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ASBMB Today

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Comments

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'Locked in the Past'

I was most impressed and pleased to read the comments in the article entitled 'Is Biology Education Locked in the Past?' in the November issue of *ASBMB Today*. I think it could not have been more on the mark, particularly on issues relating to the failure of our educational systems to integrate math and the physical sciences (and chemistry) with biology and placing at least some of the blame on the pre-med curriculum. I wanted to draw your attention to an article in *Academic Medicine* (December issue) wherein I authored an article that suggests many similar ideas but from the perspective of one who teaches biochemistry/genetics/cell biology to first year medical students who have been under-educated by their pre-med experiences. I wrote my article in response to the vocalizations of stress from many course directors and faculty in hopes of providing some context for rethinking what we have done and could do. I have even gone as far as to proposed a revision for the undergraduate curriculum in the biology/pre-med major.

I would like to suggest that many of the ASBMB members are finding themselves with similar perspectives as you and I are professing. I hope that there may be an opportunity to contribute further comment in upcoming issues of *ASBMB Today* as I believe change will only come from continued expression such as ours.

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Tell Us What You Think

We appreciate receiving letters, that are suitable for publication in *ASBMB Today,* from ASBMB members with their comments on issues of importance or articles that have appeared in the magazine. Letters should be sent to the editor, John Thompson, at the address at the left, and must contain the writer's address and telephone number. The editor reserves the right to edit all letters.

A Home for Proteomics Data?

By Matthias Mann

This article from the November 7, 2002, issue of the journal *Nature* is reprinted in its entirety with the permission of the publisher.

Molecular and Cellular Proteomics
Editor Ralph A. Bradshaw
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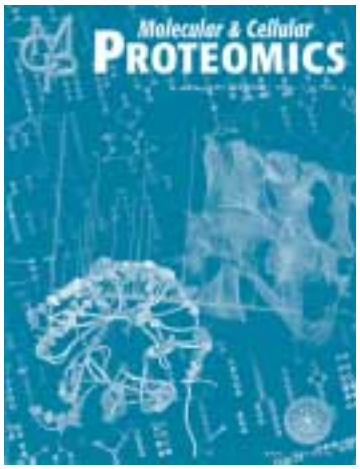

Suppose you have just finished an exciting study involving the identification of hundreds of proteins that are part of a complex, or that change in response to some condition. Where can you publish your results? This is a real problem. If you send them to a biological journal, the reviewers may tell you that that you should get functional data for the proteins, which could take you the rest of your career. If you send them to a technologically or analytically orientated journal, they will say that your methods have already been adequately described in the literature and so your paper is not very interesting. So you may just sit on your proteins, and have them worked up by incoming graduate students over the years, which would be a loss to the scientific community.

Enter *Molecular and Cellular Proteomics (MCP),* a spin-off from the *Journal of Biological Chemistry (JBC),* the official outlet for the American Society for Biochemistry and Molecular Biology. This new journal is dedicated to studies just like the one described above, and therefore meets a real need.

Judging from the articles published in the first few issues, the mission statement and the composition of the editorial board, *MCP* takes an expansive view of proteomics, embracing subjects such as bioinformatics related to proteomics, protein databases, two-hybrid methods for protein interactions, two-dimensional gel studies, and mass-spectrometric methods.

There are three categories for original articles: research, database and technology. Another new feature is the online site, which, as well as displaying an electronic version of the printed journal, is intended to function as an associated database for the proteomics investigations described in the papers. This material can be much more extensive than usual, and *MCP* is working on navigation and visualization features. The quality of papers published so far is good, with a few groundbreaking papers already in the bag.

Publication speed is, in my experience, quite rapid, with the additional advantage that accepted papers are put on the web immediately, even while the paper is being edited into the final version. This can be quite useful for authors in a publishing race.

Where should *MCP* stake its claim in the publishing food chain? The premier position in proteomics is taken by *Nature Biotechnology,* and breakthrough biological results will also probably be reported elsewhere. *MCP* is well positioned to become to proteomics research what *JBC* is to biological research, a standard place for solid results that have undergone stringent peer review and that will be easily accessible to almost everyone. For this to happen *MCP* needs to maintain or even strengthen its reviewing standards, and focus on the quality of papers rather than the number published if it is to achieve an impact factor similar to that of *JBC.*

Once the journal is firmly established and its identity is clear in everybody's mind, there should be no shortage of papers as proteomics methods and proteomic-scale experiments become more commonplace. The *Journal of Proteome Research,* launched at almost the same time by the American Chemical Society, is likely to concentrate more on technological advances, and *Electrophoresis* and *Proteomics* will probably continue to be more focused on the two-dimensional-gel community.

The format of *MCP* articles varies somewhat, and standardization would make the journal more visually appealing. In extension of its online features mentioned above, *MCP* could perform a great service by helping to establish some standard as to how proteomics data collections are published and visualized so that they can actually be used by biologists.

In conclusion, faced with the dilemma I outlined at the start, I would encourage you to publish your proteins in *MCP.* Scientists with similar data should think 'out of the box' and submit their proteomics data for the community to use, and now there is a place for them to do it.

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www.mcponline.org

Researchers Identify Cause of

Researchers have generated a mouse model of a new type of tumor suppressor gene that triggers a rapidly advancing cancer that affects children. The discovery of the fast-onset cancers that result from inactivation of the gene and the technique used to generate the model will likely prove useful in studying genes involved in other forms of cancer.

The research team, which was led by ASBMB member Stuart H. Orkin, Howard Hughes Medical Institute Investigator and Professor and Chair, Department of Oncology, Dana Farber Cancer Institute and Harvard University, and Dr. Charles Roberts, Children's Hospital, Boston, and Harvard Medical School, reported its findings in the November 2002 issue of the journal *Cancer Cell*.

The tumor suppressor gene, called SNF5, codes for a protein that is a component of a large complex called SWI/SNF that attaches to chromatin to regulate the expression of genes. Chromatin is the complex of DNA and proteins in the nucleus of the cell.

"There has been indirect evidence that some types of chromatin remodeling complexes might play a role in cancer," said Dr. Roberts. In a key finding reported in 1998, French researchers showed that mutations that inactivated SNF5 were present in tissue samples from children with malignant rhabdoid tumors. "That's what first caught our interest, that we might be dealing with a new type of tumor suppressor," he added. Malignant rhabdoid tumors are rare but highly aggressive cancers that usually appear in infancy. These tumors are resistant to treatment and usually cause death within a year of diagnosis.

With the initial evidence that SNF5 was involved in such tumors, the team set out to establish in mice that loss of SNF5 did indeed produce cancers. The problem, said Dr. Roberts, was that the usual methods for knocking out the gene did not produce a useful model of rhabdoid tumors in the mice.

Dr. Stuart Orkin

"Mice that are deficient in SNF5 die very early in embryonic development, and therefore cannot be used to analyze for cancer," he said. "And mice that lack only one of the two genes show a relatively low prevalence of tumors, with a median onset of about twelve months." Thus, while these mouse models did demonstrate that SNF5 was necessary for development, and that its loss caused cancer, such mice could not be used to analyze how SNF5 loss affected the development of this form of cancer.

To construct a more useful model, the scientists turned to a "conditional targeting approach" that enabled them to knock out SNF5 in some mouse cells but not others. This approach involved engineering the mice so that the SNF5 gene would function normally throughout development, but could later be

ASBMB Member Receives Energy Department Award

Secretary of Energy Spencer Abraham has presented The Institute for Genomic Research (TIGR) President and Director, Claire M. Fraser, Ph.D., with the E.O. Lawrence Award for her "contributions to genome analysis technology, its extension to the understanding of microbial diversity, and its application to human pathogens."

Claire M. Fraser, Ph.D

Dr. Fraser, an ASBMB member received the award along with six other prominent scientists at a ceremony in Washington, D.C. The Lawrence Award was established in 1959 to honor the memory of the late Dr. Ernest Orlando Lawrence, who invented the cyclotron particle accelerator. Two major Energy Department laboratories, in Berkeley and in Livermore, California, are named after Lawrence.

Dr. Fraser was honored in the award's Life Science category. She received a gold medal, a citation and $25,000. The award is given for outstanding contributions in the field of atomic energy, which has influenced many other fields of science, such as environmental research, materials science, and nuclear medicine.

She led the TIGR teams that sequenced the genomes of *Mycoplasma genitalium*, the spirochetes *Treponema pallidum* and *Borrelia burgdorfei*, and two species of *Chlamydia*. She is now overseeing several major research projects, including the genomic sequencing of Bacillus anthracis, and is a member of National Research Council committees on countering bioterrorism and on domestic animal genomics.

Aggressive Childhood Cancer

knocked out in adult mice by the introduction of a triggering chemical. This trigger chemical activates an enzyme that excises the gene under study.

> ***"It will be especially important to link this tumor suppressor with a known pathway of tumorigenesis."***
>
> **—ASBMB member Stuart H. Orkin**

Deletion of SNF5 in the mice revealed that SNF5 was required for the survival of adult mice and, in fact, for survival of virtually all normal cells. In order to circumvent the lethality and generate a working cancer model, Dr. Roberts and Dr. Orkin took the conditional targeting a step further. They engineered the knockout system so that instead of being snipped out, the SNF5 gene would randomly invert in the process of being knocked out. In some cells, the gene would assume a normal orientation after triggering, and in others it would be inverted, and thus nonfunctional.

"This was an adaptation of a technique that researchers Kong-Peng Lam and Klaus Rajewski had used to study lymphoid cells, but it had not been applied to cancer modeling," said Dr. Orkin. "The trick was to make the gene we wanted to delete, instead of being excised, to flip back and forth and then randomly settle in either the active or inactive orientation."

By employing this technique, the team created mice whose tissues had a delicate balance of cells with normal and inactivated SNF5 genes. There were enough cells with normal SNF5 to allow the mice to live longer, but enough with inactivated SNF5 genes to give rise to cancers. According to Dr. Orkin, the mice engineered to have the "reversible, inverting conditional" knockout genes showed immediate onset of cancers. Most of the mice developed malignant lymphomas, or cancers of the blood cells, while many also developed rhabdoid tumors.

"The fact that the mice showed consistent oncogenesis in a very short time means that we can crossbreed the animals with other genetically altered mice to sort out the cellular pathways that are affected," he stated. "It will be especially important to link this tumor suppressor with a known pathway of tumorigenesis. Ultimately, if we know what pathway is affected, we can target therapies to that pathway." Dr. Orkin and his colleagues believe that the reversible knockout technique could be applied generally to aid the study of other tumor suppressor genes in which complete deletion of the gene proves lethal.

According to Dr. Roberts, understanding the mechanism of SNF5-related cancers could have significant clinical impact. "There have been many papers showing the role of SNF5 loss in human cancers," he said. "It's clear that the gene is involved in malignant rhabdoid tumors and that it may be involved in certain other aggressive cancers in early childhood. This work has led us to realize the existence of an entirely novel tumor suppressor pathway, the SWI/SNF complex of which SNF5 is a core member. And, we believe that understanding the basic genetics, biochemistry and molecular biology of SWI/SNF, is likely to generate significant new understanding, and potentially therapies, for many types of human cancer."

Caught Sleeping:
Study Captures Virus Dormant in Human Cells

Cytomegalovirus, hidden in most people, begins to give up secrets of its stealth

Princeton scientists have taken an important step toward understanding a virus that infects and lies dormant in most people, but emerges as a serious illness in transplant patients, some newborns and other people with weakened immune systems.

The virus, called human cytomegalovirus, enters the bone marrow and can hide there for a lifetime. Until now, however, scientists had not been able to study the virus in its latent stage because it infects only humans and does not readily infect or become dormant in laboratory strains of bone marrow cells.

In a study published online Nov. 27, Felicia Goodrum, a postdoctoral fellow, and ASBMB member Thomas Shenk, Professor of Molecular Biology, demonstrated a laboratory system for studying the virus in its latent stage. They showed they could establish a latent infection in freshly collected bone marrow cells and then retrigger an active infection. They drew on their system to discover a set of genes that the virus uses in its latent state and that may give the virus its great capacity for stealth.

Knowing what genes the virus uses to hide and re-emerge could give pharmaceutical companies targets for designing drugs that disrupt those mechanisms. "So you could dream that some day in the future we could clear the virus from a person and not just treat the symptoms that occur when the virus re-emerges," said Dr. Shenk.

Cytomegalovirus is in a broad family of herpes-related viruses, which includes the virus that causes chicken pox and shingles. The only treatment doctors currently have for cytomegalovirus is an antiviral drug called gancyclovir, which stops the virus from replicating during its active infection phase, but has no effect during the latent stage, when the virus does not replicate.

Another possible use for the research would be to develop a diagnostic test that indicates when the virus is likely to reactivate itself. If scientists could pinpoint genes that turn on just in advance of reactivation, then doctors could use that information in deciding whether to administer antiviral drugs to their patients. Currently, doctors prescribe gancyclovir preemptively for many patients, even though it has significant side effects.

The researchers described their results in an online edition of the *Proceedings of the National Academy of Sciences*. Dr. Goodrum and Dr. Shenk collaborated with Dr. Craig Jordan of the University of Kentucky Medical Center and Dr. Kevin High of the Wake Forest University School of Medicine, who supplied human bone marrow cells and expertise in working with them.

The key to the study's success, said Dr. Shenk, was Dr. Goodrum's painstaking work in learning to handle freshly harvested bone marrow cells in the lab and to maintain them in a state that matches as closely as possible their condition in the human body. Her supply of cells was limited because they are badly needed for bone marrow transplantations, so she could use only cells that were caught in a filter used in transplant procedures.

Dr. Shenk said her work makes it possible to answer big questions that have long eluded researchers. It is unknown, for example, what specific cells the virus infects among the many constituents of bone marrow. In their study, Dr. Goodrum narrowed the search to a group of cells that constitute just 1 percent of bone marrow cells. The next step, she said, will be to look at even smaller subpopulations of cells and compare the activity of the virus and its genes in each of them.

"We'd like to know the answers to some very basic questions," said Dr. Goodrum. "How many copies of the virus are there in an infected cell? And how exactly do they get passed along?"

"These are all things you get to think about when you have a model system," said Dr. Shenk. "You couldn't do it without the system Felicia developed."

Understanding the virus is important because roughly half of all organ or bone marrow transplant patients, who are always given immune-suppressing drugs, experience some complication with cytomegalovirus, he said. Women who become infected or experience a reactivation during a pregnancy risk passing the virus to the fetus, which can lead to birth defects, including deafness and developmental disorders.

Between 50% and 85% of Americans become infected with cytomegalovirus by age 40, according to the National Institutes of Health. Dr. Shenk said he believes the figure may be even higher, because every sample Dr. Goodrum has studied had at least some cells that were infected with the virus.

ASBMB Members Among Six To Share GSK Award

Two ASBMB members are among the six HIV/AIDS researchers who will split $500,000 as the 2002 recipients of the GlaxoSmithKline (GSK) Drug Discovery and Development Award. The unrestricted research award program is funded by GSK to support independent, innovative, and novel research in the development of HIV/AIDS therapeutics.

The ASBMB members named to share the award are Irwin Chaiken, Research Professor, Department of Medicine, University of Pennsylvia School of Medicine, and Elias Lolis, Associate Professor, Department of Pharmacology, Yale University.

Dr. Chaiken's award was for his work studying the interactions between proteins that allow HIV to recognize and enter a host cell, research that potentially will lead to drugs that prevent the virus-cell fusion process; Dr. Lolis received the award for his work in attempting to solve likely side effects of some of the experimental entry inhibitor drugs.

Dr. Irwin Chaiken

"The latest therapies have worked very well in keeping the deadly AIDS virus at bay, but HIV is crafty and continually is mutating and developing resistance to drugs," said Doug Manion, M.D., Vice President of Clinical Development for GSK. "HIV and AIDS therapy research must continually move forward if we are to stay one step ahead of this disease. We feel strongly that the best way to do that is to encourage and reward support researchers attempting to develop new approaches to therapies with no strings attached."

Preventing HIV From Infecting Host Cells

Dr. Elias Lolis

HIV works by invading a target immune cell in the human body and turning it into an HIV factory, leading to the infection of new host cells, the overwhelming of the immune system, and eventually, AIDS. Ideally, a drug would be developed to prevent HIV from docking on a host cell to begin with, stopping the infection process.

Many researchers are feverishly working toward such a drug. Among them is Dr. Chaiken who has been awarded $150,000 by GSK for his work. When HIV meets a potential host cell, a series of interactions occurs between the viral proteins and the host cell receptor proteins, leading to the eventual fusion of the virus with the cell.

Dr. Chaiken is studying specific protein interactions in that pathway. "We want to learn how the virus initially sees the host cell, so we can determine how to inhibit its binding to the cell," he explains. "Current HIV medications attack enzymes that are being produced once the cell has been infected. If drugs could be developed to prevent the virus from docking on the cell, we could stop the infection process in the earliest stages of cell invasion. This methodology also could have implications for treatment of other viral diseases, such as hepatitis and influenza."

Overcoming a Therapeutic Dilemma

Entry inhibitors are some of the newer drugs that are being tested. They aim to interfere with the early process of the virus infecting the host cell. Included in the chain of events that comprise that process is the involvement of a host cell surface protein, CXCR4.

"Blocking CXCR4 is problematic, because research suggests it is necessary for proper immune system function," says Dr. Lolis who was awarded $50,000 for his research. That research involves attempting to identify molecules—allosteric agonists—which would allow the use of entry inhibitor drugs while overcoming this problem.

ASBMB Member to Join National Science Board

President Bush has nominated ASBMB member Douglas D. Randall, Professor of Biochemistry and Director of the Interdisciplinary Program on Plant Biochemistry-Physiology at the University of Missouri, to the National Science Board. Dr. Randall previously served as Assistant Professor for Agricultural Chemistry at the University of Missouri.

Also to be nominated are Ray M. Bowen, former President of Texas A&M University; Jo Anne Vasquez of Arizona an author and national science consultant; Steven C. Beering, President Emeritus of Purdue University; Barry C. Barish, Linde Professor of Physics at the California Institute of Technology; Daniel E. Hastings, Associate Director of the Engineering Systems Division at the Massachusetts Institute of Technology; Kenneth M. Ford; and Delores M. Etter, Professor of Electrical Engineering at the United States Naval Academy.

The New Congress and the Implications for Biomedical Research

By Peter Farnham, ASBMB Public Affairs Officer

The Senate will be more conservative, more willing to cut taxes, and less inclined to compromise with their Democratic colleagues when Congress reconvenes in January. Spending on biomedical research and other science programs will likely be affected, although perhaps not as much as many might expect.

The GOP gained two Senate seats and had a majority of 51-48, with 1 independent (Jim Jeffords of Vermont).

The most important change in the Senate as a result of the switch to GOP control is that all committee and subcommittee chairs will change. Here are some of the most important changes for science.

The Senate Appropriations Committee chairmanship will switch from Senator Robert Byrd (D-WV) back to Senator Ted Stevens (R-AK). This will probably be helpful for biomedical research, as Stevens has long been a supporter of NIH, and chaired the committee during the early years of the doubling campaign.

The new chairman of the Senate Budget Committee is expected to be Don Nickles (R-OK), who is known as a tax-cutter. The Budget Committee is responsible for coming up with a broad, overall spending plan each year. However, the only binding number developed by the Committee that can affect biomedical research is the overall total for domestic discretionary spending. This figure (which includes defense and non-defense spending) is what is left over after mandatory spending (on social security and other programs where spending levels are determined by law) and interest on the national debt are subtracted from the total amount of money available.

But, the allocation of domestic discretionary spending among federal domestic programs is under the jurisdiction of the Appropriations Committee, and with Senator Stevens in charge there, it is pretty likely that NIH will not be affected by the new regime at Budget.

It is unclear at the moment who will end up chairing the Commerce, Science and Transportation Committee, which oversees some science agencies such as the National Science Foundation. John McCain (R-AZ) is slated to take over based strictly on seniority. If McCain takes the chairmanship, his sometimes quirky, maverick style may lead to some surprises.

However, there are rumors that Arlen Specter (R-PA) may want to chair this committee. This has sparked fears that he might decide to give up his chairmanship of the Appropriations Subcommittee on Labor, HHS and Education, where he has been biomedical research's staunchest friend in the Senate during the campaign to double the NIH budget. If he were to step down as chairman of this key subcommittee, next in line would be Thad Cochran (R-MS), a much more conservative politician than Specter. This could impact the size of future increases for NIH, as Cochran would likely go along with much smaller increases than Specter would tolerate.

Senator Judd Gregg (R-NH) is in line to take the chairmanship of the Committee on Health, Education, Labor and Pensions, replacing outgoing chairman Edward Kennedy (D-MA). This committee has oversight over NIH and the education programs at the National Science Foundation. This is an important change, as Gregg is far more conservative than Kennedy and would be much more averse to spending increases. On the other hand, he has been a backer of education reform, and spent time on the House Science Committee in the 1980s.

The new chairman of the Senate Judiciary Committee is expected to be Orrin Hatch (R-UT), a solid friend and supporter of biomedical research, including stem cell research. Hatch would take over from Patrick Leahy (D-VT), who supports biomedical research but is not particularly vocal about it. However, under Hatch's leadership, the Judiciary Committee will likely try to chip away at the backlog of unconfirmed judges, and so this will probably take up a great deal of Hatch's time next year.

Legislation banning human cloning is certain to be reintroduced this year, and we are likely to see dueling versions of the legislation, with one banning any use of embryos in research, and the other

drawing the line on human cloning at implantation of a cloned embryo. The Judiciary Committee played a role in this controversy last spring, and may well do so again this year. It is likely that neither version of a ban will have enough votes to pass the Senate, as 60 votes will be needed to overcome a certain filibuster.

In the House, a strict ban along the lines of the Weldon bill would likely pass if introduced, but opponents will make a much tougher fight than they did in the last Congress, as they will have time to organize and launch a counter campaign in favor of medical research.

The Republicans retain the majority in the House which they gained in 1994, and now have 229 seats (with 218 needed for control). This is a 6-seat gain.

Science Committee Chairman Sherwood Boehlert (R-NY) was reelected handily after surviving a tough primary. Also reelected was Rep. Jim Walsh (R-NY), chairman of the VA/HUD Appropriations Subcommittee, and Rep. Ralph Regula (R-OH), chairman of the L/HHS Appropriations Subcommittee. Ranking Democrats on these two subcommittees Alan Mollohan of West Virginia (who was running unopposed) and David Obey of Wisconsin also were reelected.

An interesting rules change in the House Republican Caucus takes effect in the new Congress—all committee and subcommittee chairs must be approved by the whole caucus. This is widely perceived as an effort of the House leadership to rein in certain appropriations subcommittee chairmen who habitually try to spend more than the President wants. Therefore, there could be internal GOP fights over spending for NIH and NSF in 2003. So far, however, there is no hint that there will be wholesale changes in House committee and subcommittee chairmanships, although a few surprises are of course possible once Congress gets down to serious business in early February after the President's State of the Union address.

The only two Republicans who lost reelection bids were co-chairs of the Congressional Biomedical Research Caucus. Rep. George Gekas (R-PA) lost his race, 51-49%, to another incumbent, Democrat Tim Holden, who through redistricting had been thrown into a race against Gekas. Gekas' district had been redrawn to make it more reliably Republican, and President Bush made several visits to Gekas' district in an effort to keep him in office, but Holden ran an unexpectedly tough campaign.

Another tough loss among our champions is Rep. Connie Morella (R-MD), who represented Montgomery County (home of NIH) for 8 terms. She lost to Chris van Hollen, a former Maryland state legislator. This district has been highly Democratic for many years and redistricting following the 1990 census made it more so. Morella was also a co-chairman of the Biomedical Research Caucus.

In fact, of the six caucus co-chairs, four will not be returning in the 108th Congress. In addition to Gekas and Morella, Rep. Ken Bentsen (D-TX) lost his seat when he unsuccessfully ran for the Senate last spring; and Rep. Sonny Callahan (D-AL) is retiring. A fifth co-chair, Nancy Pelosi (D-CA), has been elected Minority Leader, replacing Rep. Richard Gephart (D-MO), and is unlikely to continue as caucus co-chair. The sole remaining incumbent chair is Lois Capps (D-CA), who has not been a particularly well known supporter of biomedical research.

Gene Profiling Reveals the Essence of 'Stemness'

"We were quite stringent in our criteria for which stem cells to look at, choosing only those that everyone agreed were, indeed, stem cells," said ASBMB member Douglas A. Melton, an HHMI Investigator and Professor in the Department of Molecular and Cell Biology, Harvard University.

An extensive genetic comparison of different types of stem cells and terminally differentiated cells has revealed that hundreds of genes are likely to be involved in shaping the characteristic properties of stem cells. The studies show that embryonic, neural and hematopoietic (blood-cell-forming) stem cells seem to share a common genetic program that may be important for "stemness."

These initial gene-profiling studies provide basic information about the nature of stem cells that should aid long-term efforts to induce stem cells to differentiate into cells that can be used to replace tissue damaged by disease or trauma.

Dr. Melton and his colleagues at Harvard University described their findings in an article in the September 12 issue of *Science Express*, which provides electronic publication of select articles from the journal *Science*.

"There has been a great deal of excitement about the possibility that adult stem cells are entirely plastic, that is, they are able to become any tissue in the body," said Dr. Melton. "However, there have been questions about whether such conclusions were correct. This led us to wonder if we could figure out whether stem cells were, in fact, all similar. And a related and critical scientific question is what genes or genetic programs are important for stem cells to have their special properties, or 'stemness.'"

To get at the answers to those questions, he and his colleagues developed experiments to survey thousands of genes in different kinds of stem cells and mature cells to determine if there are patterns of gene activity that are distinct to stem cells.

The scientists compared embryonic stem cells, neural stem cells and hematopoietic stem cells—all from the mouse. The researchers compared the patterns of gene activity in stem cells to the gene activity exhibited in differentiated forms of these cells, including adult brain cells and bone marrow cells. Their studies identified stem-cell-specific genes that were distinct from those involved in the normal growth of mature cells.

The researchers performed their surveys by first isolating the messenger RNA (mRNA) from the cells. The presence of mRNA indicates that genes are expressed. They then used commercial DNA arrays containing some 12,000 genes to determine which genes were active in the cells. Statistical analysis of the results offered insights into the genetic programs used by stem cells.

"First, we showed that there is a common genetic program among bona fide stem cells," said Dr. Melton. "But we also found that these three types of stem cells were not identical."

The researchers identified 216 "stemness" genes that are active in each of the three types of stem cells that were studied. An important sign that the analysis was valid, said Dr. Melton, was that the genes that were enriched in the stem cells included those that are commonly used as distinguishing markers for the cells.

The Harvard researcher said the "stemness" genes they found fit into categories that reflect the activities that stem cells must perform to self-renew and differentiate. "For example, these stem cells seem to be highly enriched in gene products involved in dealing with environmental toxins, which enables them to cope with stress," he explained. "Beyond that, they seem to have unregulated genes for receptors that enable them to receive signals from extracellular proteins. These might be important for signaling the cells to start differentiating."

While the scientists did find that the stem cells were genetically distinct from one another, there were interesting differences between stem cells and their differentiated counterparts. "One very nice happenstance was the finding that embryonic stem cells and neural stem cells are much more similar to each other than they are to their differentiated counterparts," said Dr. Melton. "This fits with a 'default model' we proposed, which is that the default fate of embryonic stem cells is to become neurons."

The studies show that embryonic, neural and hematopoietic (blood-cell-forming) stem cells seem to share a common genetic program that may be important for "stemness".

Comparing stem cells with their differentiated counterparts revealed genetic differences that will offer clues to developing techniques to induce

continued next page, column 3

Congress Returns With Last Year's Money Bills Still Unpassed

Congress was set to return in early January with a new Republican majority in the Senate, an expanded Republican majority in the House, and with only two of the 13 regular appropriations bills for FY 2003 having been passed—over three months into the fiscal year. Most of the government is operating under a continuing resolution in effect until January 11. Continuing resolutions are temporary spending measures that fund government operations at current spending levels.

Congress has two choices—it can complete work on some or all of the appropriations bills for 2003, or it can continue to govern by continuing resolution. Unfortunately, the latter is becoming more likely, with even senior legislators acknowledging the possibility. What is worse, there is now serious talk of a one-year continuing resolution, funding the government for the rest of the year at last year's levels.

The Labor/HHS bill is always one of the most contentious appropriations bills (it has been signed on time only three times in the past thirty years). This year the bill has been caught in a fight over the total for discretionary spending, with conservative House Republicans wanting to keep the bill at the administration-proposed level, and most Democrats and moderate Republicans wanting $9 billion more in additional funding, along the lines of the Senate Appropriations Committee L/HHS bill passed in July.

It would of course be best for the biomedical research community for the funding situation regarding NIH to be resolved as quickly as possible after the new year. If it remains unresolved into the spring—or worse, if NIH gets caught up in a one-year continuing resolution—NIH may not get the funds needed to complete the doubling of its budget on time.

Other factors outside the purview of biomedical research could also work against a completion of the doubling. A war with Iraq, another major terrorist attack on American soil, and an economy that continues to sputter, could all weaken NIH's claim to funding priority. In addition, the education community continues to press for additional resources, and education remains a very high priority even for many NIH champions.

NIH continues to enjoy strong support, however. At the end of the last Congress, Senator Arlen Specter (R-PA) introduced a resolution calling for a tripling of NIH by Fiscal Year 2008, with the base being the NIH's 1999 budget of $13.6 billion. Under this resolution, the NIH budget would rise to almost $41 billion by 2008. This would require about 8.5% increases from 2004 through 2008. Although the resolution went nowhere in the waning days of the 107th Congress, Senator Specter will undoubtedly reintroduce it next year.

What about NSF?

The National Science Foundation's funding situation is slightly better than NIH's, but the agency may still suffer, as Congress has not approved the VA/HUD bill either (a second perennially contentious funding bill). Both House and Senate appropriations subcommittees have approved NSF increases of about 13% overall, with about 15% increases for research. The House report calls for a management review of the agency, signaling some congressional discomfort with the agency's policies and management practices.

Gene Profiling ...

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stem cells to differentiate into adult cells, he added. "These findings provide a starting point to help people think how to cause stem cells to differentiate down specific pathways, such as becoming neurons that could rejuvenate brain tissue lost to neurodegenerative diseases," he said.

According to Dr. Melton, the findings are likely to aid the search for new types of stem cells. "For example, nobody has yet been able to identify adult pancreatic stem cells—a central effort in our laboratory," he said. "But now we know that if we're going to isolate such cells, we should look for those that express many of these 'stemness' genes."

Another significant development, he noted, was that the studies revealed that the stem cells expressed large numbers of "expressed sequence tags," which mark genes of unknown function. "For young scientists, this finding is especially exciting because it shows that these stem cells express a large number of genes that no one has a clue what the gene products do," he said. "What's more, it's easily a decade's worth of work just to define the functions of the genes that we have defined as characteristically active in these stem cells."

ASBMB Annual Meeting

April 11-15, 2003 San Diego

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EB 2003

Late-Breaking Abstract Deadline: February 26

Early Bird Registration Deadline: February 13

Housing Deadline: March 7

Opening Lecture
Fritz Lipmann Lectureship:

Friday, April 11 - 6:00 p.m.
"Ion Channels"
Roderick MacKinnon, HHMI, The Rockefeller Univ.

Public Affairs Lecture:

Sunday, April 13, 8:30 - 9:30 a.m.
Elias Zerhouni, Director, NIH

Award Lectures:

FASEB Excellence in Science Award
Saturday, April 12 - 8:30 - 9:30 a.m.
Joan A. Steitz, HHMI, Yale Univ.

ASBMB-Merck Award
Monday, April 14, 8:30 - 9:30 a.m.
Stephen J. Benkovic, The Penn State Univ.

William C. Rose Award
Monday, April 14, 5:00 - 6:00 p.m.
Jack E. Dixon, Univ. of Michigan Med. Sch.

ASBMB-Avanti Award in Lipids
Tuesday, April 15, 8:30 - 9:30 a.m.
Robert Bittman, Queens College, CUNY

Schering-Plough Research Institute Award
Sunday, April 13, 5:00 - 6:00 p.m.
Catherine Drennan, MIT

NIH Director to Address ASBMB Annual Meeting

NIH Director Elias Zerhouni will address ASBMB members at 8:30 a.m. Sunday, April 13, at the Society's Annual Meeting in San Diego.

Dr. Zerhouni, who was sworn in as NIH Director last May, will update the audience on the latest developments concerning the Institutes' goals, priorities, and research projects, and is expected to be available for questions from the audience following his address.

After taking office, he held a series of "town meetings" with NIH staff and residents in the area around the Institutes' Bethesda campus, in which he outlined some of his thoughts about his new responsibility.

Regarding priorities, he said, "I really think that the life sciences are a top national priority for the first half of the 21st century. … It's an area where we know the least, and it is still the number one scientific challenge for mankind.

"We do not exist in a stable relationship with our environment, there are emerging and reemerging diseases. … We need to establish our research priorities in order to accelerate our efforts. We've been generously supported, and now the challenge is what to do with it."

Regarding NIH funding, he told one "town hall" meeting that he never wants to be without an answer to the question, "What did you do with the budget?"

About Stem Cells

Asked, at one meeting, about an alleged slowness to develop stem cells, Dr. Zerhouni argued that stem cell research is still in a very early stage, and that it is too early to say whether adult stem cells are less valuable than those harvested from human embryos. "It would be presumptuous to guess where therapeutic advances will be made," he said. "We need to walk before we run. We need to pursue the field, and invest in it because disease knows no politics. I believe that we at NIH must be factual, not factional."

Dr. Elias Zerhouni

At the Senate committee hearing on his nomination, Dr. Zerhouni said he would live within established guidelines on stem cells and conduct such research in an "open and transparent" manner; emphasized that NIH should play a major role in "ingraining a culture of safety" in trials involving humans; explained that clinical trials have their own "ecosystem" that must be managed and understood; and maintained NIH must do more to understand the self-destructive behaviors that lie behind much preventable disease.

In testimony before the Senate Appropriations Subcommittee on Labor, HHS, Education in September, Dr. Zerhouni testified:

"Properly harnessed, adult and embryonic stem cells have the potential to replace cells that are damaged or diseased to restore vital functions of the human body. They offer the promise of curing disease and ending disabilities at some point in the future. So there are ample reasons for excitement about stem cell research, and high expectations for new treatments are understandable. But such expectations should be tempered by the enormous challenges that must be addressed before the research evolves into proven therapy.

"These challenges involve both human embryonic stem cell research and adult stem cell research. Human embryonic stem cells and adult stem cells have potential as future therapies. I believe that NIH should continue to fund research on both types of cells.

"We are at a very early stage of embryonic stem cell research, and have a great deal of basic research to conduct before we can unlock the potential of these cells and fulfill their promise. I will describe the pathway of discovery that I believe will unfold as the research evolves from stem cell lines to cell based therapy. In the basic research phase, which is the current focus of NIH-supported activities, we first need to build the scientific capacity. As is true for any area of research, progress depends on attracting outstanding scientists to design and perform the needed studies. NIH is providing opportunities for the scientific community to develop training courses for researchers to acquire the skills needed to culture embryonic stem cells, as well as opportunities to support stem cell research career pathways. NIH has already taken major steps to accomplish this goal by supporting infrastructure awards to expand cell lines, refine culture methods, and establish improved methods to select the most desirable embryonic stem cell populations."

Former ASBMB President

The 2003 William C. Rose Award will be presented to Jack E. Dixon, who served as ASBMB President in 1996. He also served on the *JBC* Editorial Board, as has his wife, Dr. Claudia Kent. The Award recognizes outstanding contributions to biochemical and molecular biological research and a demonstrated commitment to the training of younger scientists, as epitomized by the late Dr. Rose. Recipients over the past five years include Robert Simoni, Richard W. Hanson, Rowena G. Matthews, Marc W. Kirschner, and Gordon Hammes. Nominators and nominees need not be members of the Society. The Award consists of a plaque, a stipend, and transportation to the 2003 Annual Meeting to present a lecture, Monday, April 14, 5 p.m. to 6 p.m.

Currently the Minor J. Coon Professor of Biological Chemistry, University of Michigan Medical School, in February Dr. Dixon will join the University of California, San Diego as Professor in the Department of Pharmacology, Cellular and Molecular Medicine, as well as having an appointment in Chemistry and Biochemistry. He will be continuing his research and also serving as Dean of Scientific Affairs.

Dr. Dixon has brought a strong chemical background and expertise in biochemistry and molecular biology to his research investigations. Early in his career, he was a leader in research on the biosynthesis and post-translational processing of polypeptide hormones. He adopted the tools of molecular biology as they became available in the late 1970s, and his laboratory was among the first to use a synthetic oligonucleotide to isolate a cDNA for peptide hormones that are expressed at low levels. The deduced amino acid sequences of the precursors to somatostatin, cholecystokinin, and neuropeptide Y revealed that the peptides are synthesized as much larger precursors, which undergo proteolytic processing and other modifications necessary to generate the secreted peptides.

Using the tools of protein chemistry and fast atom bombardment mass spectrometry (FABMS), Dr. Dixon and his associates demonstrated previously unknown modifications of peptide hormones such as hydroxylation and O-linked glycosylation. He also pioneered in the use of FABMS to identify the chemical nature of the post-translational modification in studies that resulted in a new approach for assigning disulfide bonds in proteins.

In the late 1980s, Dr. Dixon's lab turned its attention to the recently discovered protein tyrosine phosphatases (PTPases). His lab has been a pioneer and intellectual leader in the structure and function of the PTPases as well as determining many of their important roles in signal transduction. He has demonstrated that the unique catalytic mechanism of the PTPases proceeds via a novel cysteine-phosphate intermediate. He discovered the first dual-specificity phosphatase, which led to the identification of the cell cycle protein, $p80^{cdc25}$, as a phosphatase. He also showed that the bacteria responsible for the plague or "black death" harbor the most active PTPase ever described. He and his colleagues went on to demonstrate that this PTPase gene product is essential of the pathogenesis for the bacteria. He and his colleague, Dr. Mark Saper, also determined X-ray structures for both tyrosine and dual specificity phosphatases.

Dr. Dixon also found that sequences outside of the PTPase catalytic domain could function to direct the subcellular localization of the PTPases and to restrict their substrate specificity. This is now a widely acknowledged regulatory paradigm for the PTPases. Recently, his lab also determined the function of the tumor suppressor gene PTEN, which shares sequence identity with the PTPases.

Although the PTPases function to dephosphorylate phosphoproteins, Dr. Dixon's lab demonstrated that PTEN catalyzes the dephosphorylation of a lipid second messenger, Phosphatidylinositol 3,4,5- trisphosphate (PIP3). PIP3 activates the protein kinase, AKT, which plays a critical role in controlling apoptosis and cell survival. The loss of the PTEN gene elevates PIP3 levels leading to constitutive activated AKT. Activated AKT signals cells to survive, and these surviving cells can become oncogenic. This insightful biochemical observation has contributed greatly to our understanding of how PTEN functions as a tumor suppressor gene.

Dr. Dixon's unexpected and insightful observations on PTEN function have radically altered thinking about this tumor suppressor gene. His observations have had an important effect on cancer biology due to the importance and wide spread loss of PTEN in many human cancers. In collaboration with Dr. Nikola Paveltich, the lab also determined the crystal structure for PTEN, which in turn suggested how PTEN functions as a specific phosphoinositide phosphatase.

The discovery that PTEN was a phosphoinositide phosphatase promoted the search for other presumed "protein phosphatases" that might function as inisitol lipid phos-

to Get William Rose Award

Dr. Jack E. Dixon

phatases.

Recently Dr. Dixon's lab identified a protein phosphatase known as myotubularin as the second example of a phosphoinositide phosphatase. Myotubularin specifically dephosphorylates Phosphatidylinositol 3 phosphate. Mutations in the myotubularin gene cause a disease known as X-linked myotubular myopathy. The unanticipated identification of the novel function of myotubularin suggests that the underlying cause of this muscle myopathy involves aberration in phosphoinoside metabolism.

Two recent studies from the lab illustrate the breadth of Dr. Dixon's scientific contributions. Since the discovery of the PTPase in the pathogen bacteria responsible for the plague, his lab has continued its interest in the molecular aspects of bacterial pathogenesis. His lab has recently demonstrated that a Yersinia effector protein (YopJ) is a protease that degrades ubiquitin-like proteins. YopJ homologs are found in bacteria pathogenic to animals, plants, and plant symbionts, suggesting that this mechanism of proteolysis is used to modulate a wide variety of signaling pathways present in the animal and plant kingdoms. Finally, in collaboration with ASBMB member Dr. Larry Zipursky at UCLA, Dr. Dixon's lab identified a novel receptor that is required for axonal guidance in the fly. Remarkably, the gene encoding this receptor can undergo alternative splicing to generate more than 38,000 different receptor isoforms. This molecular diversity is likely to contribute to the specificity of neuronal connectivity.

In summary, Dr. Dixon has made a number of important discoveries in his career that spans almost 30 years. He is perhaps best known today for his striking discoveries on the biological function and mechanism of action of the protein tyrosine phosphatases. You can meet him at the ASBMB Annual Meeting.

Jack Dixon as Teacher

The William Rose Award is given in recognition of a demonstrated commitment to the training of younger scientists, and ASBMB member Howard Zalkin, Professor Emeritus of Biochemistry at Purdue University, speaks eloquently of Dr. Dixon's commitment in this regard.

"Jack and I were close faculty colleagues when Jack was in the Department of Biochemistry at Purdue University," wrote Dr. Zalkin in support of Dr. Dixon's nomination for the Award. "When I returned in the summer of 1973 from a sabbatical at Stanford, Jack was a newly arrived Assistant Professor and was setting up his lab in the basement of Smith Hall, a small Dairy Science building adjacent to the main Biochemistry Department building. Jack was recruiting a group of new biochemistry graduate students, some undergraduates and technicians and was enthusiastically promoting his research ideas.

"Some of Jack's early students were, quite frankly, a collection of less than superbly motivated, research-challenged individuals. There was "Stormin Norman" whose main interest was playing in the Purdue marching band, another was a ballroom dancer who spent considerable time at Arthur Murray's dance studio, and one was a superb singer who distinguished herself in the Lafayette Bach Chorale. Jack exhibited a combination of enthusiasm, frustration, encouragement and firmness and was able to coax a surprising amount of accomplishment and productivity from this challenging group, as can be seen from their publications. That some of these early students developed an interest in research and continued their training in postdoctoral positions is a testament to Jack's skillful mentoring.

"In the years that followed, Jack built one of the most impressive laboratories in the life sciences at Purdue (the other was Michael Rossman's in protein and virus crystallography). It was based on exciting, state of the art science, a supportive environment, terrific lab facilities and high expectations for success. His lab was perceived to be one to join for a timely project and top preparation for a research career. Jack attracted and trained some of our top students. One example that comes to mind is Bob Deschenes (Professor of Biochemistry, University of Iowa). Bob when he interviewed in 1999 and declined an offer to be Head of the Department of Biochemistry at Purdue credited Jack as his model for how to do research and provide an environment for success.

There are others like Bob but I am

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Stephen Benkovic to Receive

Stephen J. Benkovic, Evan Pugh Professor and Eberly Chair in Chemistry, at Pennsylvania State University, has been selected to receive the 2003 ASBMB-Merck Award. The Award recognizes outstanding contributions to research in biochemistry and molecular biology. Recipients over the past five years include Paul Zamecnik, Alexander Rich, Robert L. Baldwin, Peter H. von Hippel, in 2001 the Award was shared by Avram Hershko and Alexander J. Varshavsky, and in 2002 by Robert G. Roeder and Robert D. Kornberger. Nominations must be originated by Society members, but the nominees need not be ASBMB members. The Award consists of a stipend, plaque, and transportation and expenses of the recipient and spouse to the 2003 Annual Meeting to present a lecture. Dr. Benkovic's lecture will be Monday, April 14, 8:30 - 9:30 a.m.

In nominating him for the Award, Gordon Hammes, University Distinguished Professor of Biochemistry, Duke University, wrote:

"Dr. Benkovic is one of the leading mechanistic enzymologists in the world. In fact, I would put him at the top of the list. He has made many important contributions in many different areas: his versatility has been remarkable. What sets his work apart from others is his mastery of many different fields: organic chemistry, physical chemistry, biochemistry, and molecular biology. For example, he has carried out studies of model enzyme reactions using state of the art physical organic chemistry methods and synthetic techniques. His studies of enzyme mechanisms utilize these same techniques, as well as modern kinetics, especially stopped flow, and physical chemistry, for example, fluorescence resonance energy transfer. He has studied many different enzyme systems, ranging from glycolytic enzymes to folate requiring enzymes to DNA polymerase, including the very complex T4 replication system. The biochemistry and molecular biology utilized for this mechanistic work, in addition to the organic and physical chemistry, are very impressive.

Dr. Stephen Benkovic

"His studies of folate requiring enzymes have been the foundation for understanding the mechanism of action of these enzymes in molecular detail. Studies from many other laboratories have used this research as a starting point. This work has also been of fundamental importance in the design of cancer drugs. His recent work on DNA polymerase, especially the T4 complex, has been the class of the field in elucidating the molecular mechanisms. The T4 replication complex is incredibly complex; yet Dr. Benkovic has managed to delineate clearly the sequence of molecular events by use of a myriad of techniques and is now approaching a molecular understanding of the structure/function relationships in this system. He has also contributed to the more global question of how enzymes work, for example, in his recent provocative work suggesting that motions far from the catalytic site may be important in catalysis."

Scientific Accomplishments

Dr. Benkovic prepared for his research in enzymology with training in physical bioorganic chemistry under ASBMB member Dr. Thomas C. Bruice, with whom he co-authored the classic two-volume set of texts, *Bioorganic Mechanisms*. He then moved from studies of organic models for biological phosphoryl and one-carbon unit transfer into investigations of the enzymes themselves. His experimental approaches are multidimensional and enriched by challenging syntheses, stereochemical analyses, various types of spectroscopy—especially NMR and fluorescence, isotopic labeling, transient kinetic methods, and various recombinant techniques.

With dihydrofolate reductase as the paradigm, he has explored a long standing puzzle, namely the source of the high catalytic efficiency of enzymes. This subject has been worked on by many prominent investigators, but he and an impressive list of collaborators have gathered over two decades compelling evidence for a perspective on biological catalysis differing from the traditional "transition state stabilization" as the primary cause for an enzyme's catalytic process.

The Benkovic group first dissected into individual steps the catalytic cycle used by dihydrofolate reductase (DHFR) using pre-steady state methods and pinpointed the contribution of various amino acids both within and outside the active site to specific steps. Surprisingly, significant changes in the rates of hydride transfer were not limited to active site residues, nor were the effects of multiple mutations additive in terms of free energy. The amide backbone and side chains of these distal residues were found by NMR to be in regions of high frequency motion (psec) and by molecular dynamic simulations (nsec) to be coupled. Genomic analysis of multiple DHFR sequences revealed low overall DNA sequence homology (30%), but surprisingly high conservation in the same regions and

ASBMB-Merck Award

specifically at the amino acids implicated in catalysis by kinetic analysis, NMR measurements and molecular dynamics simulations. A recent collaboration using a more sophisticated theory (electron valance bond methods) directly tied these distal residues to a movement along the reaction coordinate coupled to the hydride transfer.

In simple terms the perspective on biological catalysis proposed is one in which the Michaelis complex is preorganized so that active site residues and substrates are in conformations close to the transition state conformation. Only a small change triggered by movement in the protein fold along the network of conserved residues is needed to surmount the reaction barrier. The implications of this hypothesis are far reaching: protein folds dictate the type of chemistry that class of enzymes can accomplish (a rationale for the common mechanistic element extant in protein super-families); allosteric effects are a consequence of creating or inhibiting such networks; and drugs can be designed that target such networks.

Dr. Benkovic also explored the polymerase enzymes expanded now to include the T4 replisome. Initially his group painstakingly elaborated primarily by various rapid quench methods the kinetic steps that a DNA polymerase (Klenow fragment) uses to discriminate between correct and incorrect incorporation of nucleotides, in short, the source of its replicative fidelity. This scheme features conformational change steps that discriminate against nucleotide incorporation before and after the chemical polymerization step (the latter allows exonuclease editing). The structural locus of such changes has now been viewed in various crystallographic structures of the polymerase in liganded state. He then progressed to a beautiful, clean and painstaking reconstruction *in vitro* of the T4 replication machine for which he is internationally recognized.

Dr. Benkovic and his colleagues have defined the pathway by which the eight separate proteins that constitute the T4 system assemble through the use of ATP hydrolysis into the *four* units that carry out leading and lagging strand synthesis at a replication fork.

The combination of methodologies is dazzling: time independent and dependent fluorescence energy transfer measurements (FRET); specific crosslinking through mutagenesis, ultracentrifugation, isothermal calorimetry, rapid quench kinetics, unique DNA substrate structures, and etc. They have defined the dynamic, molecular events that surround the operation of the clamp loader and clamp proteins in the formation of the holoenzyme (clamp protein and polymerase).

With stopped flow FRET based experiments they demonstrated the series of ring opening/closing events undergone by the clamp protein (relative to its closed crystal structure) as it is threaded onto the DNA. They then combined this description with elegant site-specific crosslinking studies to capture the interactions between the polymerase/clamp protein in the holoenzyme, thus building *from* their respective structures a molecular view of the holoenzyme. In parallel, they discovered that the primosome is built up from a series of ring-like structures; with the helicase loading protein and primase existing as hexamers in the primosome forming process. Finally, with the aid of small DNA mini circles, they showed that leading/lagging strand DNA synthesis is coupled through at least the two polymerases and single stranded binding protein.

Dr. Benkovic's accomplishments, highly original and of unusual breadth, have had a profound impact on the way we think about how proteins function as catalysts. His papers are fine examples of intellectual creativity, taut reasoning, and insightful, experimental design. What is most impressive are the breadth of techniques and freshness of his ideas—a remarkable sense of what questions to ask—that continually place his work at the forefront of chemistry being done at the chemistry/biology interface. ℵ

Rose Award ...

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most impressed with the students and postdocs that Jack developed who were "diamonds in the rough."

Writing in the same vein, Dr. Arthur Weiss, Ephraim P. Engleman Distinguished Professor at the University of California, San Francisco, commented, "Jack has had an enormous influence on a large number of young investigators. First, he has trained an exceptional cadre of scientists in his own lab who have gone on to establish their own independent careers. However, I would also mention his influence on the many young people who have been inspired by his enthusiasm and passion for science. He has been an outstanding role model.

"Moreover, he has shown enormous interest at meetings for the work of young trainees. This is evident at any meeting that Jack attends. Jack can almost always be found at a poster session engaging in encouraging and lively discussions with young students or postdocs presenting their work. Jack clearly enjoys these interactions but I suspect that he also works hard in achieving the right balance of encouragement and

HHMI's Million

Dr. Richard M. Losick

Dr. Sarah Elgin

Dr. Ellen Fanning

The Howard Hughes Medical Institute (HHMI) recently announced the appointment of 20 scientists at research universities across the nation as its first HHMI Professors. Each of these leading researchers, who include three ASBMB members, will receive $1 million over the next four years to bring the creativity they have shown in the lab to the undergraduate classroom.

"Research is advancing at a breathtaking pace, but many university students are still learning science the same old way, by listening to lectures, memorizing facts and doing cookbook lab experiments that thousands have done before," stated HHMI President Thomas R. Cech. "We want to empower scientists at research universities to become more involved in breaking the mold and bringing the excitement of research to science education."

HHMI isn't the only one to see opportunities for improving the way undergraduates are taught science. The National Academy of Sciences, the Boyer Commission on Educating Undergraduates in the Research University, and the National Science Foundation all have studied the matter and made recommendations for more engaging and effective approaches to undergraduate science education.

Teaching of undergraduates tends to be undervalued at research universities, according to Peter J. Bruns, Vice President for Grants and Special Programs at HHMI. "By rewarding great teaching and supporting a synergistic interaction between research and undergraduate education, we hope to sow seeds of a fundamental change in the culture of research universities. We want the HHMI professors to demonstrate that active, productive scientists can be effective teachers too."

HHMI invited 84 research universities to nominate faculty members. A panel of scientists and educators reviewed 150 nominees' proposals and eventually selected 20 HHMI professors at 19 universities in 13 states. Three of those selected are ASBMB members.

Richard M. Losick, Harvard College Professor and Maria Moors Cabot Professor of Biology in the Faculty of Arts and Sciences, is a molecular biologist who will apply his grant to three programs designed to stimulate, and sustain undergraduate interest in the sciences.

One program, geared toward incoming freshmen with weaker backgrounds in science, will place selected students in faculty laboratories, where they can receive mentoring and gain hands-on research experience as a complement

Dollar Professors

to their lecture classes. "The idea is that we don't lose them to the sciences their first year here, and we get them to consider a career in experimental sciences," Dr. Losick explained.

For students from disadvantaged backgrounds, matching them with host laboratories could lead to salaried summer jobs and potentially establish long-term relationships between researchers and students.

Dr. Losick, who has taught at Harvard for more than three decades, and whose creative and caring approach to learning was honored two years ago when he was named a Harvard College Professor, also plans to challenge students who have exceptional experience in the sciences. By pairing postdoctoral researchers with undergraduates who, for instance, have already cloned and sequenced DNA in high school or have similarly advanced experiences before coming to Harvard, he hopes to nurture those undergraduates' interests and guide them to senior theses and careers beyond.

Dr. Losick's third goal is to develop his use of computer animation in the classroom. "In molecular biology, Web-based animation is a powerful heuristic tool," he says. "A lot of the things I teach are very dynamic."

DNA duplication, he noted, is carried out by "molecular machines with multiple moving parts. To try to explain this with a static diagram isn't as satisfactory as an animation that can show the process over time, parts moving, so you can get a real flavor of how molecular biologists view this as it's taking place inside a cell."

Sarah Elgin, Professor, Department of Biology, Washington University, St. Louis, summarized the goal of her program as "to bring both the tools and the thinking of genomics into our undergraduate curriculum, looking for ways to broaden the undergraduate experience, to move beyond the reductionist approach of intently examining one gene, toward considering the functions of the genome as a whole."

"We want to empower scientists at research universities to become more involved in breaking the mold and bringing the excitement of research to science education."

—HHMI President Thomas R. Cech

The program will consist of three phases.

Phase I. Create and teach a one-semester upper-level laboratory course, Research Explorations in Genomics, in which 10-15 junior and senior undergraduates will participate in a research investigation of a genome and/or a genome-wide functional response, using both wet lab and computer tools. This course will be co-taught with faculty from the Genome Sequencing Center and the Computer Science Department. Funds from the grant will be used to support postdoctoral and graduate students who will collaborate in designing the research problem and will be key participants in the course.

The research problem will differ each year, to build experience in managing both a DNA sequencing project and DNA chip project, with different model systems. The goal is to enable students to become comfortable in thinking about large data sets—how to generate them, how to analyze them, how to use them—as a research tool in biology. The course will aim to generate publishable data each year, with all participants as co-authors. A final product will be a description of how to manage such a course, and an assessment of its value to undergraduates as a research experience.

Phase II. Use the above experience and other sources to add genomic investigations to Bio 297 (Fundamentals of Biology II) and Bio 3051 (Fundamentals of Biology III: Genetics), sophomore courses for biology students. Both wet lab and computer approaches will be employed to develop student familiarity with large data sets, creating a view of the genome as a complex, interactive system.

Students in these courses currently clone a yeast DNA fragment and generate sequence data, identifying "their" gene (or sequence element) by BLAST. Plans are to introduce additional genomic tools (computer and lab) to explore the place of that sequence in the yeast genome and in evolution, and its function in the context of the cell. Investigations will be designed to maximize discovery for each student.

Phase III. Bring groups of four or five teachers to campus to participate in summer research on a genomic problem, continuing during a second summer in research and K-12 curriculum development. The impact of genomics on K-12 biology will be considered, looking at societal issues, teaching orientation and learning

experiences provided, aiming to modify, adapt, and design genomics materials appropriate for the K-12 classroom.

Washington University's "Modern Genetics for All Students" program is now in use in 22 St. Louis area high schools, and participating teachers, both experienced and new to research, will be drawn primarily from these schools. Plans are to use *Drosophila* in a set of investigations that directly link DNA analysis with Mendelian genetics.

Ellen Fanning, Stevenson Professor of Biological Sciences at Vanderbilt University, presented a summary of her plans.

The goal is to create a naturally-linked community of scholars that extends from the level of beginning undergraduates through advanced undergraduate and graduate students, to postdoctoral trainees, junior, and senior faculty members, all engaged in a shared teaching/mentoring and learning experience. The focus of this diverse group will be research related to the general topic of DNA replication.

A group of 10-12 freshmen is to be recruited each spring semester, and will spend the summer before their sophomore year as full-time research interns. This is designed to introduce the students to the excitement of research, build personal and professional skills that will be useful during the academic year, reduce barriers between beginning students and faculty, and foster a sense of community. The interns will complete several short rotations through the participating laboratories, immersing themselves in all aspects of the scientific culture through reading primary literature, writing, speaking, discussing, and experimenting. Advanced undergraduates, graduate students, postdoctoral trainees, and faculty members will serve as mentors. During the academic year, the interns will be encouraged to maintain their links with the community by enrolling for research credit hours in one of the labs. In the next two summers, the students may return to the program as full-time Research Fellows, mentoring the new interns while they continue to learn from more experienced members of the laboratories.

The program is intended to stimulate undergraduates to deepen their interest in molecular biology and is expected to attract highly talented, creative students into biological research. Undergraduates will benefit from close associations with scholars at all levels, and gain self-confidence as they assume mentoring responsibility themselves. Dr. Fanning expects to eventually have about 40 undergraduates involved, and to enhance the professional development of graduate students and postdocs interested in teaching positions.

New Study Ranks Universities

A report conducted by the Institute for Scientific Information (ISI) examined the citation impact of research papers produced at the top 100 federally-funded U.S. universities from 1997-2001.

The rankings were reported in the fall edition of ScienceWatch, ISI's newsletter devoted to tracking trends and performance in basic research. The report ranks universities in 21 fields in the biological, physical, and social sciences, both by the number of papers produced and by "impact," i.e. those papers important enough to garner citations in succeeding research papers.

According to ScienceWatch, the top 10 "highest impact" U.S. universities (from 1997-2001) are: Harvard (1); Stanford (2); Massachusetts Institute of Technology (3); University of California, San Diego (4); Yale University (5); University of California, Berkeley (6); Columbia University (7); Caltech (8); University of Michigan (9); and Duke University (10). In terms of the number of citations in the 21 fields, the University of California, San Diego tied with MIT with 9 appearances, preceded by Harvard with 15 appearances and Stanford with 11 and followed by Yale, UC Berkeley, and Columbia with 8 appearances.

NIGMS Funding Opportunities

NIGMS is a sponsor or co-sponsor of the recent funding announcements listed below along with the websites to access for further information.

Global Health Research Initiative Program for New Foreign Investigators RFA TW-03-006

http://grants.nih.gov/grants/guide/rfa-files/RFA-TW-03-006.html
Minority Access to Research Careers (MARC) Ancillary Training Activities Grants PAR-03-026

http://grants.nih.gov/grants/guide/pa-files/PAR-03-026.html
Research and Development of Systems and Methods for Cellular and Molecular Imaging RFA EB-03-003

http://grants.nih.gov/grants/guide/rfa-files/RFA-EB-03-003.html
Bioengineering Research Partnerships PAR-03-032

http://grants.nih.gov/grants/guide/pa-files/PAR-03-032.html

NSF Commended for Success In Streamlining Grants Process

The National Science Foundation (NSF) has been recognized as a 2002 E-Government Performance Leader by a coalition of private-sector good-government groups led by the Performance Institute. The NSF's award for Achievement of Cost Efficiencies was one of five made in four categories. The coalition report, *Creating a Performance-Based Electronic Government*, lauded NSF for its electronic process that handles 300,000 grant proposals and reviews each year.

"We're pleased to be recognized for our leadership and excellence in e-government," said NSF Director Rita Colwell. "The staff at NSF has risen to the challenge of successfully managing taxpayer resources, especially at a time of increased scrutiny and evaluation from inside and outside the federal government."

The report highlights NSF's FastLane system for electronic proposal processing. Developed by NSF's Division of Information Systems, FastLane allowed NSF to handle a 19% increase in proposals in fiscal year 2002 while reducing handling costs by 33%. FastLane has been presented to the Department of Health and Human Services as a model for a government-wide E-Grants initiative.

The result of a 24-agency research project by the good government coalition, the report provides a catalog of "citizen centered" initiatives in each agency along with key lessons learned. The Performance Institute, Reason Public Policy Institute, Fujitsu Consulting, the National Academy of Public Administration, the Council for Excellence in Government, the Progressive Policy Institute and the American Society for Public Administration sponsored the project. The project identified the best practices in defining and measuring e-government initiatives by federal agencies.

The Office of Management and Budget gave NSF the top rating in both financial management and e-government. NSF was the only one of 26 agencies to receive the top rating.

Sandia Partners With University to Offer Advanced Degree in National Security

College students have an opportunity to earn a Masters of Science Degree in National Security and Public Safety through weekend and evening classes at the University of New Haven. The program is in partnership with Sandia National Laboratories Livermore, California site, and members of Sandia's technical staff will be among those teaching specialized courses. The program is open to U.S. citizens holding a baccalaureate degree from an accredited institution.

Dr. Thomas Johnson, Dean and Director of the University's School of Public Safety and Professional Studies, said, "Our graduate concentration in Information Protection and Security, with research issues related to cyberterrorism and issues related to cyber-intelligence, will be enhanced by our ability to work with Sandia scientists."

The strategic collaboration between UNH and Sandia National Laboratories, he said, will produce graduates who will work within the intelligence community, as well as other National Security and Department of Defense entities.

Required courses include: Securing National Security Information Systems; Contemporary Issues in National Security Programs; Firewalls and Secure Enterprise Computing; Internet and Audit Based Computer Forensics; Computer Viruses and Malicious Code; Introduction to Practical Issues in Cryptography; National Security World and National Threat Modeling; National Security Charter, Legal Issues and Executive Orders.

ASBMB Welcomes New Ph.D.'s

ASBMB extends its congratulations to these individuals who recently received their Ph.D. degrees. In recognition of their achievement, ASBMB is presenting them with a free one-year membership in the Society. The new Ph.D.'s are listed below with the institution from which they received their degree.

Richard Darby
University of Southampton

Shelley L. Lusetti
University of Wisconsin, Madison

Notes From an AAMC Conference

By John D. Thompson, Editor

Maximizing faculty potential and dealing with industry were both on the agenda at "The Evolving Role of the Basic Science Department Chair," the October conference of the Association of American Medical Colleges (AAMC). And from the podium, those in attendance heard some sound advice on how to maximize the former and avoid conflict of interest with the latter.

Maximizing Faculty Potential

Diane W. Wara, Associate Dean for Minority and Women's Affairs at the University of California, San Francisco, School of Medicine, noted that "Unlike men, women tend to be stuck at the assistant professor level."

In this statement, she echoed the findings of an AAMC report, *Increasing Women's Leadership in Academic Medicine,* published in the October 2002 issue of *Academic Medicine,* that expressed concern over the failure of the nation's medical schools to open their doors to, and take advantage of, the potential of female faculty members.

That report found that women make up only 14% of tenured faculty and 12% of full professors, and concluded that, since the committee's 1996 report, there has been "incomplete and inadequate" progress in bringing women into leadership roles at the nation's medical schools. Few schools, hospitals, and professional societies, the report states, "have what might be called a critical mass of women leaders, and the pool of women from which to recruit academic leaders remains small."

Dr. Wara contrasted the lack of women leadership in medical institutions with studies documenting the success of businesses with substantial female participation at the executive level.

"Fortune 500 companies with the most women executives deliver more earnings to their shareholders than those in which males dominate the executive ranks," she said. "Diversity in leadership creates variety and can lead to qualitative change. The longterm success of academic health institutions is inextricably linked to the development of women physicians."

Despite such findings, she stated, "Men still tend to devalue women's work and allow them a narrower band of assertive behavior."

"For women," declared Dr. Wara, "this results in less space, less pay, and less progress toward a professorship." The result, she noted, was disenchantment on the part of female faculty, many of who wind up "voting with their feet" and leaving for what they perceive as greener pastures.

The AAMC report supports this claim. It found that last year 10.9% of women faculty members in medical schools were full professors, compared to 30.9% of male faculty members. In a 1985 study, the figures were 9.9% of female faculty and 31.5% of men were full professors. "Thus," commented the AAMC report, "it has taken over 15 years for the proportion of women faculty who are professors to increase a whole percent."

Commenting on this disparity, Dr. Wara declared, "The long term success of academic health institutions is inextricably linked to the development of women physicians."

Dealing with Industry: Managing Institutional and Individual Conflicts of Interest

Russell E. Kaufman, Director and CEO, The Wistar Institute, led off this session by recalling that the passage of the Bayh-Dole Act freed universities to gain revenue from their research.

"That," he said, "set in motion the potential for conflicts of interest, which a *San Diego Union-Tribune* article two years ago characterized as 'From Prof to Profit: Money and Scientists Mingle, Creating Companies and Concerns.'"

"That sardonic commentary aside," he continued, "there are, as we know, causes for concern about conflicts of interest. But, what are the safeguards against unethical research?"

According to Dr. Kaufman, the safeguards are:

- An institutional culture of research integrity.
- The scientific method.
- Proper controls.
- Independent replication of key research findings.
- Peer review.
- Double blind clinical trials.
- Multi-institutional clinical trials.

Conflicts of interest are the greatest risk to research integrity and loss of confidence, but all conflicts of interest cannot be avoided. The term 'conflict of interest' denotes a state of affairs, not a kind of behavior. Having a conflict of interest is not, ipso facto, evidence of improper behavior. Conflicts of interest are an inevitable part of the research process in academic institutions. They can arise in relation to career advancement, peer recognition, grant funding, tenure, research space, or financial matters.

However, conflicts involving money are different from other conflicts, and in the area of clinical research there is, said Dr. Kaufman, "general concern about the influence of such conflicts on human subjects' protection." The consequences, he

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New Guide Will Help Researchers Mine Genome Data

To encourage greater scientific exploration of public databases containing the human genome sequence, the National Human Genome Research Institute (NHGRI) has created "A User's Guide to the Human Genome."

Published as a supplement to *Nature Genetics* and freely available at http://www.nature.com/ng/web_specials/, the peer-reviewed, how-to manual is aimed at spreading the word about how easy it is for researchers to mine the wealth of human genomic data that is freely available online.

"There is no point amassing all of this data in data warehouses if no one is able to use it," said ASBMB member Andreas D. Baxevanis, Associate Director of NHGRI's Division of Intramural Research (DIR) and co-author of the guide. He noted that a Wellcome Trust survey of nearly 800 biomedical scientists last year found that only half of researchers using genome databases were familiar with the free, public tools for accessing sequence-based data.

"Between this information and our own anecdotal information about how people were not availing themselves of the variety of freely-available genomic databases, it really became obvious to us that a user's guide was needed to fill the void. One of the main reasons for doing the Human Genome Project was to encourage researchers to use sequence data to guide their own research. So, this guide will hopefully allow our fellow scientists to better understand what types of data are out there and how to effectively browse and search these data," said Dr. Baxevanis.

The 79-page guide focuses mainly on the three major genome portals that contain freely available data produced by the International Human Genome Sequencing Consortium and other systematic sequencing efforts. These web-based portals are the National Center for Biotechnology Information's Map Viewer; the University of California, Santa Cruz's Genome Browser; and the European Bioinformatics Institute's Ensemble system.

Arranged around a series of questions commonly encountered during the course of biomedical research, the guide provides users with practical, hands-on instructions for searching and analyzing genomic data contained in the major browsers. The NHGRI authors show users how to set about answering each question by choosing and utilizing the appropriate tools in one or more of the main browsers.

For example, Question 2 of the guide asks: "How can sequence-tagged sites (STS's) within a DNA sequence be identified?" The NHGRI authors point users to the NCBI portal's UniSTS resource, which contains an electronic PCR (e-PCR) tool that can be utilized to find STS markers within a DNA fragment. Using instructive text and figures, the guide then walks users through the steps of identifying the STS markers contained in a sample sequence of interest, in this case a sequence with accession number AF288398. The e-PCR search reveals the sample sequence contains only one STS, stSG47693. By clicking on the marker name, users can obtain more details about the STS from UniSTS, such as alternative names for the marker, primer information and PCR product size. In addition, the NHGRI authors steer users to several electronic cross references to mapping information, as well as a link to NCBI's MapViewer which allows users to see the genomic context of the STS marker in all maps to which it has been mapped.

The new user's guide will be updated at least once before the target date for finishing the human genome sequence in April 2003.

In addition to showcasing the tools available through the three main genome portals, the guide includes a convenient list of links to a wide range of additional resources: other genome browsers, genome annotation databases, public sequence databases, expressed sequence tag clustering databases, human genetic and physical maps, sequence-based search tools and model organism databases.

The guide also provides information on Human Genome Hub and Genome Central, Web sites that serve as jumping off points to major genome-based Web sites. While the guide focuses mainly on the mechanics of accessing and using human genomic data, links are also included to key Web sites for information on genetic education and ethical, legal and social issues (ELSI) related to genetic and genomic research.

AAMC...

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noted, could be bias in subject selection or adverse event reporting.

He listed consulting activities; the receipt of gifts, gratuities, loans, or special favors; receipt of cash, services, or equipment; and memberships on boards or advisory committees, as having the potential for a conflict of interest. Dr. Kaufman also advised that department heads and chairs be alert to significant financial interests that should trigger an alarm. He identified these as:

- Consulting fees, honoraria, and "in kind" compensation or equity from a single source that exceeds $10,000 in the preceding year.
- Equity interest in a company that is not publicly traded.
- Royalty income related to licensed technology.
- Gifts, gratuities, loans, or special favors.
- Service as an officer, director, or in a fiduciary role for the financially interested company.

by John D. Thompson, Editor

U.S. Companies Concerned by Slump in Drug Development

New drugs are coming into the market in the United States at the slowest rate in a decade, despite billions invested by pharmaceutical companies on research and a costly expansion by the federal agency that reviews new medicines.

This slowdown comes even though pharmaceutical companies now invest three times as much money in research as they did a decade ago, and the FDA has been revamped in an effort to accelerate its review process. However, the number of applications for innovative new drugs is down significantly, and the average time needed for FDA review is increasing.

The reasons for the decline? FDA caution after some high-profile drug withdrawals, industry shortcomings and strategies, or a combination of both—is a topic for debate.

"Industry was trying to hit home runs, and it struck out a lot," Henry McKinnell, CEO of Pfizer Inc., told the *Washington Post*. "Added to that, the FDA is giving greater scrutiny to each drug application. The result is that we are spending more time on each drug, spending much more on research, but seeing a definite drop in the number of new drugs."

The number of new drugs coming onto the market peaked in the mid-1990s, when the FDA approved more than 120 new drug applications in both 1996 and 1997 after being criticized for being too slow. However, by 2001, the number of approvals had dropped to 66 a year, and totaled a mere 46 at the end of September 2002.

Pharmaceutical industry officials say the slowdown has been caused, to some extent, by companies shifting from traditional development through chemistry to the use of cutting-edge biotechnology. This trend was highlighted by a recent Pharmaceutical Research and Manufacturers of America finding that a record 116 medicines made through biotechnology are now in the last phase of clinical testing or awaiting FDA review.

EU Seeking to Create European Research Area

The European Union's plans for research spending over the next four years were finally launched in mid-December when the European Commission issued its call for proposals. Proposals for projects to be funded under Europe's Sixth Framework Program (FP6) must then be submitted by March.

Final implementation procedure was held up by debate between national governments over research with human embryonic stem cells. The Commission finally decided, last July, not to fund research on human therapeutic cloning, and to restrict human stem-cell work to previously established cell lines. That decision is to be reexamined this year.

FP6 is a step towards achieving a European Research Area, which will provide a network of centers of excellence across Europe, according to Phillipe Busquin, the European Commissioner for Research. Networking is currently inadequate, he says, and requires far more coordination.

The Commission has devised two new project-funding options, or "instruments," designed to improve networking under FP6. The first of these are "integrated projects" — large goal-oriented collaborative projects that will involve input from at least three member states. The second, "networks of excellence," will focus on long-lasting collaborations that will persist beyond the time-limits of a single project.

Biotech Case

The government's investigation of a biotechnology company has the food industry and environmental groups concerned that the biotech industry cannot be trusted to prevent the food supply from becoming contaminated with plant-made pharmaceuticals.

According to the Associated Press, ProdiGene Inc., of College Station, Texas, may have broken laws when it failed to completely remove biotech corn from fields in Iowa and Nebraska before growing soybeans, the Agriculture Department said after inspectors found stray corn

Asian Tigers Backing Bioinformatics Industry Growth

The growth of new bioinformatics businesses in Singapore and Japan is being aided by ambitious government programs. In both Singapore and Japan, this new surge brings back memories of the "Asian tigers" heyday in the 1980s and 90s. Japan is busily finding off-shore start-ups to partner with domestic companies, while Singapore is spawning startups staffed with imported skilled labor or fueled by international partners to match immense domestic investments.

Three of Japan's major computer firms—Fujitsu, Hitachi, Itochu—are active in the bioinformatics area. Fujitsu has announced bioinformatics software for high-speed genome analysis; Hitachi has teamed with Yamanouchi Pharmaceutical and Fujitsu with Mitsubishi Chemical Corp to conduct genomic research; and Hitachi Ltd. Life Science Group selected Agilent Technology's microarrays to search for disease-related genes.

New Jersey-based Proteome Systems has joined with Itochu in a Tokyo-based venture featuring its discovery platform for high-level protein research. The partnership marries Proteome Systems' bioinformatic expertise to Itochu's strength in information technology. Last October, Mitsubishi and Fujisawa joined other major Japanese drug companies as subscribers to Gene Logic's drug discovery tool.

While Japan's approach builds on its strengths in proteomics, Singapore is matching brainpower and technical partners from abroad with heavy domestic investment in its bioscience infrastructure. Since the early 1990s, the nation's Economic Development Board (EDB) has been seeking to transform Singapore into a life-science powerhouse. Two years ago, the EDB launched the National Biomedical Science Strategy, which has since pumped some $2 billion into the effort, and in November 2000 Lynk Biotechnologies, one of the first life-science startups spun off from the National University of Singapore, opened its research facilities in Singapore Science Park.

Worries Food Industry

plants growing in the fields.

The government ordered the company to burn the contaminated Iowa crop in September, and in mid-November told ProdiGene to destroy the Nebraska crop, which has been quarantined at a grain elevator in Aurora. The company makes pharmaceutical and industrial products by altering the genetic makeup of corn.

Until the government and companies have proved that those crops won't taint food, "we strongly urge the biotech industry to direct its substantial research capabilities into investigating the use of nonfood crops for the development of pharmaceuticals," said Karil Kochenderfer, Director for New Technologies at the Grocery Manufacturers of America which represents food companies nationwide.

The case has caused concern among biotech firms, a dozen of which—including ProdiGene—had agreed to a Biotechnology Industry Organization moratorium on growing genetically engineered corn for pharmaceutical development in states where it could contaminate neighboring fields planted with crops for human consumption.

GSK Fears New Drug Shortage

J.P. Garnier, CEO of GlaxoSmithKline (GSK), the UK's largest pharmaceuticals company, has admitted that the company is short of new drugs. GSK's drug pipeline, he indicated in an interview with *The Times,* is so dry that the group has no current plans for an R&D day to update investors on progress in research and development. In Britain, pharmaceutical firms regularly schedule such days to convey information about their research and development activities to investors and analysts, who look forward to such events as times when profits are forecast.

Dr. Garnier told *The Times,* "I don't want to be caught on an early R&D day on our pipeline and explain all those wonderful hopes and then find out a year or two later that those products haven't made it through proof of concept."

The lack of late-stage products in GSK's pipeline reflects the lack of R&D progress at both Glaxo Wellcome and SmithKline Beecham prior to the companies' merger at the end of 2000. Dr. Garnier said: "I inherited a pipeline conceived seven years ago. Pipelines don't get built up in two years. There is an inertia in the system that you can't do anything about."

Research!America's Mission: Higher Priority for Research

Making medical and health research a much higher national priority is the mission of Research!America, a national not-for-profit, membership-supported, public education and advocacy alliance.

The organization has been an active supporter of ASBMB's goal of doubling the NIH budget, and has consistently worked to better inform the public of the benefits of medical and health research and the institutions and organizations that perform the research.

An example of Research!America's advocacy is its 435 Project. This project aims to energize support for medical and health research and other sciences and public health programs from citizens in all 435 congressional districts. The project targets the media, elected officials, scientific community, health professionals, and business leaders, as well as the general public.

To demonstrate public support for its goals, Research!America also conducts polls such as a recent one of Illinois residents.That survey found that the state's residents want—and are willing to pay for—increased funding for prevention research concerned with preventing disease, disability and injury, and improving and promoting health. The respondents also favored more funding for research that would help ensure access to health care for all state residents.

"What the Research!America poll so clearly shows is that Illinois residents want the protection afforded by prevention research and the hope for better health for everyone, regardless of race, ethnicity, income or location in our state," said John Porter, former Congressman from Illinois' tenth district and a Research!America board member.

UT Southwestern Nobelists Find Protein Structure That May Help Fight High Cholesterol

Three University of Texas Southwestern Medical Center Nobel laureates and their colleagues have solved a protein structure that could lead to advances against diseases caused by high cholesterol.

Nobelist Dr. Johann Deisenhofer, Professor of biochemistry and senior author of the study, and Dr. Gabrielle Rudenko, Assistant Instructor of biochemistry and lead author of the study, solved the three-dimensional structure of a low-density lipoprotein (LDL) receptor's extracellular domain. LDL is known as the "bad" cholesterol because it deposits fat-like substances that clog arteries.

The LDL receptor binds LDL in the liver and clears it from the blood by pulling cholesterol inside the cells, where it is metabolized to replenish hormones, the cell membrane, vitamin D and other products.

"This research will help scientists understand the mechanics of how our bodies absorb cholesterol from the blood," Deisenhofer said. "Hopefully, we can use the information to develop treatments for people with mutations that diminish the functions of their LDL receptors."

UT Southwestern Nobel laureates ASBMB Member Dr. Michael Brown and Dr. Joseph L. Goldstein, an ASBMB Member, also assisted in the study, published in the Dec. 20 issue of *Science*. An early version is listed online at *Science Express*.

There are about 1,000 LDL receptor mutations that have been found in people with familial hypercholesterolemia (FH). FH is one of the most common "single-gene" inherited diseases and affects about one in every 500 people, Dr. Rudenko said. By revealing the structure of the receptor, scientists now can begin to understand why these different mutations cause FH, a disorder that results in very high cholesterol levels, atherosclerosis and increased risk of having a heart attack early in life.

The LDL receptor's extracellular domain consists of two major parts, the LDL binding region and the so-called "beta-propeller" region. In the study, the structure revealed that parts of the LDL binding region attach to the "beta-propeller" region at low pH and thus cannot bind to LDL. It looks as if the "beta-propeller" region competes with LDL, said Dr. Deisenhofer, who received the 1988 Nobel Prize in chemistry for research using X-ray crystallography to reveal in three-dimensional detail the structure of protein in the membrane of cells. His continuing work on understanding the detailed structure of important biological molecules makes possible the development of a new generation of drugs and vaccines. He holds the Virginia and Edward Linthicum Distinguished Chair in Biomolecular Science and is an investigator in the Howard Hughes Medical Institute.

Getting the Right Result:
Fine-Tuning Your Search With a Single Click

In early 2001, ASBMB News introduced the new "portal" site from Stanford's HighWire Press, which allows you to search all of Medline plus over 340 journals' full-text at once — including the* JBC*, of course! We began a monthly series of short articles highlighting tools or features of this new site for researchers' sore eyes. The new site is at http://highwire.stanford.edu.

The HighWire Portal contains over a million full-text articles from hundreds of the world's best journals; that's good news, but even better, it also includes over 12 million article abstracts from MEDLINE in its searching and alerting facilities. But a search across all this content can bring back so many results that you feel you are facing the proverbial "needle in the haystack" problem.

With a single click on the search result page you can easily try variations of your search if you see too many – or too few – results.

Let's suppose you were looking for a single full-text article about recent research on insulin resistance, for assignment to students in a course you are teaching. You type the words "insulin resistance" in the Quick Search box; the system searches for these words in the full text of several hundred HighWire-hosted journals, plus all MEDLINE's abstracts. In a few seconds, HighWire tells you there are over 37,000 articles and shows you the first page of ten citations.

Let's refine this search one click at a time (see the figure):

Click on **phrase** to reduce your search result to only those articles in which the words "insulin resistance" occur together as a phrase. You are left with 23,000 results; too many to assign to a class!

Click on **review articles** to further reduce your result to only those articles that are reviews. Still over 4,000!

Click on **HighWire-hosted journals** to further reduce the result to journals whose recent full-text is online. The search result will allow you to see easily which articles are accessible to you and your students online (no need for a course reader or putting the article on reserve!). Now "only" about 500 articles.

At this point it is probably efficient to scan the first 10 results show and see if any of these are just the right article to assign. Why might you get lucky in the first 10 of 500 articles? Because the HighWire portal's search engine offers "relevance-ranked" results, as well as the "most-recent-articles first" option (PubMed offers only the latter). So, if your search term is found in the title of a document, the document will be closer to the first page in your search result than if the term were found in the abstract but *not* the title; and if the term were found in the abstract, the document would be ranked higher than if the term were found only in the full text body of the article.

Since you were interested in recent research, you might next click on **within last 2 years** to be sure you are looking only at the most recent research. But there are still over 250 such articles.

You now want to limit the results to the set of journals you are most familiar and comfortable with for your own searching. Click **My Favorite Journals**. Depending on the set of journals you've selected, you might have only a dozen results, or perhaps a hundred.

You can now force the system to drop relevance ranking and simply present the results so that the most recent articles are first. Click **newest first**. While this doesn't reduce the number of articles in the result, it might make something particularly recent jump to the top, such as the *JBC* and *JLR* articles shown in our example page. You know you can assign these articles because you can see the indication that **this article is FREE to you**.

As a check to see whether you have missed anything, you note the top right of the page shows **Topics best matching my search**, which indicates some subject-based collections of articles that are about the topic you want to assign. You click on the topic name, and see that the first article, while it is from 1997, is about molecular mechanisms and signaling pathways of inherited insulin resistance, and is freely available without a subscription. So you note that as a background article for your students, and put it on your growing reading pile.

The 2001 issues of ASBMB Today *covered topics about the new HighWire Portal. The articles are online at http://highwire.stanford.edu/inthepress/asbmb/index.dtl*

Calendar of Scientific Meetings

FEBRUARY 2003

Miami Nature Biotechnology Winter Symposium 50 Years On: From The Double Helix To Molecular Medicine

February 1-5 • Radisson Deauville Resort, Miami Beach
Contact: Bill Whelan, wwhelan@miami.edu
Website: http://www.med.miami.edu/mnbws

MARCH 2003

The American Society for Microbiology (ASM) Meeting: Future Directions for Biodefense Research: Development of Countermeasures

March 9-12 • Baltimore Marriott Waterfront, Baltimore, MD
Abstract Deadline: January 30, 2003
Ph: 202-942-9248; Fx: 202-942-9340
Email: meetingsinfo@asmusa.org; www.asmbiodefense.org

Principles and Applications of Time-Resolved Fluorescence Spectroscopy

March 23-28 • University of Maryland Baltimore
Contact: Mary Rosenfeld, Tel: 410-706-8409
Email: cfs@cfs.umbi.umd.edu; Website: http://cfs.umbi.umd.edu

Keystone Symposium, Proteomics: Technologies and Applications

March 25–30 • Keystone Resort, Keystone, Colorado
Contact: Paul Lugauer; Tel.: 970-262-1230 ext. 111
Email: info@keystone.symposia.org
Website: http://www.keystonesymposia.org

APRIL 2003

Origin and Evolution of Mitochondria and Chloroplasts Advanced Lecture Course for the Federation of European Biochemical Societies (FEBS)

April 5–10 • Hvar, Croatia
Contact: Prof. Dr. Jürgen Soll
Ph: + 49 89 17861 225/273/276; Fx: + 49 89 17861 185
e-mail: hvar2003@botanik.biologie.uni-muenchen.de
Website: http://www.febs.unibe.ch/Activities/Advanced_Courses/Adoc03.htm

9th International Congress on Neuronal Ceroid Lipofuscinosis (Batten Disease)

April 9-13 • The Holiday Inn-City Centre, Chicago
Program Chair: Glyn Dawson, University of Chicago Pritzker School of Medicine; Website: http://www.ncl2003.org/

American Society for Biochemistry and Molecular Biology Annual Meeting in Conjunction with EB2003

April 11-15 • San Diego, California
Contact: EB2003 Office; Ph: 301-634-7010
Fx: 301-634-7014; Email: eb@faseb.org
Website: http://www.faseb.org/meetings/eb2003

MAY 2003

Proteomic Solutions in Cellular and Developmental Biology and Medicine

May 2–4 • Stowers Institute, Kansas City, Missouri
Contact: Kelly Gull; Tel: 301-634-7145; Fx: 301-634-7126
Email: kgull@asbmb.faseb.org; Website: http://www.asbmb.org

10th Undergraduate Microbiology Education Conference

May 16-18 • University of Maryland, College Park, Maryland
Contact: Carlos Pelham; Ph: 202-942-9317
Email: EducationResources@asmusa.org
Website: http://www.asmusa.org/edusrc/edu4c.htm

JUNE 2003

Transposition, Recombination and Applications to Plant Genomics A Plant Sciences Institute Symposium

June 5-8 • Iowa State University, Ames, Iowa
Abstracts due April 4, 2003; Registration deadline May 5, 2003
Students may apply for travel grants (applications due 4/4/03)
Contact: Gulshan Singh
Ph: 515-294-7978; Fx: 515-294-2244; E-mail:pbmb@iastate.edu
Website: http://molebio.iastate.edu/-gfst/phomepg.html

ECM IV: Bone Tissue Engineering

June 30-July 2 • Davos, Switzerland
Contact: R. Geoff Richards, Dr. Sci. M.Sc. biol.
Programme Leader AO Research Institute,
Bioperformance of Materials & Devices
email: geoff.richards@ao-asif.ch; Ph: ++41 (0) 81 4142 397
http://www.aofoundation.org/events/ao/ecm/ECMIV/index.shtml

JULY 2003

FEBS 2003 Meeting on Signal Transduction

July 4-8 • Brussels
Contact: V. Wouters; Ph: 32 2 7795959; Fx: 32 2 7795960
Email: febs@iceo.be; Website: http://www.febs-signal.be

Education in the Molecular Life Sciences: The Central Role of Biochemistry and Molecular Biology

July 18-20 • University of Toronto, Canada
Contact: Kelly Gull; Ph: 301-634-7126
Email: kgull@asbmb.faseb.org
http://www.richmond.edu/~jbell2/iubmb-satellite.html

19th International Congress of Biochemistry and Molecular Biology

July 20-24 • Toronto, Canada
Contact: Congress Secretariat; Ph: 613-993-9431
Email: iubmb2003@nrc.ca
Website: http://www.nrc.ca/confserv/iubmb2003/

AUGUST 2003

First Gordon Research Conference on Cellular Osmoregulation: Sensors, Transducers and Regulators

August 15–20 • Roger Williams University, Bristol, RI
Contacts: Janet M. Wood (jwood@uoguelph.ca) and Karlheinz Altendorf (altendorf@biologie.Uni-Osnabrueck.de)
Website: http://www.grc.uri.edu/programs/2003/cellosmo.htm
Application: http://www.grc.org/scripts/dbml.exe?Template=/Application/apply1.dbm

Sixth International Symposium on Mass Spectrometry in the Health and Life Sciences: Molecular and Cellular Proteomics

August 24-28 • Fairmont Hotel, San Francisco
Contact: Marilyn Schwartz; Ph: 415-476-4893
Email: sfms@itsa.ucsf.edu
Website: http://donatello.ucsf.edu/symposium

16th International Mass Spectrometry Society Conference

August 31–September 5 • Edinburgh, Scotland, United Kingdom
Contact: John Monaghan; Email: johnmonaghan@ed.ac.uk
Website: http://www.imsc-edinburgh2003.com

SEPTEMBER 2003

Sixth Conference on Protein Expression in Animal Cells

September 7–11 • Mont-Tremblant, QC, Canada
Contact: Marc Aucoin, Technical Officer
Biotechnology Research Institute; Email: 6thPEACe@nrc.ca
Website: http://www.bri.nrc.ca/6thPEACe

Third International Conference on the Pathobiology of Proteoglycans

September 20 - 25 • Parma, Italy
Contacts: Roberto Perris, Chair and Ariane De Agostini, Co-chair
Clinique de Stérilité de d'Endocrinologie gynécologique,
Hôpital Cantonal Universitaire de Genève
Ph: 41-22 / 382.43.46; Fx: 41-22 / 347.59.79
Email: Ariane.Deagostini@medecine.unige.ch
Website: http://www.assb.biol.unipr.it/PG2003

OCTOBER 2003

OARSI's 2003 World Congress on Osteoarthritis

October 12-15 • Palais am Funkturm, Berlin
Contact: OARSI Headquarters
Ph: 202-367-1177; Fx: 202-367-2177
Email: oarsi@oarsi.org; Website: www.oarsi.org

Cytokines, Signalling & Diseases

Oct. 26-30 • Cairns, Australia
Event Host: International Society for Interferon and Cytokine Research; Website: http://www.cytokines2003.conf.au/

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