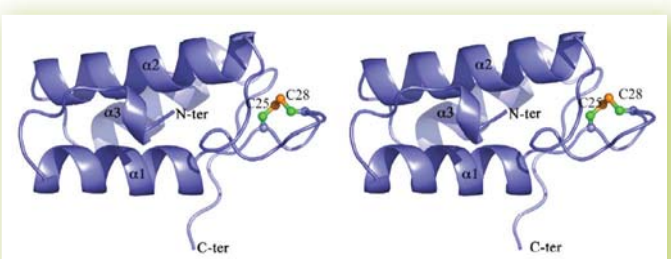

Assembling Cytochrome C. 26

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letters *to editor*

Assessing What Students Learn

To the Editor:

In the July 2007 issue of *ASBMB Today,* J. Ellis Bell calls our attention to assessment in Biochemistry and Molecular Biology (BMB) education. Bell emphasizes the inexistence of assessments that both capture and contribute to the coherence of entire BMB training programs and states that their design requires *creative thinking*.

I would like to suggest rigorous research as the basis for such creativity. In particular, rigorous research on assessments that are already in use worldwide. Extensive literature is available on, for example, how to determine the reliability and validity of assessments—how well assessments fulfill their objectives. The application of such knowledge would lead to a framework on which research could be developed. The publication of evidence-based practices in assessment design on BMB education will benefit both current faculty and BMB scientists.

Assessment is known to drive learning. Nourishing research on assessment in education has had positive impacts on education in other fields, notably in medical education. However, this has yet to happen in BMB. Despite the nearly infinite numbers of tests or the huge numbers of students that have been graded around the world, research on assessment is very scarce. More participation in research on assessment design is needed.

Like any other research enterprise, assessment research requires time and resources. Perhaps ASBMB could consider stimulating and supporting such research. The application of the results would lead to higher quality of assessments, which would also drive the quality of courses and programs forward. It is my belief that research on assessment design will constitute a very important pathway to push forward the quality of BMB education around the world.

Manuel João Costa
Life and Health Sciences Research Institute (ICVS), School of Health Sciences
University of Minho, Braga, Portugal

Response:

In his response to my July article, Manuel João Costa makes a compelling argument for the investment of both time and resources directed towards the development of suitable assessment tools for biochemistry and molecular biology and suggests that such development should be based on existing and ongoing research into assessment. He is right. Several scientific disciplines, most notably physics, have developed "concept inventories" to assist in the assessment of student learning. While scientific societies can act to stimulate the development of such tools, the costs of their development are beyond what most scientific societies can spend. Societies such as ASBMB can certainly partner with the various funding agencies that are likely to benefit from better trained students such as the National Science Foundation (undergraduate and graduate education), the National Institutes of Health (M.D. and M.D.-Ph.D. education) or independent foundations such as the Howard Hughes Medical Institute. As indicated in earlier articles, ASBMB is actively involved in discussions that can help with the development of various "concept inventories" as well as assessment tools for the various "skills" that are critical to the education of our students.

J. Ellis Bell
Laboratory for Structural Biology, Biophysics and Bioinformatics
Department of Chemistry
University of Richmond

Peer Review—The Saga Continues…

BY HEIDI HAMM

When last we "talked" through this column, I told you about the efforts since last fall of the National Institutes of Health (NIH) to begin to review the peer review process for the first time in detail since the Integrated Review Groups (IRGs) were realigned and reorganized five or six years ago. One of the facets of that reorganization was a plan for on-going and regular review to insure that the IRG structure kept up with the evolution of modern life sciences research. I am pleased to report that there has been a fair amount of progress since my last column, and I wanted to take a few lines to acquaint you with that happy reality.

Peer Review Working Group

First, the Working Group on Peer Review, under the Advisory Committee to the NIH director, held its second informational meeting in Chicago early in September. This Working Group is co-chaired by ASBMB member Keith Yamamoto, University of California, San Francisco, and Lawrence Tabak, National Institute of Dental and Craniofacial Research, NIH. Public Affairs Advisory Committee Chair Mary Hendrix attended the meeting for ASBMB. She tells me that "this regional consultation meeting permitted an unprecedented forum for exchanging ideas that will ultimately lead to improvements in the NIH peer review system. The participants were passionate about sharing their concerns with the moderators and NIH officials in attendance. There were some excellent ideas offered by the participants, including the evaluation of individual peer reviewers."

One of the most interesting pieces of news from the meeting was that women scientists are doing very well now during the NIH grant review process and have achieved rough parity in terms of percentages of men and women getting funding. In recent years, as you can see from the bar graph below (provided by CSR staff), among the applicants with scores better than 10%, women do slightly better than men.

Two more Working Group meetings are planned for this fall—one on October 8 in New York, which ASBMB Public Affairs Officer Pete Farnham will attend, and one in San Francisco on October 25, which at least one of our local members will attend. If you care about peer review and would like the opportunity to provide some advice to CSR during this important review, it would be great if you could attend as well.

IRG Open Houses

CSR is also holding IRG Open Houses to collect input on how these groups are functioning since the reorganization, and the most recent was held at NIH on August 24. ASBMB member Norma Allewell, University of Maryland, attended for ASBMB and reports that it was a most interesting meeting. The meeting focused on 4 Initial Review Groups (representing about 20 study sections) within a "cluster NIH refers to as 'Integrated Biological I'":

- Basic and Integrative Physiology/ Technology and Bioengineering
- Molecular and Cellular Mechanisms (MCM)
- Pathogenesis and Translational Research
- Clinical

After opening remarks, the meeting split up into breakout groups, each focused on one of the IRGs above. Each group was led by a study section chair and a professional society representative who co-facilitated the group as two scientific review administrators

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.

recorded the discussion. Each group considered two questions:

1. What will be the most important questions and/or enabling technologies you see forthcoming within the science of your discipline in the next 10 years?
2. Is the science of your discipline, in its present state, appropriately evaluated within the current study section alignment? Suggestions?

Pete Farnham obtained a draft summary of the meeting. The MCM group thought that questions and enabling technologies to be expected in the next 10 years included:

- Integration of molecular and cellular information into systems biology and between scientific disciplines; developmental and integrative biology.
- *Regulatory Mechanisms*: Genomics; epigenetics; individualized information at the protein, gene, RNA level; role of regulatory RNAs; disease biomarkers, metabolomics, bioengineering as a tool to understand cellular/molecular level, how genes coordinate development of various organs/tissues.
- *Non-invasive, Real-time Measuring Tools in Living Cells/Organisms*: Biochemical events taking place within cells, dynamic structure of cells and tissues, cell-cell interaction, how cells interact with environment, how cells develop into tissues, structure-function measurements in real time, protein-protein interaction, non-invasive ways, computational biology. Micro RNAs.

Regarding Question 2, the group thought that 1) only funded investigators should be reviewers, 2) ad hoc reviewers should possess broad expertise and be taken from a pool of reviewers, 3) reviewers need to be reminded about review criteria, especially for the R21 mechanism. There was also discussion about the issue of reducing the length of applications. It was also thought that triaged applications should get scores and that there often appeared to be a discrepancy between CSR scores and those obtained in IC review.

Regarding study section alignment, organ- or disease-specific alignment is good for some disciplines, but this approach makes it harder for integrated applications studying phenomena across many organs and diseases to be reviewed appropriately. In addition, applications in some fields are distributed across too many study sections.

Some attention was also paid to reviewer recruitment issues. Ways to make life easier for reviewers were considered and included more use of video conferencing and a reduced workload. The issue was raised of mandatory service on study sections for funded investigators, but the consensus of the group was that incentives for service might be more effective. Better training was also needed, the group concluded.

These conclusions were strikingly similar to those of the three other breakout sessions as well. The final summary of the breakout group should now be up on the CSR Website at cms.csr.nih.gov/AboutCSR/ReportStorage/openhousereports.htm.

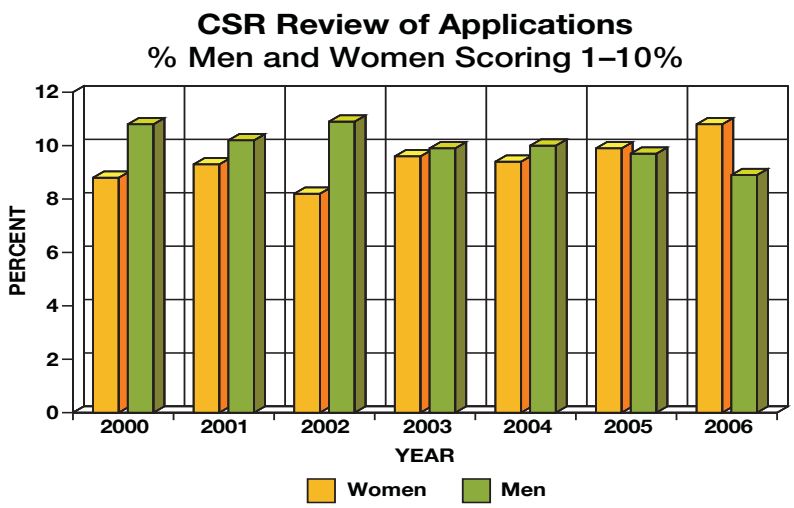
The conclusions will be presented to the NIH Peer Review Advisory Committee (PRAC) for its consideration before changes are implemented.

Recruiting Additional Reviewers

Finally, I'm pleased to note that CSR is now asking scientific societies to provide CSR with the names of possible volunteer reviewers to fill out vacancies in study sections. You'll recall that ASBMB provided CSR with a list of more than 700 names in the spring of 2006 before CSR ever asked for such assistance from the scientific community. Now a wide range of other societies are being asked to provide names, and we have heard from CSR that our list was in fact useful and a number of "great reviewers "were identified.

Of course, if you are interested and willing to serve on study section, it would be great if you let us know and we can submit your name as a possible reviewer. Service on study sections is one of those irksome tasks that no one wants to perform but that must be done by all of us at some point to ensure the continued functioning of the peer review system, which incoming President Greg Petsko, Brandies University, refers to as one of the "jewels of American science."

As always, we appreciate your comments about these columns. Please feel free to write to me in care of Pete Farnham at ASBMB, or directly to me at heidi.hamm@vanderbilt.edu.



ASBMB Comments on NCRR Strategic Plan

BY PETER FARNHAM

The ASBMB Public Affairs Advisory Committee (PAAC) wrote to the National Center for Research Resources (NCRR) on August 23 expressing its concerns about the decline in support for infrastructure, the costs associated with the Clinical and Translational Science Awards (CTSAs), the need for more support for minority institutions and closer relationships with industry, and the need for a broader representation in the choice of grant application reviewers.

These and other concerns were in response to six questions (see *ASBMB Today*, August 2007, p. 5) NCRR asked as it considers its new draft strategic plan. The complete PAAC response can be found on the ASBMB Web page (www.asbmb.org) in the What's New column.

ASBMB expressed most concern about "the decline in support for infrastructure, in particular for such programs as Shared Instrumentation" at NCRR, including development of cutting edge technologies that are open to community use. Equipment and reagents for high throughput functional analysis should be more widely available, ASBMB notes, especially bar coded RNA interference (RNAi) libraries and screening equipment.

ASBMB also recommended that animal models developed with National Institutes of Health (NIH) funding be made available to all investigators via a central clearing house after a reasonable grace period beginning with the first publication on the model. The same approach could also be used for unique plasmid/viral vector constructs for use in animal or human cells. Training for scientists in newly developed equipment should also be provided.

The committee expressed considerable concern about the size and cost of the Clinical and Translational Science Awards but noted that they were useful and appropriate for achieving certain goals. However, the program is expected eventually to cost $550 million, and there are not enough funds provided to fund the program up front without taking money from other NCRR programs (if left to grow to its planned size with no dedicated additional funds, the program will take up half of NCRR's budget when at full size).

ASBMB also recommended that CTSA grants should be "required to show real, tangible success" within the first funding period, and should not be renewable without an extremely rigorous evaluation. The whole program should also be evaluated after five years, with an emphasis on noticeable improvement of strategies for drug development and evidence of progress in this area because it is highly unlikely that new drugs can be developed within such a short time frame.

There was a feeling among the committee that CTSAs might be especially useful at predominantly minority institutions. "Perhaps there could be CTSA or core facility grant subtypes awarded to minority institutions with strong biomedical research programs; these grants could focus on unmet needs in minority communities," the committee wrote.

The committee also recommended more effort to demonstrate how new technology works and can benefit individual research programs; "many researchers do not realized what a specific technology can do for them in their research." The committee recommends "fellowships, frequent training workshops held in strategic locations at minimal or no cost to the attendees, or on-site training at instrumentation facilities" to encourage more involvement and training on highly specialized equipment such as synchrotrons and cryoelectron microscopy.

In response to the question about what organizations NCRR should seek out for future partnerships, the committee recommended institutions developing RNAi laboratories as well as companies that develop and make mouse models on a contract basis. It might also be possible to increase interaction with the pharmaceutical industry in some areas.

Finally, the committee noted the importance of maintaining "a broad representation of the constituency of the biomedical research community" on ad hoc committees and in the choice of reviewers for grants. "It is also critical that conflicts of interest on these committees be avoided," although the committee recognizes that these panels must be comprised of experts, and these experts are often NCRR funding recipients.

Small Business Research Program to Double?

Senator Evan Bayh (D-IN) has introduced legislation to double the size of the Small Business Innovation Research (SBIR) program over the next five years from 2.5% of all federally funded research and development funds to 5%. The legislation, S.1932, was introduced in August and has been referred to the Senate Committee on Small Business and Entrepreneurship, chaired by Senator John Kerry (D-MA).

No hearings are scheduled on the bill at this time, but the Small Business Act is up for reauthorization in 2008, and an increase in the size of the SBIR program is very likely to be considered next year.

The SBIR program was created in 1982. It requires that 2.5% of all federal research and development (R&D) money at 11 federal agencies be set aside to support research conducted by small businesses. In 2005, the last year for which complete statistics are available, the total amount of R&D money set aside was $1.85 billion across the whole government. About half of this comes from the Department of Defense. Another quarter comes from the Department of Health and Human Services, almost entirely from the National Institutes of Health (NIH). In 2006, more than $620 million was set aside at NIH to support grant applications from small businesses.

The SBIR program has two major types of funding. Phase 1 grants are limited to about $100,000 and one year in length. These are primarily exploratory grants and have a success rate of about 20%, which is the overall success rate for all grant applicants at NIH (counting both initial submission and allowed resubmissions). Phase 2 grants, meant to more fully develop ideas initially funded under the Phase 1s, are considerably larger at $750,000, although these can be even bigger with a waiver on the size limit. For the Phase 2s, the success rate jumps dramatically to more than 40%.

Bayh's legislation would double the size of the SBIR set-aside (as well as that of the much smaller Small Business Technology Transfer (STTR) program) over five years by raising the size of the set-aside 0.5% annually starting in FY 2009. Thus, at NIH, the program would grow to about $1.5 billion by 2013, the last year of the doubling.

A major problem with this proposal, according to many in the biomedical research community, is that the NIH budget is declining; it has lost 13% of its purchasing power since 2003. Thus, embarking on a program to double the set-aside for small business will make a difficult situation for academic researchers seeking NIH grant funding even worse than it already is, with applications being funded at a 1 in 10 rate in many NIH programs (a fact masked by the overall success rate of about 20% at NIH).

Of course, the SBIR and STTR programs are losing purchasing power at NIH as well, because their funding is tied to the size of the research budget at NIH as a whole. This is probably one of the reasons that Bayh is proposing that the program be doubled. However, a better approach, and one that would not pit different NIH constituencies against each other, would be for small business advocates to join with the broader biomedical research community and fight for increases in the NIH budget as a whole, which would of course automatically cause the SBIR and STTR programs to increase.

A recent National Academy of Sciences report gives very good marks to the SBIR and STTR programs, and biomedical research advocates with whom *ASBMB Today* has spoken have not and will not argue that the program should be disbanded or even reduced from its present level. But, given the current grant funding situation for NIH as a whole, advocates for academic research feel they have little choice but to oppose such a large increase in the program as proposed in the Bayh bill during this time of extremely tight funding at NIH.

Congress is unlikely to deal with the issue substantively in 2007 although a hearing in the House may be scheduled at such time as companion legislation is introduced there; however, interest in the effort will increase considerably in 2008 when the whole program is up for reauthorization.

Peter Farnham, CAE, is ASBMB's public affairs officer.

FASEB

FASEB Announces New Data Resource on Scientific Training and Career Development

BY CARRIE D. WOLINETZ

The Federation of American Societies for Experimental Biology (FASEB) has released a new compilation of data related to the education and employment of biological and medical scientists. The presentation, which was created by Howard Garrison and Kimberly McGuire of FASEB's Office of Public Affairs, represents an overview of national survey data on many facets of scientific training and workforce development in the life sciences, including data on graduate enrollment, doctoral awards, postdoctoral appointments, and employment status.

"We are hoping these graphs and figures will foster an informed discussion of education and employment in the biological and medical sciences," said Garrison. "By bringing together the major sources of nationally representative data, these slides represent a starting point from which those interested in training or career development issues can perform additional, more in-depth analyses." In a recent article published in *Nature*, Norka Ruiz Bravo, deputy director for extramural research at the National Institutes of Health (NIH), stated, "FASEB has performed a very useful and timely service for the biomedical research community in highlighting this important issue. It is a matter of great interest and concern for NIH."

Some of the trends illustrated by the slides include:

- **Graduate School Enrollment:** Applications to graduate school programs in the biological and health sciences have increased steadily since 2000, following several years of decline. Enrollment in doctorate granting departments has also risen since 2000.
- **Career Outcomes:** The percentage of biomedical Ph.D.s with a postdoctoral appointment within 1–2 years after receiving their doctorate has declined since 1995. The average age of first time R01 investigators has increased steadily since 1970.
- **Employment Opportunities:** The number of academically employed scientists in tenured or tenure track positions has remained relatively unchanged for 20 years, during which time the number of doctorate degrees awarded has nearly doubled. Industry is the fastest growing employment sector for biological and medical scientists.
- **Under-representation of Women and Minorities:** Education and workforce data indicate a movement towards equity in representation of women and minorities. The rise in female graduate students and doctorate recipients since 1990 is particularly large. However, the representation of women decreases as the population moves through the training and career pipeline. The increase in representation of racial and ethnic minorities has been less pronounced.
- **NIH Funding for Training and Fellowships:** The percentage of the NIH budget spent on training grants and fellowships has declined since 1986. Success rates for F32 applications have fallen since 2000.
- **Support for Postdoctoral Researchers:** The number of postdocs supported by research grants or non-federal sources has increased substantially in the last two decades. During the same period, the number supported by traineeships or fellowships has remained stable.
- **Citizenship:** Temporary residents receive an increasing percentage of the total number of doctorate degrees awarded in the biological and medical sciences and account for over half of all postdoctoral researchers in U.S. institutions.
- **NIH Funding for Research Project Grants:** The number of competing awards funded by NIH has dropped since 2003.

FASEB is encouraging its member society scientists, advocacy and policy partners, and other interested parties to use graphs and figures included in this issue of *ASBMB Today* and upcoming issues in their own presentations or publications. According to Garrison, the information will be updated as new data become available. The FASEB training and employment data resource can be found online at opa.faseb.org/pages/PolicyIssues/training_datappt.htm.

Carrie D. Wolinetz is with the FASEB Office of Public Affairs.

asbmb member spotlight

Lindquist Is Recipient of David Perlman Memorial Lectureship

Susan Lindquist has been awarded the 2007 David Perlman Memorial Lectureship from the American Chemical Society Biochemical Technology Division. The award, which is sponsored by Genzyme, honors the contributions of the late David Perlman, a professor at the University of Wisconsin.

Lindquist is a member and former director (2001–2004) of the Whitehead Institute, a professor of Biology at the Massachusetts Institute of Technology, and a Howard Hughes Medical Institute investigator.

Lindquist is a pioneer in the study of protein folding. She has shown that changes in protein folding can have profound and unexpected influences in fields as wide ranging as human disease, evolution, and nanotechnology. Her research achievements include providing definitive evidence for protein-only inheritance; identifying mechanisms by which prions propagate, work that is relevant for understanding conditions such as mad cow disease; and discovering a potential mechanism for rapid bursts of evolution.

Partridge Named President-elect of the ACDP

Nicola C. Partridge, professor and chair of the Department of Physiology and Biophysics at the University of Medicine and Dentistry of New Jersey (UMDNJ)-Robert Wood Johnson Medical School, was named president-elect of the Association of Chairs of Departments of Physiology (ACDP). Partridge will be the first woman to serve as president of the organization. Her term is for three years, and her presidency will begin this December.

"I am honored and excited to be able to serve as president of the ACDP," reports Partridge. "The organization is a model for leadership that is respected throughout the field and a genuine resource to scientists and mentors across the globe."

The ACDP is composed of individuals who serve as chairs of Departments of Physiology across the United States, Canada, Mexico, Puerto Rico, and the West Indies whose faculty members are involved in the research and teaching of physiology.

Partridge has been professor and chair of physiology and biophysics at UMDNJ-Robert Wood Johnson Medical School since July 2000. She was previously at the Saint Louis University School of Medicine, where she was professor of pharmacological and physiological science and orthopedic surgery.

Bae Receives $2 Million Komen Award

Insoo Bae, a junior faculty member of the Lombardi Comprehensive Cancer Center at Georgetown University Medical Center, recently received $2 million from the Susan G. Komen For the Cure Foundation to study the links between environmental factors and breast cancer.

Bae, an assistant professor of oncology, has developed a new methodology for studying the interaction between environmental carcinogens and genetic risk for breast cancer, a project aimed at developing novel prevention strategies for women who are genetically predisposed to breast cancer.

Komen awarded the grant to Bae so he can test this methodology on the BRCA1 mutation, one of the few inherited mutations known to predispose women to breast cancer. Bae will examine a range of environmental carcinogens—such as cigarette smoke, alcohol, and dietary factors—to identify those agents that increase the probability that BRCA1 cells will become cancerous.

Bae also plans to develop preventive agents that will protect women against cellular damage.

Schimmel Wins Stein and Moore Award

The Scripps Research Institute's Paul Schimmel has won the 2007 Stein and Moore Award from The Protein Society for his "contributions to the highest level of the study of proteins."

His major research activities have concentrated on the decoding of genetic information, with emphasis on the rules of the universal genetic code, which are established through aminoacylation reactions catalyzed by a group of enzymes known as aminoacyl tRNA synthetases. The latter are believed by many to be among the first enzymes to have arisen on this planet in the early stages of the evolution of life.

The Stein and Moore Award, sponsored by The Merck Company Foundation and named for Nobel Laureates William Stein and Stanford Moore, venerates their contribution to understanding the connection between chemical structure and catalytic activity of the active center of the ribonuclease molecule. The award was presented to Schimmel at the 21st Symposium of The Protein Society in July.

Cravatt Receives Irving Sigal Young Investigator Award

Benjamin Cravatt of The Scripps Research Institute was selected as the 2007 Irving Sigal Young Investigator Award winner by The Protein Society. The Irving Sigal Young Investigator Award, sponsored by the Merck Research Laboratories, recognizes an important contribution to the study of proteins by a scientist who is in the early stages of an independent career. Candidates are usually not more than 40 years old. The 2007 award was presented to Cravatt at the 21st Symposium of The Protein Society in July.

Cravatt has created a field referred to as "Activity-Based Protein Profiling," which utilizes a collection of small molecules, each of which reacts covalently with a subset of the enzymes in a homologous family owing to their mechanism of action. The Cravatt Laboratory has now developed activity-based probes for the majority of the physiologically important enzymes and has discovered both new enzymes and established enzymes that perform new feats using this approach. Moreover, they have used this molecular toolset to identify and elaborate inhibitors of several enzymes that were lacking inhibitors before their efforts commenced. Proteomics profiling of cancer cells and other pathological tissue has been demonstrated in the Cravatt Laboratory to be useful in establishing disease biomarkers and has suggested novel pathologic mechanisms in some cases.

Sauer Receives Hans Neurath Award

Robert T. Sauer, Salvador E. Luria Professor of Biology at the Massachusetts Institute of Technology, has been awarded the 2007 Hans Neurath Award from The Protein Society for his significant contributions to our understanding of the mechanisms of protein unfolding and degradation by the AAA+ unfoldases and proteases. These proteins include a large family of compartmentalized proteases, such as the bacterial ClpXP and ClpAP enzymes as well as the 26 S proteosome from eukaryotes. In addition, protein remodeling enzymes, such as the thermotolerance protein Hsp104, are important members of this protein family.

The Hans Neurath 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 2007 award was presented to Robert Sauer at the 21st Symposium of The Protein Society in July.

Frieden Honored with Christian B. Anfinsen Award

Carl Frieden, professor of Biochemistry and of Molecular Biophysics at the Washington University School of Medicine, was presented with the 2007 Christian B. Anfinsen Award at the 21st Symposium of the Protein Society this past July. The Christian B. Anfinsen Award, sponsored by the Aviv Family Foundation, recognizes significant technical achievements in the field of protein science.

Frieden received the award for his significant technical achievements in fluorine-NMR. Frieden was instrumental in developing the technique of incorporating ^{19}F-labeled tryptophan into proteins of interest and then monitoring their folding and unfolding in real time using NMR. He has applied this approach successfully in both equilibrium and stopped flow studies.

Frieden's long term research goal is to understand the nature of the unfolded and intermediate structures in protein unfolding and refolding pathways, including the role of proteins that assist folding (chaperonins). His work uses site-directed mutagenesis and techniques such as ^{19}F and proton NMR, circular dichroism, fluorescence measurements, and x-ray crystallography.

Hamm to Advise NIH on Peer Review

Heidi Hamm, president of the American Society for Biochemistry & Molecular Biology and chair of the Department of Pharmacology at the Vanderbilt University Medical Center, is one of eight newly appointed members to the National Institutes of Health (NIH) Peer Review Advisory Committee.

This committee provides technical and scientific advice on matters related to the procedures and policies governing the scientific and technical evaluation of NIH grant applications. Peer review is the key method NIH uses to ensure that the $20+ billion it invests in biomedical research grants each year advances the most promising research.

Established by law and charter, the Peer Review Advisory Committee meets two to three times a year and advises the NIH director, the NIH deputy director for NIH Extramural Research, and the director of the NIH Center for Scientific Review (CSR). The committee is co-chaired by Toni Scarpa, CSR director; and Jeremy Berg, director of the National Institute of General Medical Sciences.

The newly appointed committee members were announced in August by Elias Zerhouni, NIH director.

Learning on the Road: The Aspirnaut Initiative

BY NICOLE KRESGE

Two students riding a bus view short educational podcasts on their iPods.

The one-room schoolhouse is alive again thanks to the Aspirnaut Initiative founded by ASBMB member Billy Hudson of Vanderbilt University Medical Center (VUMC). The initiative provides middle and high school students in rural Arkansas with video iPods and laptop computers to use for learning math and science during their long bus rides to and from school each day. The school buses are equipped with wireless Internet access so that the students can e-mail teachers at their school and/or scientists at universities their class may partner with.

Hudson, who is internationally known for his research on autoimmune and hereditary kidney diseases, got the idea for the School Begins on the Bus project when some friends from Grapevine, Arkansas, told him that that their grandchildren were spending hours on the bus riding to school in nearby Sheridan. Hudson, who is a native of Grapevine, decided to address the national decline in student performance in math and science and turn this long bus ride into a learning opportunity.

For the duration of the program's three-year trial, which was officially launched in April 2007, students aboard the Grapevine bus will use video iPods to view short educational podcasts on scientific subjects. Other high ability students, dubbed Rigel Aspirnauts after Rigel, the brightest star in the constellation Orion, will use notebook computers donated by VUMC to work through online courses in math and science. The Rigel Aspirnauts will also be mentored by university professors by e-mail, and twice a week they will be bussed to a one-room satellite school at local church fellowship hall for additional lessons. As part of the Rigel Aspirnaut program, the students will also attend a weeklong science camp at Vanderbilt each summer. At the end of the three-year trial, students who complete the program will be allowed to keep their iPods and laptop computers.

Billy Hudson

"Our work already demonstrates that the 10 to 15 hours of commute time on the school bus can become extended learning time, particularly for math and science. The impact can be great, given that the formal school time is about 30 hours a week," says Hudson. "In the digital era, if schools do not fill the hours on the bus with quality learning opportunities, the void will be filled with other non-educational activities that utilize notebook computers and cell phones."

The Aspirnaut Initiative, named for students who aspire, seek, and achieve, is a joint venture between the Hudson family, the Grapevine community, the Sheridan School District, and the Center of Science Outreach at VUMC. Hudson has also recruited family members, friends, prominent scientists, politicians, school officials, and community leaders to the cause.

In addition to the School Begins on the Bus program, the Initiative has several other projects underway. For example, Hudson has created a non-profit organization named the Grapevine Historical Society (GHS), whose mission is to preserve history and promote education. Two teaching awards have also been established, one for an elementary and one for a secondary school teacher, and were awarded in the summers of 2006 and 2007.

Professional development is also a priority for the Aspirnaut Initiative. In the summer of 2006, 12 teachers attended a one-week Professional Development Workshop at Vanderbilt University, thanks to the support of the initiative. The workshop included presentations by professors on their research programs, educational paths toward becoming a research scientist, and ways to motivate students to pursue math and science careers. This past summer, six teachers attended a similar workshop at Vanderbilt.

After the pilot program is over, Hudson and other initiative members will evaluate the program's achievements and outcomes. They hope the Aspirnaut Initiative will eventually become a template to elevate the mathematics and science achievement of K–12 students in other rural Arkansas com-

Older students teach younger students at the one-room satellite school.

munities and throughout the nation. However, Hudson says he would like to perfect the program in the Sheridan school district before expanding it to other communities.

Hudson, who is currently the Elliot V. Newman Professor of Medicine and Biochemistry and director of the Vanderbilt Center for Matrix Biology at Vanderbilt University, planned to drop out of high school after his junior year to work on a cotton farm when his history teacher/basketball coach Robert Theus intervened and took him to Henderson State Teachers College (now Henderson State University) where Hudson was allowed to take classes. After attending college for a year, Hudson was awarded his high school degree. He earned his bachelors degree in 1962, and two years later got his masters degree in Biochemistry from the University of Tennessee. He then attended the University of Iowa, where he received his Ph.D. in 1966. He was dean of Research and professor and chairman of Biochemistry at Kansas University Medical Center before joining Vanderbilt in 2002.

Hudson believes that scientists and mathematicians in universities and other professionals have a responsibility to participate in K–12 education. "We are the ones who truly understand the professions—the educational path, the rewards and the excitement of discovery," he says. "In this time of national challenge, we must play an active role to help K–12 educators elevate science and math achievement of the youth, and by doing so we help maintain America's competitive edge in science and technology."

More information on the program can be found on the Aspirnaut Initiative Web site at www.aspirnaut.org/.

Trends in Graduate

The following graphs are part of a series of data compiled by Howard Garrison and Kimberly McGuire of FASEB's Office of Public Affairs. These graphs represent trends in graduate enrollment and training. Several more graphs, grouped by subject, will appear in upcoming issues of *ASBMB Today*.

FIGURE ONE

Full Time Biological and Medical Sciences Graduate Students by Mechanism of Support

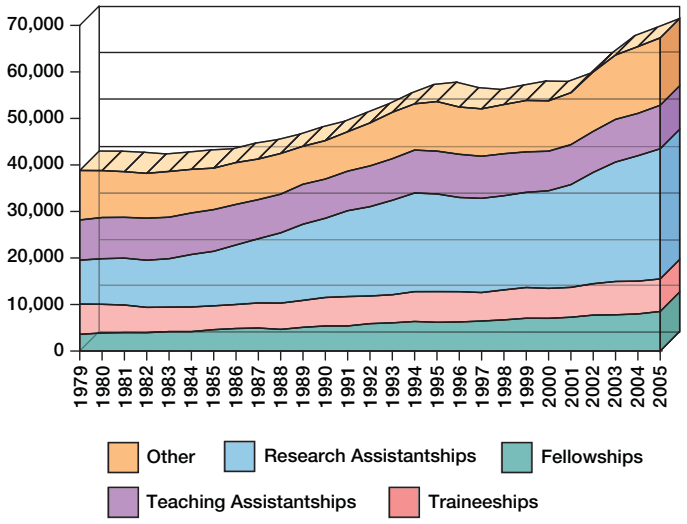


FIGURE ONE. **With the large increase in the number of graduate students in the U.S. in the past 25 years, the number of students receiving outside support has increased as well. The number of graduate students receiving research assistantships has tripled since 1979, and the number of graduate students receiving fellowships has doubled in that time period.**

Source: National Science Foundation Survey of Graduate Students and Postdoctorates in Science and Engineering.

FIGURE TWO

Total Biological and Medical Sciences Graduate Students by Gender

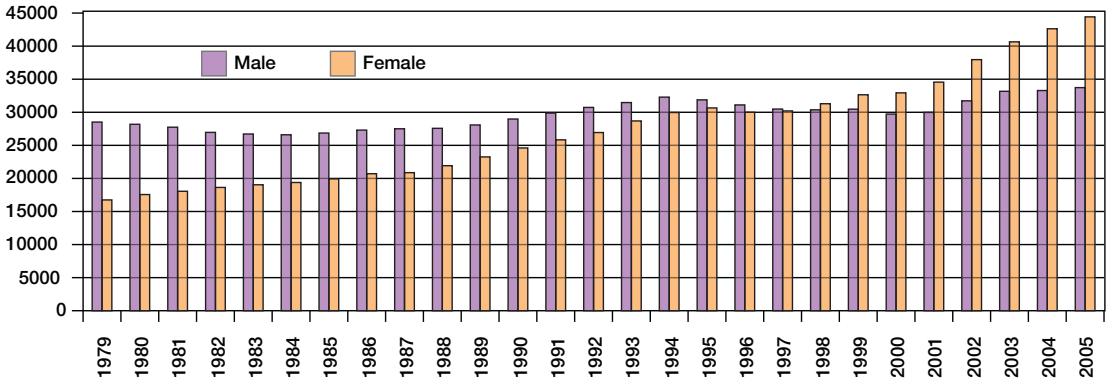


FIGURE TWO. **While the number of men enrolling in graduate programs has increased only slightly since 1979, the number of women has more than doubled. In 2005 there were more women than men enrolled in biological and medical science graduate programs.**

Source: National Science Foundation Survey of Graduate Students and Postdoctorates in Science and Engineering.

Training

FIGURE THREE

Trends in Graduate School Applications

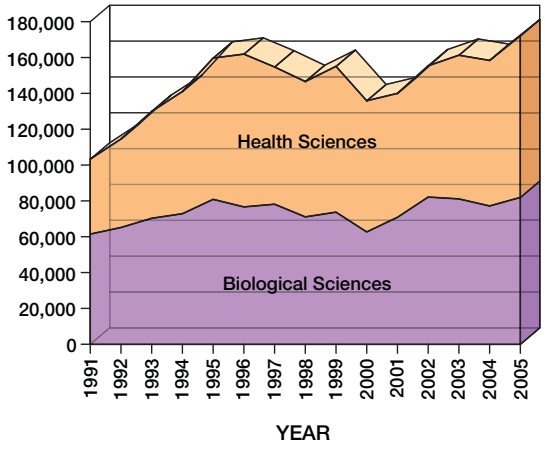


FIGURE THREE. **Applications to graduate school programs in the biological and health sciences experienced steady growth in the early 1990s. After a slight decline between 1995 and 2000, they are once again increasing.**

Source: Commission on Professionals in Science and Technology, data derived from Council of Graduate Schools, CGS/GRE Survey of Graduate Enrollment.

FIGURE FOUR

Biological and Medical Sciences Graduate Students by Citizenship/Visa Status

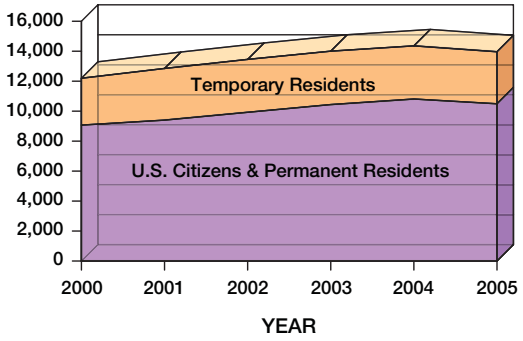


FIGURE FOUR. **Regardless of trends in graduate enrollment, temporary residents have consistently represented about a quarter of all biological and medical science graduate students.**

Source: National Science Foundation Survey of Graduate Students and Postdoctorates in Science and Engineering.

FIGURE FIVE

Biological and Medical Sciences Graduate Students by Ethnicity (U.S. Citizens and Permanent Residents Only)

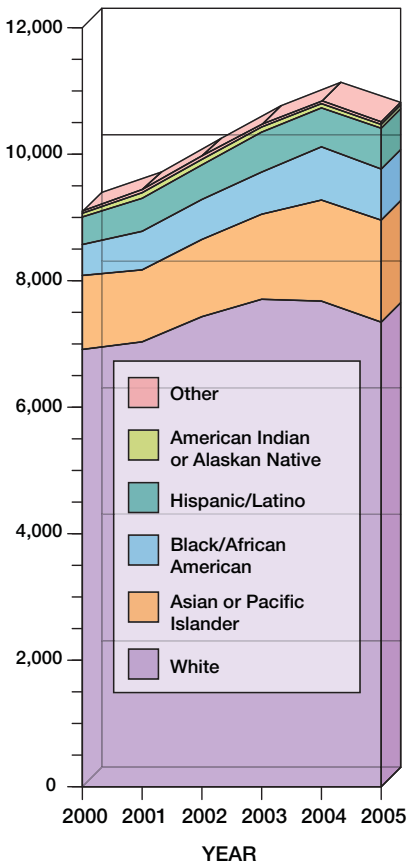


FIGURE FIVE. **While the majority of graduate students in the U.S. have been consistently white, the number of minorities entering graduate programs has steadily increased over the years.**

Source: National Science Foundation Survey of Graduate Students and Postdoctorates in Science and Engineering.

A New Focus for the Education and Professional Development Sessions

BY J. ELLIS BELL


Bell

The 2008 ASBMB annual meeting in San Diego will again feature an Education and Professional Development component. This year we are trying something different. Instead of a full slate of symposia each day, the focus will be on hands-on workshops and networking opportunities.

As always, the meeting will open with a Saturday Undergraduate Poster Competition (jointly sponsored by the Minority Affairs Committee and the Education and Professional Development Committee), where an expected 150--200 undergraduates will present their research. The competition will again be broken up into four thematic categories, each with a separate panel of judges. As in past years, there will also be time during the poster competition for students to visit with various graduate programs are supporting the event. This year, Springer-Verlag will again sponsor the poster awards, and we are grateful to them for making the competition such a success. Last year, we initiated Saturday morning workshops aimed primarily at faculty in undergraduate institutions. Building on this success, there will be two Saturday morning workshops, one focusing on best practices in incorporating research into formal laboratory courses and the other focusing on assessment issues.

On Sunday we will have the Classroom of the Future symposium, chaired by Adele Wolfson, Wellesley College, with three invited speakers presenting talks on biochemistry in a liberal arts education. As with last year, three short talks will be presented by faculty selected from the submitted abstracts. Immediately following this symposium, Michael F. Summers will be presented with the ASBMB Award for Exemplary Contributions to Education. Summers, an investigator of Howard Hughes Medical Institute at the University of Maryland, Baltimore County, is primarily engaged using nuclear magnetic resonance (NMR) to study the structure and function of proteins and macromolecular interactions. Specifically, he uses NMR and computational methods to visualize protein-protein and protein-RNA interactions that occur as retroviruses assemble in infected cells. Summers has a long standing interest in Science, Technology, Engineering and Mathematics (STEM) education and was recently featured in a round table discussion sponsored by *Science* magazine titled "Straight Talk about STEM Education." The award plenary session will also feature presentations to four undergraduate poster competition winners as well as the honorable mentions in the competition. Summers' talk will be followed by an open discussion session to gather feedback on the topics raised in the Classroom of the Future symposium.

While the first two days of the meeting resemble those of previous years, the next two will mark the introduction of a focus on hands-on workshops and networking sessions. This experiment is being tried in response to comments from attendees of the Education and Professional Development sessions over the last several years. Several attendees have expressed frustration about having to make a choice between attending the symposia offered by the various scientific themes at the meeting and the sessions organized by the Education and Professional Development Committee. Other attendees have expressed a desire for more hands-on activities instead of the traditional lecture format used in recent meetings. As a result of both comments, the Monday and Tuesday sessions will not be scheduled at the same time as scientific symposia or poster sessions.

The Monday session, titled "Writing Your First Grant Application," will focus on teaching young faculty and faculty in training about grant writing. The session will feature people from the major funding agencies as well as a number of successful grant writers from both academia and industry. Attending faculty will have the opportunity to discuss both funding opportunities and best practices in grant or proposal writing. The workshop will be followed by a social hour to encourage further discussion and networking.

On Tuesday, the "Starting and Sustaining Undergraduate Research" workshop will focus on incorporating research into the undergraduate curriculum. Topics featured will range from the benefits of incorporating formal research activities into undergraduate education to ways to successfully run an undergraduate research group and ways to integrate teaching and research activities.

These workshops and sessions are structured to foster the development of mentoring relationships and collaborations among the attendees, whether seasoned veterans or young faculty. In this way, the Education and Professional Development Committee hopes to create networking oppor-

tunities that will lead to interaction that goes well beyond the meeting itself.

Where, you might ask, is the session featuring research at undergraduate institutions that was introduced last year? The Annual Meeting Program Committee chairs and the Education and Professional Development Committee have decided that instead of having a separate session featuring undergraduate and post-undergraduate institution faculty speakers, these speakers will be integrated into the main platform sessions of the scientific themes of the meeting. The Undergraduate Affiliation Network Committee will be selecting a number of undergraduates and undergraduate institution faculty (based on submitted abstracts) who will be invited to give short talks in the various scientific themes throughout the meeting.

Education and Professional Development Sessions

ORGANIZER: J. Ellis Bell, University of Richmond

SATURDAY, APRIL 5

Assessment Issues Workshop: Incorporating Research into Formal Laboratory Courses Workshop

CHAIRS: Marilee Benore-Parsons and Joseph J. Provost

12th Annual ASBMB Undergraduate Student Research Poster Competition

ORGANIZERS: Kathleen Cornely, Phillip A. Ortiz, Joseph J. Provost, Mark A. Wallert

SUNDAY, APRIL 6

Classroom of the Future III Symposium

CHAIR: Adele J. Wolfson

ASBMB Award for Exemplary Contributions to Science Lecture

AWARD LECTURER: Michael F. Summers

Classroom of the Future III Open Discussion Session

CHAIR: Adele J. Wolfson

MONDAY, APRIL 7

Grant Writing Workshop: Writing Your First Grant Application

CHAIR: Parag Chitnis

TUESDAY, APRIL 8

Starting and Sustaining Undergraduate Research Workshop

CHAIR: J. Ellis Bell

Targets and Assays in Drug Discovery

BY STEVEN J. PROJAN AND P. JEFFREY CONN

Projan

Conn

Drug discovery in the 21st century appears to increasingly rely on larger and more diverse libraries of chemical compounds and more and more sophisticated laboratory automation. Advances in structure guided drug design, virtual screening, and structure-activity relationship analysis would seem to have streamlined the process into something resembling an assembly line. However the discovery of new drugs still relies on two key elements: 1) the validity and "drugability" of the target and 2) the sensitivity and specificities of the assays developed to probe that drug target. The symposia on drug discovery will specifically address this in three target areas.

Drug Discovery in Academic Settings: Despite tremendous progress in furthering our understanding in biology, chemistry, and related disciplines, basic scientists often fail to perform studies needed to more fully validate potential new drug targets and allow basic science discoveries to be most useful in supporting full drug discovery efforts in industry settings. Likewise, increasing fiscal pressures make it increasingly difficult for companies to invest significant resources in early exploratory basic science projects where potential therapeutic utility and drugability of a new target remains highly speculative. For the biomedical research enterprise to be maximally effective in translating new basic science discoveries into breakthrough new therapeutic agents, it will be important for scientists in academic and other non-profit settings to increase efforts to critically evaluate novel hypotheses related to new drug targets and provide data needed to allow translation of advances in basic science to drug discovery programs. This symposium will feature several efforts in which academic scientists are engaged in the earliest stages of drug discovery to provide critical data to establish drugability and early stage validation of novel therapeutic approaches. The session will end with a discussion of emerging models from an industry perspective of effective approaches to collaborations between industry and academic scientists to achieve common goals in drug discovery.

Discovery of Novel Antibacterial Drugs: To date, target based screening, despite a high degree of success in almost every over therapeutic area, has failed to produce even a single compound in late stage development, much less in clinical use. What is going on here? Perhaps the most essential of pathways in bacterial growth is DNA replication, and yet this area has been overlooked for the discovery of novel antibiotics. Is this a function of the complexity of the replication machinery, or is it short-sightedness? RNA has long been the target of most of the protein synthesis inhibitors, yet a new RNA target appears to have emerged in the "riboswitches." What are they, how do they work, and when can we expect novel riboswitch-based drugs?

Nuclear Hormone Receptors: The most common class of drug targets is the nuclear hormone receptors. They also appear to be emerging as a controversial class of targets as well. The general role in biology and drug discovery will be described, and three classes of nuclear hormone receptors will be discussed in depth.

Drug Discovery Thematic Meeting

ORGANIZERS:
Steven J. Projan, Wyeth Research, and
P. Jeffrey Conn, Vanderbilt University

Symposium: Drug Discovery in Academic Settings: Is There a Role for Academic Scientists in Early Drug Discovery?

Overview of drug discovery and development: traditional and evolving roles of academic institutions, P. Jeffrey Conn

Allosteric modulators of GPCRs as a novel approach to treatment of CNS disorders, Colleen Niswender

Target validation in academia: the chemical biology of S1P, Hugh Rosen

Exploiting small molecule and siRNA libraries to identify novel mechanisms for potential cancer therapeutic agents, John S. Lazo

Universities and drug discovery: an industry perspective on how academic scientists can contribute to industry discovery,, Robert A. Zivin

Symposium: Targets for Drug Discovery: Has Target-Based Screening Failed for Antibacterials?

Target-based antibacterial drug discovery. Zero for the 20th Century, Steven J. Projan

Riboswitches as drug targets, Ken Blount

Targeting the bacterial replication complex, Charlie McHenry

Symposium: Targets for Drug Discovery: Nuclear Hormone Receptors

Novel mechanisms for old targets: new ways of looking at steroid receptors, Len Freedman

COUP-TFII in development and disease (some very exciting new data), Sophia Tsai

Development of GW501516, a selective PPAR-delta agonist, Timothy M. Willson

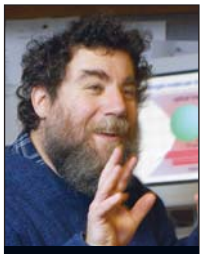
The Form and Function of Molecular Machines

BY STEVEN M. BLOCK AND LEEMOR JOSHUA-TOR

To survive and replicate, the cell takes advantage of an amazing variety of molecular machines. This thematic program brings together structural biologists and single-molecule biophysicists, whose common goal is to decipher how these machines work in molecular detail. The past decade has seen noteworthy advances in technology that enable a mechanistic understanding of these nanoscale devices, coupled with a new appreciation of their intricacy. Structural biologists and single-molecule biophysicists have much in common and much to talk about. High resolution structural and dynamic information combine in a synergistic way to reveal the interplay between form and function. This theme is focused on biological processes where both methodologies have had a particularly significant impact.

The Form & Function of Molecular Machines symposia at the upcoming ASBMB meeting will focus on four main topics: Helicases, DNA Replication, Gene Expression, and Filament Dynamics. The Helicase session (chaired by Taekjip Ha, University of Illinois) will focus on how DNA is first unwound and then translocated by different classes of enzymes. Leemor Joshua-Tor (Cold Spring Harbor Laboratory) will describe a proposed mechanism for DNA translocation by replicative hexameric helicases, based on her structure of the E1 helicase from papillomavirus. Taekjip Ha (University of Illinois) will present some of his latest single-molecule, fluorescence resonance energy transfer (FRET)-based measurements for the motions of a variety of helicases. Wei Yang (National Institutes of Health) will follow with her structural studies of the UvrD helicase captured in different conformational states.

The session on Replication (chaired by Antoine van Oijen, Harvard Medical School) will focus on recent insights into the DNA replication apparatus as revealed by new structures of the replisome and new biophysical assays for enzyme motion during replication. Antoine van Oijen will describe a novel single-molecule approach that allows the visualization of replication fork progression in real time. Michael O'Donnell (Rockefeller University) will discuss structures of replisome complexes and their functional significance. Keir Neuman (National Institutes of Health) will conclude the session by reporting recent findings from a single-molecule DNA unwinding assay using topoisomerase IV.


Block


Joshua-Tor

The Gene Expression session (chaired by Steven Block, Stanford University) will showcase the latest developments in the study of RNA polymerases, including bacterial RNA polymerase (RNAP) and reverse transcriptases. Block will describe a recent series of optical trapping studies on single molecules of *Escherichia coli* RNAP involved in transcriptional termination. Xiaowei Zhuang (Harvard University) will discuss insights into the mechanism of reverse transcriptase (RT) gleaned through single-molecule FRET studies of HIV-RT and telomerase. Seth Darst (Rockefeller University) will round out the session with his structural studies on transcription-coupled repair.

Finally, a special session has been convened on Filament Dynamics, which play key roles in both the cytoskeleton and aspects of gene regulation. Eva Nogales (Howard Hughes Medical Institution/University of California, Berkeley), who also chairs the session, will describe ultrastructural electron microscope studies of the microtubule-kinetochore interface. Chip Asbury (University of Washington) will follow with his results from optical trapping experiments that track the DAM1 complex along depolymerizing microtubules—a process that is thought to drive chromosomal movement. Concluding this session, general insights into the diverse roles of protein polymers will be offered by Edward Egelman (University of Virginia).

These principal talks will be complemented by short presentations to be selected from submitted abstracts in the general areas of structural and single-molecule biology that emphasize mechanistic insights. We look forward to a terrific week of symposia and many stimulating interactions in sunny San Diego. *See you there!*

Form and Function of Molecular Machines Thematic Meeting

ORGANIZERS: Steven M. Block, Stanford University, and Leemor Joshua-Tor, Cold Spring Harbor Laboratory

Symposium: Replication

Under the hood of the replisome: A single-molecule view of DNA replication, *Antoine van Oijen*

Assembly and function of multiprotein replisome machines, *Mike O'Donnell*

Untwisting and untangling DNA: symmetry breaking by topoisomerases, *Keir Neuman*

Symposium: Helicases

DNA translocation in a replicative hexameric helicase, *Leemor Joshua-Tor*

Single-molecule views of DNA translocation and unwinding mechanisms of helicases, *Taekjip Ha*

Stop action movie of UvrD helicase unwinding DNA, *Wei Yang*

Symposium: Filament Dynamics

Microtubule-kinetochore interface, *Eva Nogales*

How are chromosomes moved during mitosis? Biophysics at the kinetochore-microtubule interface, *Charles Asbury*

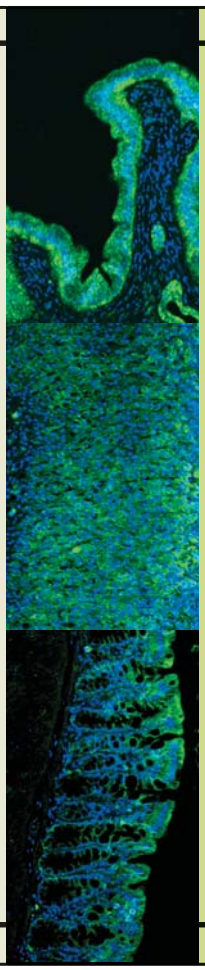
Polymorphic perversity in protein polymers: The biological role of multiple interfaces, *Ed Egelman*

Symposium: Gene Expression

Single-molecule studies of transcriptional termination, *Steven Block*

A tale of two reverse transcriptases–assembly and function of telomerase and HIV reverse transcriptase, *Xiaowei Zhuang*

Structural studies of prokaryotic transcription, *Seth Darst*



Principles & Applications of Immunocytochemistry

A Short Course at Experimental Biology 2008

8 AM-4:30 PM, April 5, 2008, San Diego Marriott & Marina

Organizers: Denis G. Baskin and William L. Stahl

The Histochemical Society is offering a course in the techniques of immunocytochemistry that is aimed at investigators and students who are new to the field but is also useful for experienced investigators. The course provides an understanding of the basic principles and applications of immunocytochemistry for research in biochemistry, molecular biology, cell biology and pathology. Topics include fixation, antigen retrieval, double labeling, and contols.

Space is limited and advance registration is required by February 15, 2008. There will be no on-site registration. Registration is $250 for graduate students and $300 for all others. Registration includes all course materials, refreshment breaks and lunch.

For further information, please visit: http://immunocytochem.wordpress.com & http://www.histochemicalsociety.org

HCS

MAC Sessions to Focus on Mental Health

BY GEORGE HILL


Hill

The former surgeon general, David Satcher, stated in the "Surgeon General's Report, Mental Health, A Report of the Surgeon General, 1999" that "Promoting mental health for all Americans will require scientific know-how but, even more importantly, a societal resolve that we will make the needed investment. The investment does not call for massive budgets; rather, it calls for the willingness of each of us to educate ourselves and others about mental health and mental illness, and thus to confront the attitudes, fear, and misunderstanding that remain as barriers before us. It is my intent that this report will usher in a healthy era of mind and body for the Nation." In preparation for the 2008 ASBMB Annual Meeting in San Diego, the ASBMB Minority Affairs Committee (MAC) organized its Mental Health Sessions to provide such information and education to Society members and other meeting attendees.

An important supplement published in 2001, "Mental Health: Culture, Race, Ethnicity—Supplement to Mental Health: Report of the Surgeon General," offers documentation on the effect of race and ethnicity on one's mental health status. For example, while non-Hispanic whites are nearly twice as likely as African-Americans to commit suicide, suicide rates among young black men are as high as those of young white men and have increased significantly in the past 10 years. African-Americans are also over-represented in high need populations such as the homeless, the incarcerated, children in foster care, and people exposed to violence—all of whom are particularly at risk for mental illnesses. Reports have noted that Latino youth experience proportionately more anxiety-related and delinquency problem behaviors, depression, and drug use than do non-Hispanic white youth. In addition, adult Mexican immigrants have lower rates of mental disorders than Mexican-Americans born in the U.S., and adult Puerto Ricans living on the island tend to have lower rates of depressions than Puerto Ricans living on the mainland.

Native American populations also have been affected by mental health issues, for example, having a higher incidence of people exposed to trauma. The rate of violent victimization of Native Americans is more than twice the national average.

As noted in the 2001 report, because of disparities in mental health services a disproportionate number of minorities with mental illnesses do not fully benefit from or contribute to the opportunities and prosperity of our society. This preventable disability from mental illness exacts a high societal toll and affects all Americans. It is MAC's hope that their meeting sessions will provide information and stimulate discussions to help address these major public health concerns. We also hope to share the importance and effects of mental health on all populations as well as note the impact that it sometimes has on minority populations.

More than 4.5 million Americans are believed to have Alzheimer disease, and by 2050 the number could increase to 13.2 million. Each year, approximately 65,800 victims die, and 350,000 new cases of Alzheimer disease are diagnosed. America is not alone in dealing with this terrible affliction. In every nation where life expectancy has increased, so has the incidence of Alzheimer disease. Alzheimer disease is becoming tragically common. It is estimated that there are currently 26 million people worldwide with Alzheimer disease. This figure is projected to grow to more than 106 million people by 2050.

A timely session entitled, "Over Health Disparities in Alzheimer's disease: Advances in Understanding Disease Pathogenesis," will be chaired by Takita F. Sumter of Winthrop University. Farah Mohamed, Johns Hopkins University School of Medicine, will talk about Alzheimer β-secretase in health and disease. Thomas J. Montine, University of Washington, will discuss mechanisms of cognitive impairment in the elderly. This session will also include a presentation by Lisa N. Gentile, University of Richmond, on the role of presenilin-I in early onset familial Alzheimer disease.

The incidence of stress, anxiety, depression, and drug abuse have reached all time highs in our country. This impacts the well being of not only the individual involved but his or her family and acquaintances as well and their mental health. Marcos E. Milla, Roche Pharmaceuticals, will chair a session called "Central Nervous System (CNS) Diseases—Depression and Anxiety." In this session, Charles I. Chavkin, University of Washington, will dis-

cuss opioid receptors in disease and substance abuse. Satinder K. Singh, Oregon Health & Science University, will also describe structural models of neurotransmitter reuptake transporters, and Renee Martin, Roche Pharmaceuticals, will discuss thermodynamics of drug-SERT transporter interactions.

Complementing this session will be one organized by Phillip A. Ortiz, Empire State College, entitled "Drug Abuse." An estimated 14.8 million Americans currently use illicit drugs, representing 6.7% of the population ages 12 years and older. Marijuana is the most common illicit drug, used by 75% of people reporting illicit substance use. Approximately 4.3% of the population (an estimated 6.4 million Americans) uses other illicit drugs, such as cocaine, heroin, crack, hallucinogens, and other psychotherapeutic medications taken non-medically or without prescription. Methamphetamine is a powerfully addictive stimulant that dramatically affects the central nervous system. The drug is made easily in clandestine laboratories with relatively inexpensive over-the-counter ingredients. These factors combine to make methamphetamine a drug with high potential for widespread abuse. Recent reports reveal an increase of 300,000 to 400,000 new addicts each year.

In the Drug Abuse session, Sanika S. Chirwa, Meharry Medical College, will comment on *in utero* exposure to methamphetamine and the risks and adverse outcomes in offspring. This is an increasing problem observed in states with high incidence of methamphetamine use and is seen in public and private hospitals. Habibeh Khoshbouei, Meharry Medical College, will discuss the dopamine transporter and its relationship to methamphetamine. Nancy R. Zahniser, University of Colorado Health Sciences Center, Denver, will give a talk titled, "Individual Differences in Cocaine Activation and Self-Administration: Insights from Studies in Outbred Rats about a Role for the Dopamine Transporter."

Also included in the MAC sessions each year is a very important session focusing on "Discovery and Applications" that highlights advances and technologies that will continue to have an impact on biomedical research. The chairs for this session will be Craig E. Cameron, The Pennsylvania State University, and Jerome C. Nwachukwu, New York University School of Medicine. In this session, James L. Sherley, Boston Biomedical Research Institute, will speak about discovering adult stem cell expansion technologies. Pamela L. Sharpe, Dupont, will provide information on metabolic engineering of a methanotroph for the production of C40 carotenoids for aquaculture applications, and Craig E. Cameron will discuss a universal strategy for viral attenuation and vaccine development.

Together these MAC sessions will provide exciting discussions and enthusiastic presentations. We look forward to seeing you at these sessions!

Minority Affairs—Mental Health Thematic Meeting

ORGANIZER: George C. Hill, Vanderbilt University

Symposium: Health Disparities in Alzheimer Disease: Advances in Understanding Disease Pathogenesis

Alzheimer β-secretase in health and disease, *Farah Mohamed*

Mechanisms of cognitive impairment in the elderly, *Thomas J. Montine*

The role of presenilin-I in early onset familial Alzheimer disease, *Lisa N. Gentile*

Symposium: CNS Diseases—Depression and Anxiety

Opioid receptors in disease and substance abuse, *Charles I. Chavkin*

Structural models of neurotransmitter reuptake transporters, *Satinder K. Singh*

Thermodynamics of drug-SERT transporter interactions, *Renee Martin*

Symposium: Discovery and Applications

Discovering adult stem cell expansion technologies, *James L. Sherley*

Metabolic engineering of a methanotroph for the production of C40 carotenoids for aquaculture applications, *Pamela L. Sharpe*

Universal strategy for viral attenuation and vaccine development, *Craig E. Cameron*

Symposium: Drug Abuse

In utero exposure to methamphetamine: Risks and adverse outcomes in offspring, *Sanika S. Chirwa*

For the dopamine transporter methamphetamine is not just another amphetamine, *Habibeh Khoshbouei*

Individual differences in cocaine activation and self-administration: Insights from studies in outbred rats about a role for the dopamine transporter, *Nancy R. Zahniser*

Careers in Publishing

BY EVELYN JABRI

The publishing industry offers many jobs that may appeal to someone with a scientific degree. If being a bench scientist or professor is not calling you, or if life circumstances require that you change careers, consider how skills learned in graduate school can be retooled for a career in publishing.

Understanding Publishing Jobs

To gain an understanding of professional and scholarly publishing, I recommend several papers from The American Association of Publishers (AAP) Professional and Scholarly Publishing (PSP) division and the Bookjobs Website[1,2]. Here, I will provide a broad overview of opportunities in journal publishing focusing on four main job classes: Editorial, Production, News Writing, and Freelancing. Information about opportunities in Technology, Business/Finance, Distribution/Customer Service, and Marketing can be found in the AAP/PSP publications.

Editorial and Acquisition Positions

Scientific editors (ranging in title from assistant, associate, senior, executive, and chief) have a Ph.D. (and often postdoctoral experience) in the sciences. They work with an editorial board or within a staff editorial group to evaluate manuscripts and manage peer review. Scientific editors read and digest the scientific literature; commission new content, such as reviews; attend scientific conferences; write news pieces on published papers; and contribute scientific content to Web features, such as blogs, Wikis, and forums. They attend meetings and conferences focused on publishing to keep abreast of key trends. They also manage a small group of staff (science writers, art directors, and Webmasters). Executive editors plan and manage the journal by working with scientific editors, managing editors, marketing representatives, and a publisher to develop new features for the journal in print and on the Web. Acquisition editors ensure that a group of journals remains strong and functions within budget. They may or may not have a scientific background, but they will generally have experience in publishing. They have extensive contacts with both the external scientific editors of a group of journals and the in-house staff, including those in production, sales and marketing, and Web delivery. They develop proposals for and launch new print and Web products as well as monitor the existing journals, ensuring that they continue to serve the needs of the authors and readers while remaining competitive and profitable. Editorial directors manage the acquisitions editors and take responsibility for the entire journal portfolio of a publishing group.

Production Positions

Once a paper is accepted by a scientific editor, it must pass through a production process to become a journal article in print and on the Web. An extensive staff, many with scientific degrees, chaperone the paper through this process. Often, this production staff works as a large team to process papers from all journals in the portfolio. Production editors focus on the detailed production of an accepted paper and track manuscripts from composition (generating a galley proof) through proofreading of the final PDF proofs and printing. Production editors interact with their in-house colleagues and also with external vendors who manage many aspects of production (composition to printing). A managing editor ensures that copyediting, production, printing, binding, and fulfillment are completed on time and within budget for a specific journal. They usually have publishing experience and may or may not have a scientific background. They interact with the editorial group of a journal and the responsible production staff to ensure timely publication. They often manage a small team of copyeditors (those who edit the text to make it accessible to a broader audience in proper English), art directors, and Webmasters.

Evelyn Jabri

Evelyn Jabri is a senior acquisitions editor for *Biological Chemistry* at the American Chemical Society. She made the transition from an assistant professor to publishing in 2003 and has enjoyed working on the editorial side of publishing. She is also chief executive officer of the RNA Society. Jabri can be reached via e-mail at e_jabri@acs.org.

News Editor and Science Writer Positions

News editors and science writers handle the non-peer reviewed material in a journal. News editors generally have a scientific background (from a B.S. to a Ph.D.) and also come in many flavors (assistant, associate, senior). News editors focus on commissioning news pieces (such as highlights, commentaries, perspectives, and sometimes reviews) for a journal or a group of journals. Like the scientific editors, news editors must keep in close contact with scientists and attend conferences to keep up to date on the latest scientific discoveries and policies. Science writers are journalists who write about scientific discoveries, science policy, and industry trends. With the rise of Web publishing, news editors and science writers have to be adept at contributing to blogs and forums in addition to writing more traditional news features. News editors work closely with science writers, copyeditors, and art directors to ensure appropriate and accessible presentation of the news. They may also work with the managing editor to coordinate the publication of a news piece with specific manuscripts and with the communication department to send out press releases to other journalists.

Freelancers

Although not a formal staff position at a publishing house, freelancers often make significant contributions to a publishing group. Freelancers are generally hired for a job that does not warrant a full-time staff member or that has a finite timeline. They can work as science writers, perform copyediting, develop art for the journal, or serve as consultants to a publishing group. Freelancers are generally employed on a contractual basis and are paid per item or per hour, without benefits. They do set their own schedules and work outside of the office, which can provide necessary flexibility to pursue other interests and obligations. Most freelancers have extensive experience and professional contacts in the publishing industry before they "go it alone." They often don't work from 9 to 5, and to be successful they must be flexible, work with tight deadlines, and be adept at multitasking. Freelancers can face "feast or famine" work loads, and financially they must plan accordingly.

Identifying the Necessary Skill Set

Regardless of the position, those entering the publishing world must have strong written and spoken communication skills so that they can express their thoughts clearly and accurately to scientists and fellow staff members. *For those pursuing scientific or news editor positions, it is essential to have* a broad understanding of science (the research and policy sides) as well as a willingness to expand it on the job. Other nonscientific strengths, such as critical thinking and problem solving are also very valuable. *Both will come in handy when making decisions on manuscripts, resolving production issues, or completing publication projects.* As is clear from the general job description above, staff members who work on a manuscript's peer review, production, delivery to the Web, and promotion to a large audience work together as a larger cross-functional team. To be productive in such an environment, it is essential to work on common team goals. They must have the creativity to contribute to the process, the self-confidence to do so, the ability to listen to fellow team members, and the adaptability to change course as necessary. Web savviness can also be helpful because content published in a print journal transitions from a print-based operation to a Web-based environment. In addition, content that is published only online (such as forums and blogs) is increasing.

For those pursuing scientific or news editor positions, it is essential to have a broad understanding of science

Finding the Job

There are two types of publishing houses—nonprofits and for-profits—and each group can have unique approaches to publishing. A little research on the Web will help a prospective employee evaluate the policies and practices of each publishing house. Positions in publishing are advertised in many places, including local newspapers and Web sites of publishers, journals, and scientific societies. Some sites that may be particularly helpful to those looking for editorial and production positions are Society for Scholarly Publishing[3], AAP/PSP[4], Science Careers[5], Naturejobs[6], and ChemJobs[7]. For those looking for copyeditor and science writer positions, MediaBistro[8] and the National Association of Science Writers[9] are good resources.

Identifying the right job requires an honest assessment of professional and personal goals. This may include asking yourself some questions: Is it important to keep working with scientists and reading papers? Is writ-

ing about science important to me? Opportunities to move between different types of jobs do exist in most publishing companies. However, it is best to have a good sense of where to start based on strengths and personal interests.

Once you identify a few interesting jobs, the process of applying and interviewing is no different than that for any other corporate job. Your résumé should be tailored to highlight the relevant skills for these positions. Specifically, highlight scientific strengths, show examples of problem solving skills, discuss projects implemented and completed, discuss examples of teamwork, and showcase writing skills, including professional contributions on the Web. Also include relevant skills learned in volunteer jobs, such as project development or management. A careful but succinct cover letter should explain the match between your skills and the advertised job and should summarize the key points in your résumé.

Once you identify a few interesting jobs, the process of applying and interviewing is no different than that for any other corporate job

Making the Transition

Keep in mind that the corporate world is different from the academic setting. With any job, it is important to pay attention to the environment during the interview to ensure a good fit between you and the company. A job in publishing offers many advantages. There's an "instant gratification" in seeing a journal go out every month or a project implemented. The salary is not dependent on grants, and you may receive a bonus for exceptional work. In addition, the benefits are usually quite good and may include generous maternity leave policies, partner benefits, and flexible schedules.

Furthermore, companies often provide training to improve and expand skills. Publishing staff generally work during business hours (sometimes longer if the project requires it). To some this will be a relief—no more late nights in the lab! Those who like working in the wee hours of the night may have to adjust their sleep schedules. The new staff member may also have to ditch the jeans and change to a business wardrobe. For most journal publications, a monthly schedule is essential to producing the journal on time. This may not satisfy those easily bored with routines—they may need to take on volunteer activities to satisfy creative needs. Managing people also brings an additional level of challenge: managers must motivate their teams and work with other groups to achieve business goals. Regardless of when the transition from academia to publishing occurs, reevaluating your starting skill set and obtaining additional training (if necessary) will help ensure a smooth transition into your new job. Those making the transition to publishing may want to get a head start on their new job by attending an AAP/PSP publishing boot camp[10]. This intensive four-day camp is offered every two years and exposes participants to all aspects of journal publishing.

The scientific publishing industry is changing quickly, so those choosing a career in publishing should be prepared for a dynamic work place. As with any job, it will be important to keep an open mind and work toward professional goals without compromising your personal needs. Redirecting a career is not easy, but it can be very rewarding.

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3. Society for Scholarly Publishing: www.sspnet.org/forward/job_results.aspx
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6. Naturejobs: www.nature.com/naturejobs/index.html
7. ChemJobs: pubs.acs.org/chemjobs/
8. MediaBistro: www.mediabistro.com/joblistings/
9. National Association of Science Writers: www.nasw.org/
10. AAP/PSP Publishing boot camp: www.pspcentral.org

Do You Know an Outstanding Undergraduate?

BY J. ELLIS BELL

The UAN's six geographical regions

If you know any outstanding undergraduate students, please nominate them for membership in XΩΛ, the Biochemistry & Molecular Biology Honor Society for outstanding undergraduate students pursuing a degree in the molecular life sciences.

The XΩΛ honor society, which is open to students at colleges and universities that are members of the Undergraduate Affiliation Network (UAN), was initiated by the American Society for Biochemistry & Molecular Biology. Member institutions automatically qualify to create a local chapter of XΩΛ, and local chapters may also nominate eligible students for election to the National XΩΛ Honor Society. The honor society Web page can be found at www.faseb.org/asbmb/epd/Honor.html. Upon election to the National Honor Roll, students receive a certificate of membership, an ASBMB travel award to the next ASBMB annual meeting, and the XΩΛ lapel pin.

Who May Nominate Students?

Faculty advisors of UAN chapters or any faculty in a school with a UAN chapter may nominate students. A maximum of three junior year and three senior year students may be nominated each year for election to the honor society. If your school does not already have a chapter of the UAN, it is easy to get started—for $200 a school can initiate a chapter. Each new chapter gets a $400 travel award for the ASBMB annual meeting. This award can be given to any student in the program who is presenting at the next national ASBMB meeting. Details on the UAN and how to join are given at the end of this article.

Nomination materials should include:

- **A letter of nomination.**
- **An unofficial transcript indicating science courses taken and GPA.**
- **A one page CV for the student indicating presentations made at scientific meetings, publications, and outreach activities the student has engaged in.**
- **Letters of support: No more than three letters of support may be submitted.**
- **A copy of an abstract submitted for the next ASBMB Meeting.**
- **E-mail addresses for both the student and the nominating faculty member.**

There is a target date for nominations each year: for 2007 all materials should be received by November 30. Students elected to the National Chapter of XΩΛ will be notified by January 1. Nomination materials should be e-mailed (as either a Word doc file or a pdf file) to uan@asbmb.org.

The UAN

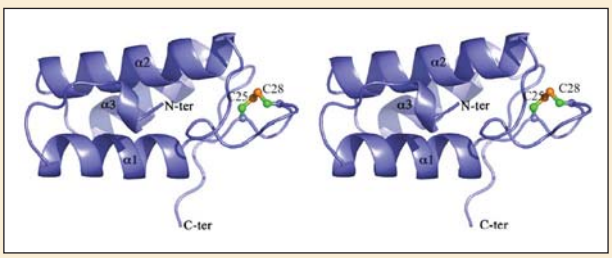
The Undergraduate Affiliates Network offers undergraduates and undergraduate faculty an opportunity to connect with their future by providing a variety of regional and national networking opportunities including seminar and research opportunities, access to the UAN newsletter *Enzymatic,* travel awards (for students and faculty) to attend the ASBMB Annual Meeting, and eligibility to participate in the Undergraduate Poster Competition at the annual meeting. More details on the UAN and application materials can be found at www.faseb.org/asbmb/epd/UAN.html.

The Undergraduate Affiliate Network (UAN) aims to form scientific and educational communities across the world to help academic institutions develop the best possible undergraduate curricula and to provide more research and learning opportunities for students by pooling their resources and working together. The UAN is divided into six geographical regions, each of which has a regional director and dedicated Website.

ASBMB looks forward to seeing your best undergraduates at the 2008 Meeting in San Diego, which kicks off with the Undergraduate Poster Competition. We hope you will come too to see the quality of research being conducted by undergraduates around the nation—you never know, you might even recruit a few good graduate students!

Assembling Cytochrome *c*

Cytochrome *c* is a small heme protein that is an essential component of oxidation. The maturation of bacterial cytochrome *c* occurs in the periplasm, where the apo-protein is covalently linked to a heme group via reduction of two cysteines in the protein's heme binding motif. Cytochrome c maturation protein H (CcmH) is one of the proteins that participate in thioreduction in this maturation pathway. In this *JBC* paper, the authors present the 1.7Å crystal structure of the soluble periplasmic domain of CcmH from *Pseudomonas aeruginosa*. The domain adopts a peculiar three-helix bundle fold that involves an unusual arrangement of active site cysteine residues that is different from that of all other thioloxidoreductases reported so far. From their structure and related functional data, the authors propose that cytochrome *c* biogenesis occurs in an assembly line fashion in which reduced CcmH specifically recognizes, binds to, and reduces oxidized apo-cytochrome *c* via the formation of a mixed disulfide complex.



CcmH adopts a peculiar three-helix bundle fold.

A Strategic Protein in Cytochrome *c* Maturation: 3D Structure of CcmH and Binding to Apocytochrome *c*

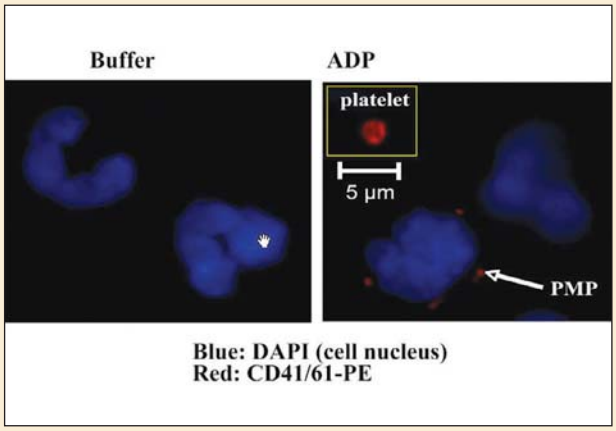
Adele Di Matteo, Stefano Gianni, M. Eugenia Schininà, Alessandra Giorgi, Fabio Altieri, Nicoletta Calosci, Maurizio Brunori, and Carlo Travaglini-Allocatelli

J. Biol. Chem. 2007 **282**, 27012-27019.

jbc

Receptor Transfer in Inflammation

Cells sometimes use microparticles to transfer receptors to other cells that lack particular receptors. For example, platelet-derived microparticles (PMPs) are generated during inflammation and contain receptors that can be acquired by components of the vessel wall and by blood-borne cells such as neutrophils. In this *JBC* paper, the authors tested whether functional GPIIb/IIIa receptors could be acquired by neutrophils via PMPs and whether these receptors participate in pro-inflammatory signaling. They found that PMPs do indeed transfer GPIIb/IIIa receptors to isolated and whole blood neutrophils and that these newly acquired receptors cooperate with κ2-integrins to activate NF-βB signaling. From these results, the authors propose that GPIIb/IIIa receptors could be a new therapeutic target in neutrophil-induced inflammation.



Platelet-derived microparticles (PMPs) can transfer GPIIb/IIIa receptors (CD41/61-PE) to neutrophils.

Beta 2-integrins and Acquired GPIIb/IIIa Receptors Cooperate in NF-κB Activation of Human Neutrophils

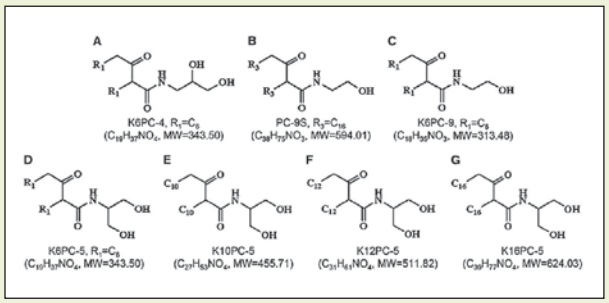
Birgit Salanova, Mira Choi, Susanne Rolle, Maren Wellner, Friedrich C. Luft, and Ralph Kettritz

J. Biol. Chem. 2007 **282**, 27960-27969.

jbc

Skin Cell Signaling

Ceramides are a family of lipid molecules composed of sphingosine and a fatty acid. They are found in high concentrations within the cell membrane and are thought to play an important role in skin permeability. For years, it was assumed that ceramides were purely structural elements. However, it is now known that they are also involved in cellular signaling. In this paper, the authors synthesized several ceramide derivatives and investigated their effects on keratinocyte differentiation. They found that several of these derivatives markedly increased keratin 1 and involucrin expression in normal human epidermal keratinocytes cultured *in vitro*. These ceramide derivatives also elicited a rapid transient increase in intracellular calcium levels and stimulated the phosphorylation of p42/44 extracellular signal-regulated kinase and c-Jun N-terminal kinase. These results indicate that novel synthetic ceramide derivatives have the potential to promote keratinocyte differentiation, suggesting a potential use for treating skin diseases involving abnormal keratinocyte differentiation.



Several ceramide derivatives were synthesized.

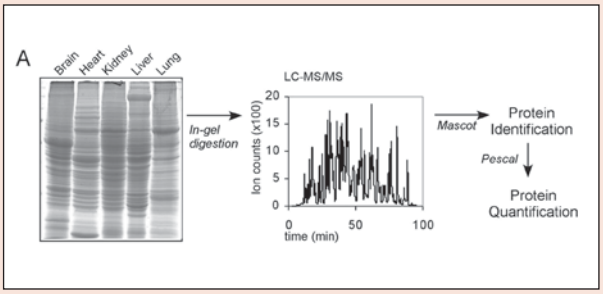
Novel Synthetic Ceramide Derivatives Increase Intracellular Calcium Levels and Promote Epidermal Keratinocyte Differentiation

Yoo Bin Kwon, Chang Deok Kim, Jong-Kyung Youm, Hyung Sub Gwak, Byeong Deog Park, Seung Hun Lee, Saewha Jeon, Bo Joong Kim, Young-Joon Seo, Jang-Kyu Park, and Jeung-Hoon Lee

J. Lipid Res. 2007 **48**, 1936-1943.

A New Way to Phenotype Mice

The laboratory mouse has been extremely helpful in advancing our understanding of how genes control fundamental processes of mammalian physiology. However, once a new transgenic mouse is created, the task of finding its phenotype is not trivial. But, with the publication of this paper, this task may have gotten a little easier. The authors have developed a new high throughput method for profiling the proteomes of primary tissues in a quantitative fashion. They developed a computer program and normalization procedures that allowed them to quantify mixtures of proteins, including those in mammalian primary tissues, using label-free LC-MS/MS. The authors applied their approach to quantitatively characterize the most abundant proteins in murine brain, heart, kidney, liver, and lung. These results not only provide new insights into the major similarities and differences between the protein compositions of the main murine organs, they also serve as an example of how label-free quantitative MS can be used to characterize the phenotype of mammalian primary tissues at the molecular level.



Strategy for the identification and quantification of mouse primary tissue proteins.

Quantitative Profile of Five Murine Core Proteomes Using Label-free Functional Proteomics

Pedro R. Cutillas and Bart Vanhaesebroeck

Mol. Cell. Proteomics 2007 **6**, 1560-1573

Vern Schramm: Using Transition States to Create Powerful Drugs

BY PAT PAGES

Most drugs cause side effects because they affect not only the source of a disease but other healthy tissues as well. But thanks to groundbreaking research pioneered by Vern Schramm, Ruth Merns Chair of Biochemistry at the Albert Einstein College of Medicine of Yeshiva University, New York, new drugs that may have significantly fewer side effects are being tested for diseases ranging from cancer to multiple sclerosis and malaria.

For most of his career, Schramm has studied how molecules change shape during enzymatically catalyzed chemical reactions. His research has led him to design compounds to inhibit enzymes that are targets for human disease. Such compounds are now being tested in both humans and animals for their effects on diseases such as cancer, malaria, and various infectious diseases.

"This work has led to some of the tightest binding enzyme inhibitors known," Schramm says. "These inhibitors can be used as drugs that last longer and result in significantly fewer side effects than many drugs currently available."

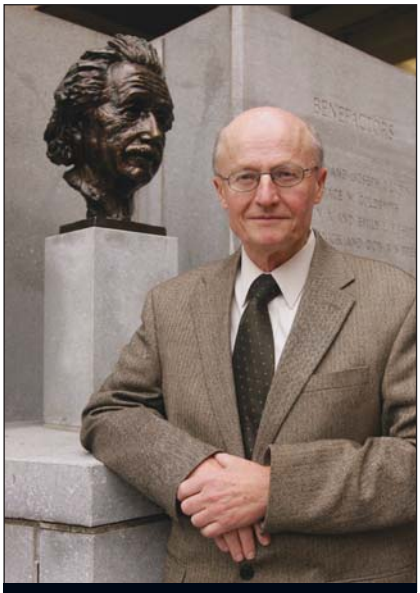
Schramm grew up in Howard, South Dakota. As a child, he liked tinkering with things and spending countless hours playing with his chemistry set. In the high school he attended he also spent hours in the library reading chemistry articles in the Encyclopedia Britannica. "I really enjoyed learning," Schramm says. "My high school was pretty small, and the teachers, who were both very good and ready to help, were probably the reason I pursued science later."

Schramm went to South Dakota State University in Brookings, about 60 miles from his hometown. To pay for his tuition during the first three years, he worked part-time in the chemistry stockroom, where he and other chemistry majors were responsible for stocking the chemistry teaching laboratories. Between his junior and senior years, Schramm became a research assistant in the Microbiology Department, which fostered his interest in microbiology and influenced him to major in the subject.

After graduating in 1963, Schramm went to Harvard University to pursue a master's degree in nutrition. There he took his first course in biochemistry from Nobel Prizewinner Konrad E. Bloch. He also took courses in nutrition, radiochemistry, and protein science at Harvard Medical School and pursued research under the supervision of Robert Geyer, professor of Nutrition at Harvard's School of Public Health.

"These inhibitors can be used as drugs that last longer and result in significantly fewer side effects"

When he was about to complete his master's degree, Schramm saw a recruiting announcement at Harvard Medical School's library for a Ph.D. position at the Australian National University, Canberra. The successful candidate would receive a stipend along with paid travel. Excited about the topic of the Ph.D. thesis—understanding enzyme mechanisms—and the location, Schramm applied and was accepted. With his wife and first child, Schramm drove to California and boarded the P&O Orient ship "Himalaya" to Australia.



Vern Schramm

At the Australian National University, Schramm worked for his Ph.D. thesis with John Morrison, professor of Biochemistry in the John Curtin School of Medical Research. Schramm spent three years trying to better understand the mechanisms involved in the enzymatic formation of bonds between nucleotides and phosphates. He also studied the interaction of the allosteric and active sites of enzymes.

When he came back to the U.S.,

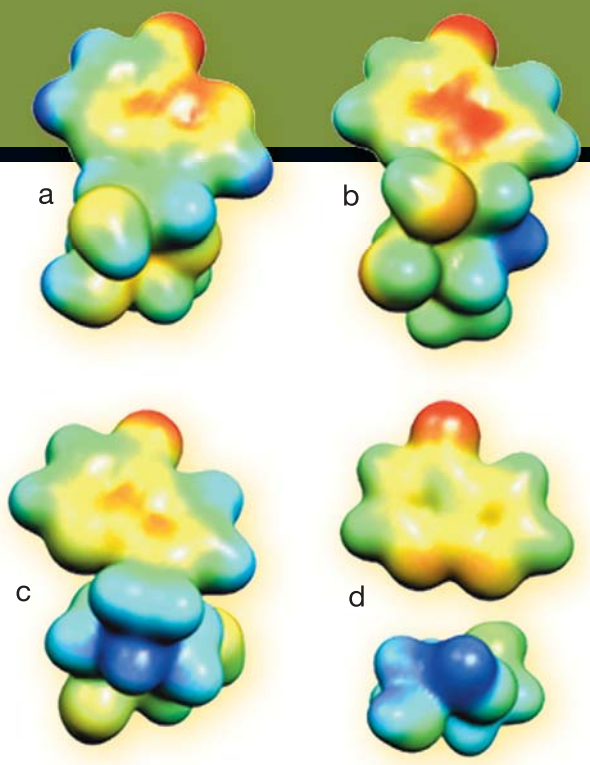


Fig. 1. Transition states and transition state analog inhibitors for human PNP. a, molecular electrostatic potential (MEP) surface for inosine, a substrate for PNP. b, MEP for Immucillin-H, a transition state analog for early PNP transition state. c, MEP of DADMe-Immucillin-H, a transition state analog for late PNP transition states. d, MEP for the transition state of human PNP, a late transition state.

Schramm applied for a National Research Council-National Science Foundation postdoctoral fellowship. He proposed a research project which, if funded, could be pursued at any federally supported research laboratory. He was awarded the fellowship and chose to go to the Biological Sciences Division of NASA's Ames Research Laboratory, Mountain View, California. The laboratory was conveniently located on the grounds of Moffett Field Naval Air Station, where Schramm earned a private pilot license in his spare time.

At Ames, Schramm began his studies of *N*-ribosyltransferases, enzymes of microbes living under extreme environments—such as very high or very low temperatures—to understand how potential microbes on other planets may survive similar harsh environments. Later, he began what would become a life-long interest in purine metabolism with research on the enzymatic mechanism of purine nucleoside phosphorylase.

In 1971, Schramm joined the Department of Biochemistry at Temple University School of Medicine, where he remained as a member of the faculty for the next 16 years. At Temple, he studied how substrates interact with enzymes in the course of chemical reactions and initiated his studies of transition states—the activated forms of substrates that have partly undergone a chemical reaction.

"Enzymes have evolved to efficiently form the transition state, and they also bind tightly to compounds called transition state analogs that mimic the transition state," Schramm says. "Enzymatically catalyzed reactions are typically one billion to one million billion times faster than uncatalyzed reactions, and transition state analogs have the potential to bind this much tighter to the enzyme than a substrate."

Schramm and his chemistry collaborators at Industrial Research Ltd., New Zealand, designed transition state analogs which, when given to patients, bind tightly to specific disease causing enzymes and inhibit them.

Because many diseases can be treated by inhibiting enzymes, the idea of using enzyme inhibitors as drugs—first suggested by quantum chemist and biochemist Linus Pauling in 1946—is now well established, and one-third of the drugs approved by the U.S. Food and Drug Administration act as enzyme inhibitors. But despite the wide appeal for the use of transition state analogs as drugs, designing the analogs has not been easy.

While at Temple, and later at the Albert Einstein College of Medicine, Schramm and colleagues took on the difficult task of designing such analogs. To determine precisely the chemical structure of the transition state, the researchers exploited the fact that the rate of a chemical reaction varies when an atom in the substrate is replaced by one of its isotopes, a

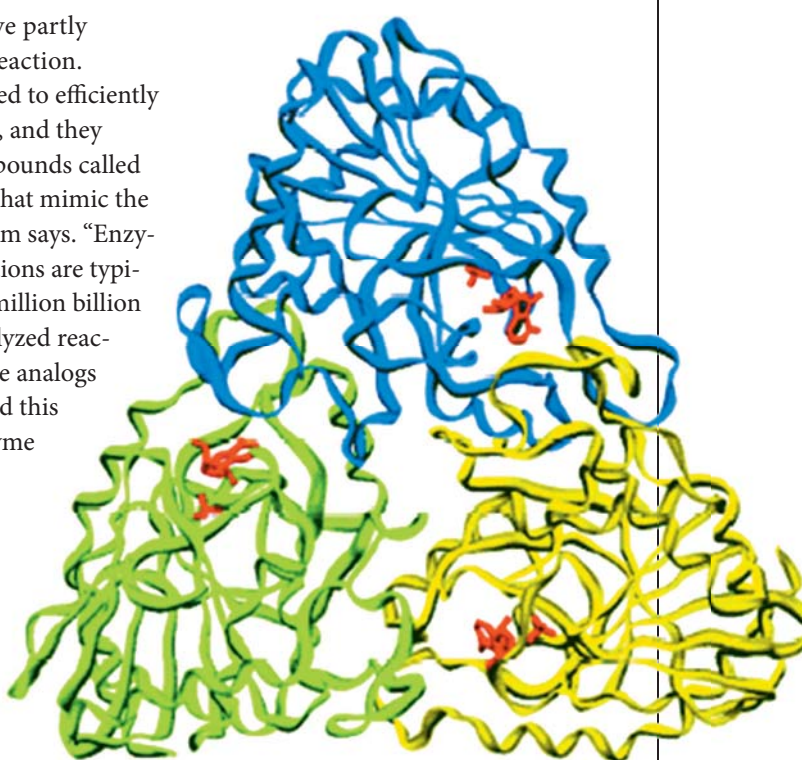


Fig. 2. PNP bound to its inhibitor complex, Immucillin-H and phosphate (in red).

property called the kinetic isotope effect. For example, a reaction in which a CH bond is broken proceeds more slowly if the hydrogen atom is replaced with a deuterium.

Schramm and colleagues replaced different atoms—usually, hydrogen, carbon, oxygen, and nitrogen—at the reaction site of the substrate with their isotopes and determined how the rate of a given chemical reaction changes following these substitutions. Then the researchers performed mathematical calculations that predict the chemical structure of the transition state based on the various chemical rates. The calculations, which are now performed by computers, led to a three-dimensional representation of the transition state.

The scientists then synthesized a chemically stable molecule that closely resembled the transition state. "The transition state analog does not need to be exactly like the transition state molecule," Schramm says. "Even when analogs are only similar to the transition state, they still bind very tightly to the enzyme."

During the past decade, Schramm's team has designed a large family of transition state analogs that act as powerful inhibitors of many disease-related enzymes.

One such inhibitor is a promising anticancer agent that blocks purine nucleoside phosphorylase (PNP), an enzyme essential for the rapid division of cells that cause T cell leukemia. Called Immucillin-H, this drug candidate is currently in phase II clinical trials—which are carried out on patients to test the effectiveness of the drug—at sites in the U.S. and Europe. Although the transition state of PNP was identified in 1993, it took four years of meticulous work to make the first transition state analog and three more years before the inhibitor could be tested in clinical trials.

Another transition state inhibitor developed by Schramm is now being studied as a possible treatment for autoimmune diseases such as psoriasis, rheumatoid arthritis, multiple sclerosis, and inflammatory bowel disorders and for preventing the rejection of transplanted organs.

Schramm's team has also designed an inhibitor that blocks methylthioadenosine phosphorylase (MTAP), an enzyme involved in the polyamine pathway and in recycling by-products of the pathway to *S*-adenosylmethionine. In 2004, the scientists reported a family of powerful transition state analogs that inhibit MTAP. Inhibition of MTAP prevents the proliferation of head and neck tumors. Although one inhibitor has already shown promise in animal models of cancer, it has not yet reached clinical trials.

In 2005, Schramm's group reported a family of powerful inhibitors of 5'-methylthioadenosine/*S*-adenosylhomocysteine (MTAN), a bacterial enzyme that is involved in the synthesis of molecules used by bacteria to communicate with one another and cause prolonged chronic infections. The inhibitor is now being tested in animal models as an antimicrobial agent.

Encouraged by these successes, Schramm's team is now working on transition state analogs for the treatment and possible prevention of malaria. He is also working on a rescue therapy for ricin, a lethal plant toxin that attacks mammalian ribosomes and is used in cancer immunochemotherapy.

While Schramm continues to work on the fundamentals of enzyme transition state theory, he is also excited about the therapeutic applications of his research. "When we started working on transition state structure and analog design, their medical prospects were clearly appealing, but we didn't know how long it would take us to design actual drug candidates," Schramm says. "It has been satisfying to see the work progress so well and also that our results may one day provide new approaches to treat such important diseases as malaria, cancer, and autoimmune disorders."

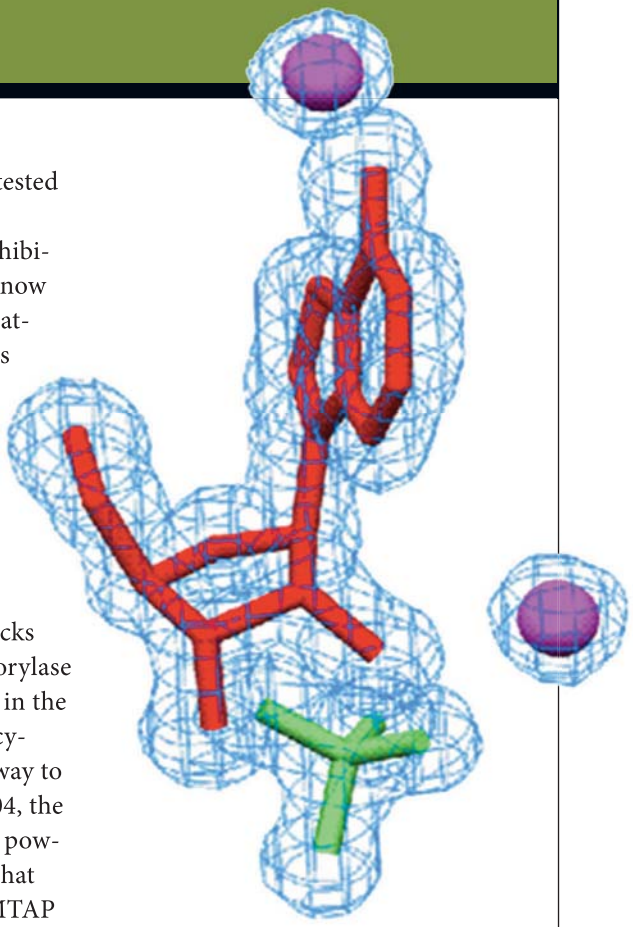


Fig. 3. Close up of the electron density of Immucillin-H at the catalytic site of bovine PNP.

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Celia Schiffer: Avoiding Drug Resistance

BY PAT PAGES

Celia Schiffer

Despite intense research efforts and improved access to treatment, AIDS is still claiming millions of lives worldwide every year. Although many infected individuals survive through therapies that combine various drugs, HIV mutates relatively quickly, limiting the effectiveness and longevity of the drugs and requiring the constant development of new drugs.

But designing more effective and longer lasting drugs by limiting viral resistance may be possible, thanks to research performed by Celia A. Schiffer, professor of Biochemistry at the University of Massachusetts Medical School, Worcester. For the past 10 years, Schiffer and colleagues have been trying to understand how drugs that initially block HIV-1 protease—a protein that helps HIV mature and spread—become ineffective over time. Her work has shown how proteases become drug-resistant and how to counter such resistance by designing better drugs.

"Amazingly, modern drug design rarely considers the occurrence of drug resistance," Schiffer says. "Traditional drug design techniques do not focus on how the drug interacts with its target—such as HIV-1 protease inhibitors as an example of AIDS drugs—but rather focus only on disrupting the target's activity. We are starting a new strategy to avoid drug resistance from occurring in the first place."

Schiffer and colleagues are designing novel potential drugs that promise to be more effective and relieve AIDS patients from having to change their drug regimen regularly. The new strategy also may reduce drug resistance in other diseases, including lung cancer and hepatitis C.

Early Interests in Logical Reasoning and Science

Schiffer grew up in the Chicago suburbs in a close and supportive family of scientists, the daughter of John P. and Marianne Schiffer, both senior scientists at the U.S. Department of Energy's Argonne National Laboratory, near Chicago. During her childhood, she was curious about the world around her, especially the outdoors and the natural environment. Although she remembers reading books about biology, such as *Microbe Hunters*, by Paul de Kruif, and popular physics books by Isaac Asimov, what Schiffer liked most was how to solve problems and answer questions in a logical manner.

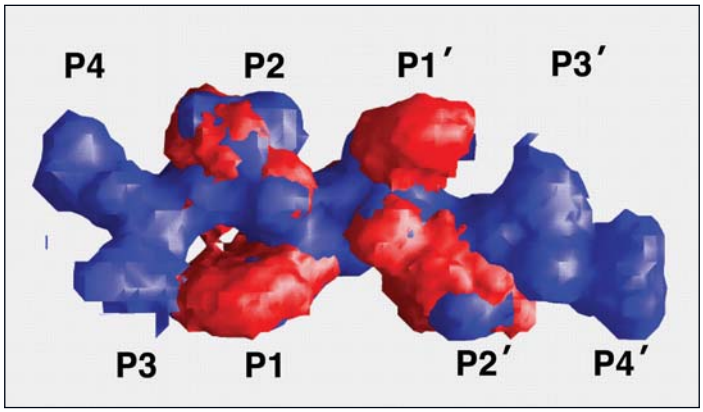

Fig. 1. The "substrate envelope" (*blue*) overlapping the "inhibitor envelope" (*red*).
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In the first two years of high school, Schiffer was involved in a history fair, where students carried out historical research on a particular topic and presented their results in a competition similar to a science fair. She was also on the high school debate team, where she and a partner developed a "case" that they would defend against other schools' teams throughout the debating season.

"Debate taught me how to form and defend a logical argument, how to think on my feet, and how to speak in a public forum," Schiffer says. "These skills became invaluable since I have used them continuously throughout my career."

Schiffer went to college at the University of Chicago, where she majored in physics. "Physics taught me how to think," she says. Over

the years, Schiffer also developed a keen interest in chemistry and biology. "I always saw the separations of the different fields of science as artificial," she says. "For me, physics, chemistry, and biology have always been a continuum, not distinct fields."

During her junior and senior years, Schiffer did some research in biophysics. She learned how to use an electron microscope and study crystalline intermediates of sickle cell hemoglobin. "It was fascinating to look into an electron microscope and actually see the structure of biological macromolecules that have medical relevance," Schiffer says.

Scientific Research across Disciplines and Continents

After earning her B.A. in physics, Schiffer went to the University of California, San Francisco, to pursue a Ph.D. in biophysics. She worked with Robert M. Stroud, a professor in the Department of Biochemistry and Biophysics, learning protein crystallography and solving the crystal structure of human thymidylate synthase, a key enzyme in the production of DNA precursors and a target in the treatment of colorectal cancer. She found that the active site folded in an unexpected way, suggesting that the protein was more dynamic than scientists had recognized previously.

Schiffer also worked with the late Peter A. Kollman, professor of Chemistry and Pharmaceutical Chemistry, developing "homology modeling" computer programs to determine the structure of an unfamiliar protein by comparing it with a protein with known structure and function.

After completing her Ph.D. in 1992, Schiffer went to the Swiss Federal Institute of Technology, Zurich, Switzerland, where she was a postdoctoral associate in the laboratory of Wilfred F. van Gunsteren, professor of Computer-Aided Chemistry. She simulated the dynamic behavior of proteins and other biomolecules often combined with NMR spectroscopy and crystallographic data to study protein folding and their interactions.

In 1994, Schiffer was hired by Genentech, Inc., South San Francisco, as a postdoctoral associate in the Protein Engineering Department under the supervision of Anthony A. Kossiakoff, currently chair of the Department of Biochemistry and Molecular Biology at the University of Chicago. At Genentech, Schiffer pursued basic research while mastering some experimental techniques in molecular biology. Her research focused on understanding the molecular basis of how a high affinity variant of a human growth hormone optimally binds to its receptor.

"For me, physics, chemistry, and biology have always been a continuum, not distinct fields."

"Genentech offered me a very energetic environment, opened my eyes to new avenues of research, and taught me how to run an experimental lab," Schiffer says. "Before working at Genentech, most of my experience was in computational research, but the scientists I worked with showed me another side of research that complemented nicely what I learned from the academic world."

Understanding Drug Resistance in HIV

In 1998, Schiffer was hired as an assistant professor at the University of Massachusetts' Department of Biochemistry and Molecular Pharmacology, where she set up her own laboratory. Since then, Schiffer uses structural biology to investigate how HIV-1 becomes resistant to protease inhibitors.

Protease inhibitors, used in combination with other anti-HIV drugs—most commonly reverse transcriptase inhibitors—can reduce the amount of HIV in the blood to an undetectable level. But the virus often can become resistant to these drugs relatively quickly, and new drugs need to be developed to counter the HIV resistance.

Protease inhibitors block HIV-1 protease, which is used by HIV to allow the maturation of new viral particles. Once HIV infects a cell, it hijacks the cell's machinery to make large viral proteins called polyproteins, which contain the viral enzymes and structural proteins. The protease then recognizes and cuts the polyproteins at specific sites, releasing individual proteins that assemble into new infectious viruses.

Protease inhibitors prevent the protease from cleaving the polyproteins. Since viral maturation cannot occur without the processing of these polyproteins, viral replication is stopped.

Schiffer and her team noticed in their crystal structures that although the protein sequences of the substrates are very different from one another, their overall shapes are very similar. So the scientists decided to compare the average volume occupied by all substrates, defined as the "substrate envelope," in the protease active site to the volume occupied by the inhibitors, or "inhibitor envelope."

They discovered that although the substrate and inhibitor envelopes largely overlap, they vary at several positions. In particular, the inhibitors protrude beyond the substrate envelope, making contacts with residues in the active site that are not made by the substrates (Fig. 1). Schiffer's team noticed that HIV drug resistance evolves through mutations at these residues. As a result, the mutations preferentially prevent the inhibitors from binding to the protease but do not

significantly affect the recognition of the polyprotein substrates.

New Drug Design Paradigm

Based on these results, Schiffer and colleagues hypothesized that drug resistance could be avoided if a given inhibitor stayed within the volume of the substrate envelope (Fig. 2). "If this is the case, a mutation in the active site would simultaneously prevent the binding of the inhibitor to the active site and the recognition of at least half of the 10 substrate sites," Schiffer says. "It's basically a no-win situation for the protease—if it doesn't mutate, it is blocked by the inhibitor; if it mutates, it can't efficiently cleave the polyproteins. For the infected patient, it's good news, because the virus is compromised."

"But drug resistance could still occur—although it would be unlikely—as both the protease and five or more of the substrate sites within polyproteins would need to simultaneously co-evolve," Schiffer notes. "Although cases in which both HIV-1 protease and a single substrate site mutate together have been reported, multiple substrates simultaneously co-evolving have not been observed."

Schiffer's laboratory has been involved in the structural and biophysical characterization of the protease inhibitor Darunavir, developed by Tibotec, Inc., Mechelen, Belgium, and recently approved by the U.S. Food and Drug Administration. This drug has served as a proof of principle that clinically viable inhibitors can fit within the substrate envelope and has successfully reduced the viral load of infected patients resistant to other protease inhibitors.

"The clinical success of Darunavir likely results from the fact that it binds extremely strongly to the protease and that it predominantly fits within the substrate envelope, thus making it more difficult for resistance to evolve," Schiffer says.

In 2001, Schiffer started a program that brought together research groups from around the country, spanning the fields of medicine, virology, computational chemistry, and organic chemistry, to understand how drug resistance arises and to design protease inhibitors that are less susceptible to drug resistance by using her substrate envelope hypothesis. So far, the scientists involved in this program have designed thousands of new inhibitors and synthesized and tested hundreds of them.

"Many of these new inhibitors look promising, retaining high affinity for many drug-resistant forms of HIV-1 protease and fitting within the substrate envelope," Schiffer says.

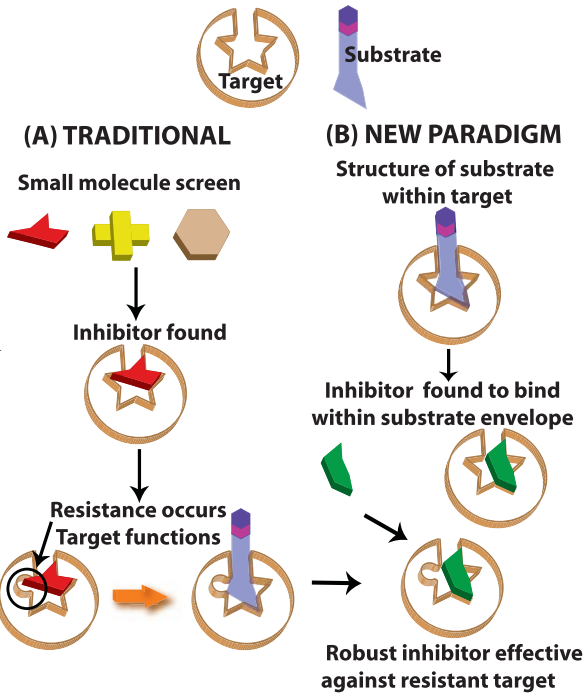

Fig. 2. (A) traditional drug design strategy and occurrence of drug resistance; (B) novel "substrate envelope" inhibitor design strategy to avoid drug resistance.

Beyond HIV

Schiffer and colleagues have recently initiated a research program to study the molecular details of substrate recognition and inhibitor binding by serine protease NS3, a therapeutic target for hepatitis C. The program's goal is to compare the substrate envelope with some of the inhibitors currently in clinical trials in a way similar to what Schiffer and colleagues did with HIV protease inhibitors and eventually design new inhibitors that will be less susceptible to resistance.

"Designing inhibitors that are not susceptible to drug resistance by studying how substrates are recognized by a given molecular target—such as HIV-1 protease in the case of AIDS—represents a paradigm shift in drug development and could be used to treat not only AIDS but also many other quickly evolving diseases," Schiffer says. "I hope that this new drug design paradigm will soon lead to more effective and longer lasting drugs for diseases for which drug resistance is a critical issue, such as AIDS, hepatitis C, and cancer."

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- Assessment Issues Workshop
- Classroom of the Future III
- Incorporating Research into Formal Laboratory Courses Workshop
- Starting and Sustaining Undergraduate Research Workshop
- Writing Your First Grant Application Workshop

Public Affairs

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Abstract Submission Deadline: November 7, 2007