SEPTEMBER 2002

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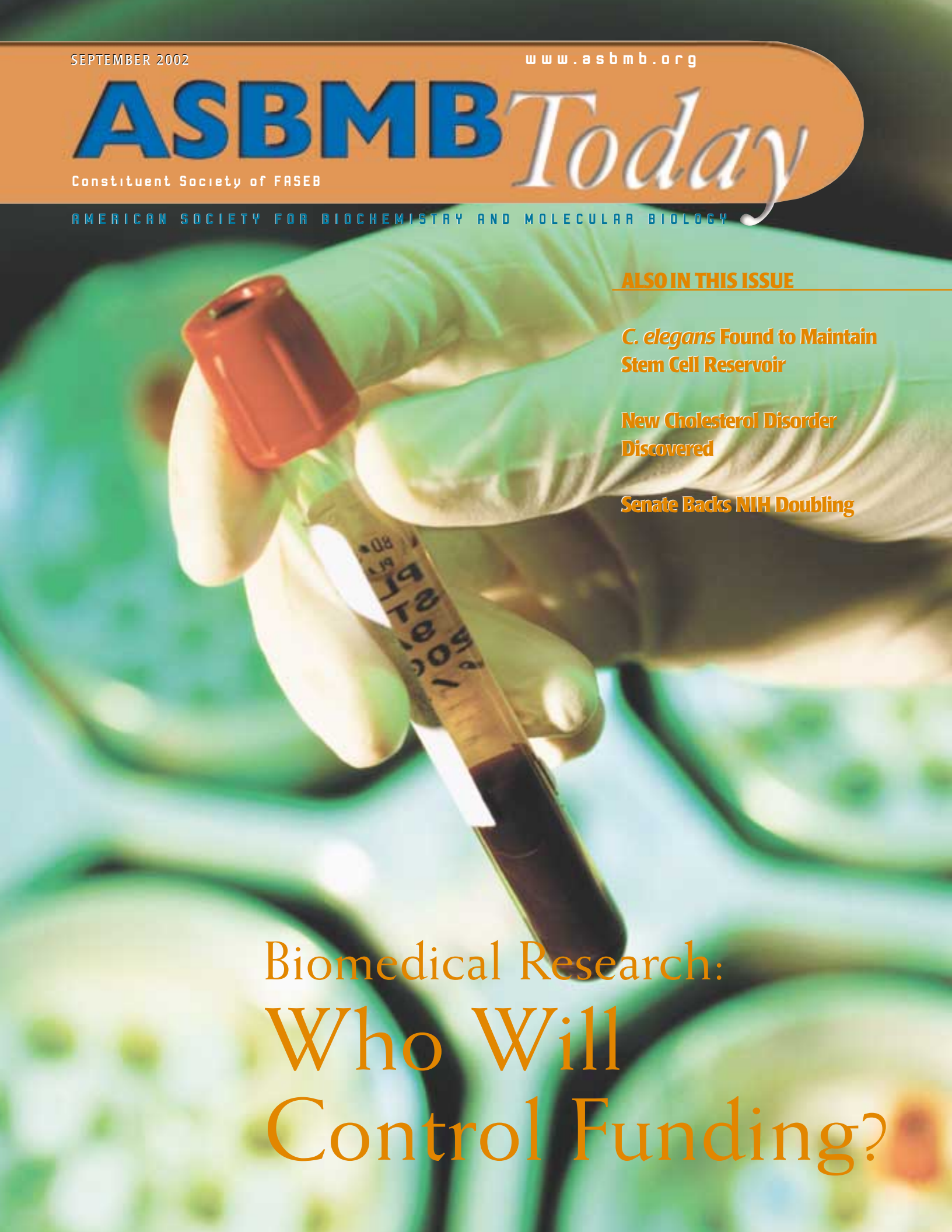

ALSO IN THIS ISSUE

C. elegans Found to Maintain Stem Cell Reservoir

New Cholesterol Disorder Discovered

Senate Backs NIH Doubling

Biomedical Research: Who Will Control Funding?

Experimental Biology 2003

April 11-15, 2003
San Diego, CA

Additional Speakers will be chosen from the abstracts submitted to the ASBMB Biological Catalysis topic categories. Abstract deadline: 11/13/02

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"TRANSLATING THE GENOME"

ASBMB BIOLOGICAL CATALYSIS MEETING planned for EB 2003 in San Diego!

ASBMB Annual Meeting in Conjunction with Experimental Biology 2003 April 11 – 15, 2003 • San Diego, California

Organized by Tadhg Begley, *Cornell University*

Plenary Lecture

OXYGEN REACTIVITY IN ENZYMES: PROBLEMS AND SOLUTIONS
Judith P. Klinman, *UC, Berkeley*

Macromolecular Machines and Protein Assembly Lines

UNDERSTANDING THE MODULARITY OF POLYKETIDE SYNTHASES
*Chaitan Khosla, *Stanford Univ.*

DYNAMICS OF TRANSLATION
Joseph Puglisi, *Stanford Univ.*

ENERGY-DEPENDENT PROTEIN UNFOLDING AND DEGRADATION
Robert T. Sauer, *MIT*

NONRIBOSOMAL PEPTIDE SYNTHETASES: ENZYMATIC ASSEMBLY LINES
Christopher T. Walsh, *Harvard Med. School*

Fundamental and Emerging Issues in Enzymatic Catalysis

*Judith P. Klinman, *UC, Berkeley*

MOLECULAR DYNAMICS STUDIES OF THE RELATION BETWEEN ENZYME MOTION AND ACTIVITY
Sharon Hammes-Schiffer, *Penn State Univ.*

THE ASCENT OF RADICALS AS ENZYMATIC INTERMEDIATES
Perry A. Frey, *Univ. of Wisconsin-Madison*

THE DYNAMICS OF PROTEIN LOOP MOTION AND ENZYMATIC CATALYSIS PROBED BY TEMPERATURE JUMP RELAXATION SPECTROSCOPY
Robert Callender, *Albert Einstein Col. of Med.*

HYDROCARBON ACTIVATION CHEMISTRY OF METHANE MONOOXYGENASE: COMPOUND Q AND HYDROGEN TUNNELING
John D. Lipscomb, *Univ. of Minnesota, Minneapolis*

Enzymology of Post-Translational Modification

SIR-2: MECHANISM OF AN NAD-DEPENDENT PROTEIN DEACETYLASE
*Vern Schramm, *Albert Einstein Col. of Med.*

DYNAMICS OF PROTEIN KINASE-A REGULATION AND CATALYSIS
Susan S. Taylor, *UCSD*

OLIGOSACCHARYL TRANSFERASES
Barbara Imperiali, *MIT*

MECHANISM OF PROTEIN FARNESYL TRANSFERASES
Carol Ann Fierke, *Univ. of Michigan*

Complex Biological Oxidations

*Tadhg Begley, *Cornell University*

THE STRUCTURAL ENZYMOLOGY OF HEME AND NON-HEME IRON OXYGENASES
Brian Crane, *Cornell Univ.*

HEME AND NON-HEME IRON OXIDATIVE REARRANGEMENTS IN NATURAL PRODUCT BIOSYNTHESIS
Craig Townsend, *Johns Hopkins Univ.*

MECHANISTIC STUDIES ON A NOVEL BIOLOGICAL C-O BOND FORMING REACTION
Hung-wen (Ben) Liu, *Univ. of Texas, Austin*

OXIDATIONS CATALYZED BY NON-HEME IRON CENTERS
Larry Que, Jr., *Univ. of Minnesota, Minneapolis*

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SEPTEMBER 2002,
Volume 1, Issue 6

features

2 Biomedical Research Funding an Issue

3 Senate Backs NIH Doubling

4 C. Elegans Maintains Stem Cell Reservoir

6 Developing Ways to Engineer Organisms

8 New Cholesterol Disorder Discovered

10 130-Year Old Mysteries Solved

12 New Metabolic Switches

16 Improved Website to Study Genes

17 New Skin Cancer Gene

20 Molecular Biology Times Two

22 Search All of Medline

8

departments

2 News From the Hill

4 Members in the News
and also page 15

18 Biotech Business

24 Calendar

12

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Comments

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Control of Biomedical Research

By Peter Farnham, CAE, Public Affairs Officer

Subtle differences concerning control of the bioterrorism research agenda—and the funding to go with it—in the House and Senate bills establishing the new Department of Homeland Security will no doubt prove to be the most important issues for the biomedical research community is concerned. Many in the biomedical community are concerned that nearly $2 billion of biomedical research funding may end up under the control of non-scientists.

The House passed H.R.5005 establishing the new department, following extensive markup by numerous House committees and subcommittees and a newly created Select Committee on Homeland Security. This bill changes key provisions about which ASBMB was concerned in the original bill.

The President's original proposal transferred $1.7 billion from the NIH and the Centers for Disease Control and Prevention (CDC) to the new department. The money was then to be transferred back to HHS in the form of grants and contracts.

The original bill would have given decision-making authority to the new department over how the transferred money was to be spent to fight bioterrorism. The original language called for the secretary of the new department to decide research and funding priorities. The HHS secretary was to be "consulted." However, decision-making authority seems to have been given to the secretary of the new department.

The Select Committee on Homeland Security, during its July 19 markup, adopted the following amendment to correct this problem.

"With respect to civilian human health-related research and development activities relating to countermeasures for chemical, biological, radiological, and nuclear and other emerging terrorist threats carried out by the Department of Health and Human Services (including the Public Health Service), the Secretary of Health and Human Services shall set priorities for such activities in collaboration with the Secretary of the Department of Homeland Security."

The concern about HHS control over spending relates to a minor language change in the final version of the bill. HHS would retain the authority to set its own priorities, goals, objectives and policies and develop a coordinating strategy. However, the bill now calls for collaboration with the new department "to ensure consistency with the national policy and strategic plan" to be developed by Homeland Security's undersecretary for science and technology.

The biomedical community was extremely concerned about the transfer of authority over spending, but the new language apparently solves that problem.

Meanwhile, in the Senate…

A homeland security bill is also moving in the Senate. The Governmental Affairs Committee, chaired by Senator Joseph Lieberman (D-CT), marked up its homeland security bill, S.2452, on July 25. Language clarifying the relationship between the HHS secretary and the new department's secretary, and reportedly acceptable to the White House, allows Homeland Security more involvement in setting

Funding An Issue in Homeland Security Bill

research priorities than does the House bill.

The Senate bill gives the new department "authority to establish general research priorities," which would be embodied in strategic agreements with the HHS secretary. The HHS secretary would then develop the "specific scientific research agenda" to implement these agreements, in consultation with the homeland security secretary, to ensure that they conform with homeland security priorities.

The Lieberman bill was approved by the Governmental Affairs Committee this spring, but after the President's bill was sent to Congress, Lieberman began reshaping his bill to bring it closer to the President's. Reportedly, Senator Edward Kennedy (D-MA) has been following development of the Lieberman bill very closely to ensure that HHS programs are not undermined. In addition, Senator Arlen Specter (R-PA) has indicated that NIH money would not be transferred to the new department.

Senate Backs NIH Doubling; House Recesses Without Acting

The Senate Appropriations Committee on Labor/HHS/Education markup of the NIH appropriation for FY 2003 includes the final 15% annual increase needed to complete the 5-year budget doubling begun in FY 1999. This would bring the NIH budget to $27.2 billion, with a $3.7 billion increase planned for the coming year.

Senator Tom Harkin (D-IA) noted that as a result of the doubling effort, since 1998, NIH is now funding 10,000 more grants each year. Also, there are 40% more research centers, 1,500 more training slots for new scientists, and spending in clinical trials has doubled to $2.8 billion. The bill's next step is to the Senate floor after Labor Day. As of the end of July, the House bill had still not been introduced.

A variety of problems prevented introduction of a Labor/ HHS bill in the House. When the total amount of discretionary spending available for FY 2003 was divided up among the 13 appropriations subcommittees, several House appropriations bills were given virtually all the money the subcommittee chairmen said was needed. However, the Labor-HHS spending bill received only what the President had asked for—$129.9 billion. That is $4.3 billion less than in the Senate bill.

This maneuver will allow many of the "easy" spending bills to clear Congress with little difficulty, while leaving the Labor-HHS bill for the "end game." Under this scenario, Congress, eager to go home to campaign, will presumably be more willing to provide additional money for the Labor-HHS bill, since a battle over spending levels will delay their departure.

This is precisely the strategy followed a couple of years ago to force massive spending increases in both the Labor-HHS and VA-HUD bills. This time, however, there is very little Republican agreement over the wisdom of the approach.

A group of 15 GOP moderates went to the House leadership in late July and indicated that moderate Republicans will find it difficult to vote for a Labor-HHS spending bill at the $129.9 billion level, since it is not enough to fund adequately all of the politically popular programs in the bill.

The Republican leadership is also getting pressure from conservatives seeking to hold total domestic discretionary spending at the $759 billion level in the President's budget proposal. This group has been able to force the leadership to promise that the Labor-HHS bill will come to the House floor in September, before Congress adjourns. Even if the bill is defeated, many believe such a vote will help them politically by having allowed them to demonstrate their fiscal conservatism.

The House leadership has several options. They can bring the Labor-HHS bill to the floor at the President's level of $129.9 billion, and hope that enough Democrats can be persuaded to vote for the bill to make up the loss of any GOP votes. Another option is to take money out of other appropriations and put it into the Labor-HHS bill, but this would cause problems, particularly when the other bills go to conference with the Senate, as the Senate's discretionary spending total is almost $11 billion higher than that of the House. A third option is to offset increases in especially sensitive programs with cuts elsewhere, or to write a continuing resolution that could put off the politically charged votes until after the election.

Nowhere in all of this is there any indication that NIH is directly threatened. However, as of now we are a long way from being able to celebrate completion of the five-year doubling plan.

C. elegans Found to Maintain Stem Cell Reservoir

Researchers studying the roundworm *C. elegans* have discovered a protein that maintains a reservoir of germline stem cells, the cells that are the wellspring of sperm and eggs.

ASBMB member Judith E. Kimble, Professor of Biochemistry and HHMI Investigator, and her colleagues at the University of Wisconsin, Madison have found that the *C. elegans* protein FBF, a member of the PUF family of proteins, is necessary for germline stem cells; without FBF, all of the germline stem cells mature into sperm.

> ***"C. elegans is a simple, manipulable system in which we can genetically pick apart the control of germline stem cells, an important and unsolved problem in biology."***
>
> **—Dr. Judith E. Kimble**

The scientists draw comparisons between FBF and other members of the PUF protein family, which have been identified in worms, flies and humans. The common theme among the various members of this family is that they promote cell division at the expense of differentiation, in which daughter cells become increasingly specialized.

Dr. Kimble and her group discovered FBF's role in maintaining germline stem cells while studying how the protein controls the switch from making sperm to making eggs. Since some *C. elegans* are hermaphrodites, they can switch from making sperm to making eggs. Nearly 20 years ago, Dr. Kimble discovered that a single cell in *C. elegans*, called the distal tip cell, controls germline stem cells during larval development and adulthood. She has been working on the sperm/oocyte decision as a parallel project in the lab.

Dr. Judith E. Kimble

Since then, she and her colleagues have been dissecting the molecular controls that regulate how germline stem cells are able to simultaneously maintain exact copies of themselves while dividing to produce cells that will become sperm or eggs. In developing worms, a production line begins with stem cells at one end and proceeds to mature sperm or eggs at the other end within the worm sex organ, or gonad.

"Few organisms have a single cell that governs germline fate decisions," said Dr. Kimble. "*C. elegans* is a simple, manipulable system in which we can genetically pick apart the control of germline stem cells, an important and unsolved problem in biology."

The scientists discovered in 1997 that FBF (fem-3 RNA binding factor) controls sex determination in worms. In an effort to further understand its role, they created a mutant worm in which they deleted two genes, fbf-1 and fbf-2, that encode FBF. To their surprise, Dr. Kimble discovered that the worms carrying the gene knockouts had no germline stem cells. All of their germline stem cells had become mature sperm during larval development, and there was no reservoir for future gamete production.

Further investigation showed that FBF acts by binding to and inhibiting the messenger RNA encoding a protein called GLD-1, whose role is to drive germline cells into meiosis, a specialized type of cell division involved in the creation of mature sperm and eggs. FBF represses GLD-1 in the distal germline region, thus maintaining stem cells, while germ cells move out of the distal region to become sperm or eggs. Without FBF, GLD-1 drives all the cells to become mature sperm.

The finding helps bring together a growing body of evidence showing how stem cells are regulated at the molecular level. The fact that PUF proteins are found in a variety of organisms likely means they have an important and conserved role, said Dr. Kimble.

"PUF proteins control many biological events, but the primordial function or ancient function is probably to promote mitosis," she explained. "We know FBF functions in regulating germline stem cells in *C. elegans*. While we don't yet know its role in humans, a PUF protein has been localized to human testes. My bet is that homologs of PUF proteins will be found to control germline stem cells in humans. I think that's a reasonable prediction."

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Plenary Lecture

MUCIN LIGANDS FOR SELECTINS: STRUCTURE AND BIOSYNTHETIC REGULATION
Richard D. Cummings, *Oklahoma Hlth. Sci. Ctr.*

Novel Aspects of Glycan Synthesis and Function

*Gerald W. Hart, *Johns Hopkins Univ. Sch. of Med.*

ORPHAN GLYCOSYLTRANSFERASES: IDENTIFYING ACTIVITY AND BIOLOGICAL FUNCTIONS
*Pamela Stanley, *Albert Einstein Coll. Med.*

POST-GENOMIC DISCOVERY OF CARBOHYDRATE FUNCTION *IN VIVO* BY MAMMALIAN GENETIC TECHNOLOGIES
Jamey D. Marth, *UCSD*

CMP-NEU5AC SYNTHESIS: WHY IN THE CELL NUCLEUS?
Rita Gerardy-Schann, *Hanover Medical School, Germany*

N-LINKED PROTEIN GLYCOSYLATION: FROM ENDOPLASMIC RETICULUM OF EUKARYOTES TO THE PLASMA MEMBRANE OF BACTERIA
Markus Aebi, *Swiss Federal Institute of Technology, Zurich*

Biological Functions of Glycosphingolipids and Glycosylphosphatidylinositols

GANGLIOSIDE-MEDIATED SIGNALING IN THE CONTROL OF NERVE REGENERATION
*Ronald Schnaar, *Johns Hopkins Univ. Sch. of Med.*

ASSEMBLY OF GPI-ANCHORED PROTEINS IN THE ENDOPLASMIC RETICULUM
*Anant Menon, *Univ. of Wisconsin, Madison*

GLYCOSPHINGOLIPID METABOLISM AT MEMBRANE-WATER INTERPHASES AND ITS PATHOBIOCHEMISTRY
Konrad Sandhoff, *Univ. of Bonn, Germany*

Biochemical and genetic analysis of LPG, a GPI-anchored phosphoglycan of *Leishmania* parasites
Salvatore J. Turco, *Univ. of Kentucky Med. Ctr.*

Roles of Glycans in Cell Adhesion and Trafficking

SULFATED LIGANDS INVOLVED IN LEUKOCYTE TRAFFICKING
*Steve Rosen, *UCSF*

PATHOLOGICAL INTERACTIONS OF SELECTINS WITH CARCINOMA-DERIVED GLYCAN LIGANDS
*Ajit Varki, *UCSD*

GLYCAN-DEPENDENT CONTROL OF LEUKOCYTE BIOLOGY
John Lowe, *Univ. of Michigan Med. Sch.*

IMMUNOBIOLOGY OF MGL, MACROPHAGE GALACTOSE-TYPE C-TYPE LECTINS
Tatsuro Irimura, *Univ. of Tokyo*

Biological Functions of Proteoglycans and Glycoproteins in the Extracellular Matrix

MORPHOGENESIS DEPENDENT ON PROTEOGLYCANS
*Jeffrey D. Esko, *UCSD*

PROTEOGLYCANS IN THE BRAIN: WHAT DO THEY DO AND HOW?
*Yu Yamaguchi, *Burnham Institute*

REMODELING OF THE EXTRACELLULAR MICROENVIRONMENT IN DEVELOPMENT AND NEOPLASTIC PROGRESSION
Zena Werb, *UCSF*

MECHANISMS OF PROTEOGLYCAN ACTION IN MORPHOGEN SIGNALING
Arthur Lander, *Univ. of California, Irvine*

HEPARAN SULFATE REGULATION OF FGF AND FGF RECEPTOR RECOGNITION
Alan Rapraeger, *Univ. of Wisconsin Med. Sch.*

**denotes chairperson*

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Researcher Using Nature's Command and Control Network To Develop Ways to Engineer Organisms

ASBMB member Peter Kennelly, Professor of Biochemistry at Virginia Tech University, is probing nature's own command and control network to understand how it functions and to develop new strategies for genetically engineering organisms. By mapping the mechanisms already in place to find the switch that controls a certain action, Dr. Kennelly is working to find ways to turn on processes that normally would not be active.

"Living organisms do an amazing amount of chemistry," says Dr. Kennelly. "The goals of life sciences are not only to take advantage of that machinery, but to control it so it can do more sophisticated tasks. Currently when we want a desirable trait in an organism, we introduce a gene that we put under artificial control to make a large quantity of the protein product of that gene."

The protein forces the organism to perform the desired task, but this is an inefficient and stressful method because it requires cells to produce hundreds of times more protein than is needed. "We tend to stress the organism because it has to use most of its resources to do the task," he explained.

In contrast, turning on a specific switch already in place within the organism is more efficient and economical because the response is more proportionate. The maintenance of a more balanced distribution of resources among cellular processes also makes the organism more viable and robust. One application of the new method is in the development of biosensors, enzymes that are intermediaries in the natural sensing of outside events.

"If we did this from scratch, it would take us a long time, but we're able to do it more quickly if we take advantage of nature's existing engineering and modify it," Dr. Kennelly said.

He likens the way he works to the process used to develop airplanes, in which inventors looked at birds for the basic components and then modified those parts to work in something man made.

Events taking place within a cell are linked together in networks that allow the cell to process information and make a "decision" about what to do (the response).

"As we learn more about how the networks perform, we can engineer them to be more sophisticated, efficient, and adaptable," he says.

For example, Dr. Kennelly's collaborator, Professor of Biochemistry Malcolm Potts, who is also an ASBMB member, works with cyanobacterium. These organisms make a protective carbohydrate material that helps the organism survive drought, temperature extremes, and radioactivity. In the future, they hope to find a way to not only use this type of coating as protection, but also to engineer it to be self-renewing and adaptive.

"What if we could embed that microorganism in the coating on the hull of a ship?" Dr. Kennelly asked. "It would provide excellent protection because it can survive a long time. And since it's photosynthetic, it just needs light and air to perform useful tasks. Imagine if we engineered it so it knows that the coating is wearing out, and makes more when this occurs. It also could change as needed depending on the temperature and other conditions."

> *"As we learn more about how the networks perform, we can engineer them to be more sophisticated, efficient, and adaptable"*
>
> —Dr. Peter Kennelly

"In a sense," he added, "it's like going from controlling a stereo system by just plugging and unplugging it to being able to manipulate the bass, treble, balance, volume, and all other control systems.

"We're going to be able to modify it to meet our needs and fine-tune each system the way we want it. We'll not only get something in between off and full volume, but we also can manipulate it to very specific tasks. This is what the next generation of genetic engineering will be. In our lab, what we're doing is learning what the parts are so that we can learn how to control them."

The mechanism is a fundamental target of medicine. "In the future, artificial cells could be engineered that will sense when your body needs something and then supply it," predicted Dr. Kennelly. "For example, we could place a microbe inside people or animals that makes an antibiotic when the need is sensed, or that engineers an artificial pancreas that knows when to turn on and off, since you can't just make insulin all the time. This is a dream for the future."

Dr. Kennelly has been working in this area for 23 years, starting as a graduate student. His interest in science began when he performed research as an undergraduate. His current research is supported in part by a $715,400 four-year NIH grant, a $273,900 NSF three-year grant, and a just renewed Hatch grant from Virginia Tech's College of Agriculture and Life Sciences.

Science's Next Wave

Career Information for ASBMB Members

Science's Next Wave, www.nextwave.org, is the weekly online publication that focuses on the careers of scientists—from undergraduates to faculty. As an ASBMB member, you have FREE access! Simply go to the "For ASBMB Members Only" section at www.jbc.org, and follow the links to NextWave. This site includes weekly news, alternative career profiles, academic career advice, discussion forums, and funding information.

Below is a sampling of articles that will appeal to students, faculty, and early career scientists. Although there are sections for particular groups listed below, please check out the other sections, especially the For Everyone section at the very end. Contact Next Wave at nextwave@aaas.org with any questions or comments.

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How to Present Your Weaknesses During an Interview
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For Graduate Students

The GrantDoctor
Financing medical school and finding research grants for foreign nationals working in the U.S.
http://nextwave.sciencemag.org/cgi/content/full/2001/08/22/1

Higher Hurdles: Doing Science as a Single Mom
http://nextwave.sciencemag.org/cgi/content/full/2001/08/29/1

For Postdocs and Postdoc Administrators

The mission of the Postdoc Network is to connect postdocs, their associations, and institutional offices, allowing these groups to share information and ideas.

The PostdocNetwork's one-of-a-kind database includes useful links to postdoc association, office, program Web pages, institutional policies, and salary/benefit information.
http://nextwave.sciencemag.org/cgi/content/full/2000/11/06/5

For Faculty

Women without Tenure, Part II: Science's Gender Sieve
An in-depth assessment of the perforated scientific pipeline, which leaks women from the time they enter as college undergraduates until the time a select few attain full professorship.
http://intl-nextwave.sciencemag.org/cgi/content/full/2002/01/24/7

MentorCoach
Modeled after the GrantDoctor column within the Career Development Center on *Science's* Next Wave, the MentorCoach will answer questions from mentors on their roles and responsibilities.
http://nextwave.sciencemag.org/miscinet/mentors/coach.dtl

Minority Scientists Network
In February, *Science's* Next Wave launched its Minority Scientists Network (MiSciNet). MiSciNet is a collaborative effort involving AAAS's Next Wave and its directorate for Education and Human Restheces. MiSciNet has two major emphases: supporting the science education of underrepresented minority students at the undergraduate level; and enctheaging those students to make the transition into graduate education. http://nextwave.sciencemag.org/miscinet/

For Everyone

Information on Biotech Start-up Companies

On the Inside: What to Expect Inside a Biotech Start-up
http://nextwave.sciencemag.org/cgi/content/full/2001/08/21/1
Taking the Plunge: Preparing for a Startup Interview
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New to Next Wave?

Go to http://nextwave.sciencemag.org/cgi/content/full/2001/09/18/2 to find out what the Next Wave site can offer you.

New Cholesterol Disorder Discovered;

A team led by University of California, San Francisco medical researchers has discovered a new disorder that can cause severely elevated blood cholesterol levels and may affect several hundred thousand people in the U.S. and Europe to varying degrees. The malady is caused by a single gene defect.

Discovery of the disorder started from a deduction: Researchers knew the gene's function, so they hypothesized how mutations would affect cholesterol levels, vulnerability to gallstones and other factors. They then searched a genetic database of some 12,000 patients and identified a number of people who had mutations in that gene. They studied the family of one patient and found that carriers of mutations in the gene did indeed have elevated cholesterol, including three siblings with dangerously elevated levels.

> ***"By understanding the mechanism—how this gene affects cholesterol regulation—we can diagnose those at risk earlier and choose better treatments for them."***
>
> **—Dr. John Kane**

"We went from a hypothesis to identifying the disorder in patients, rather than the more conventional route of seeing a disorder in patients and searching for the cause," said ASBMB member John Kane, MD, PhD, UCSF Professor of Medicine and senior author of a report on the findings in the July issue of *The Journal of Clinical Investigation*.

"Our finding adds to the roster of genes that can cause a disorder of cholesterol in the blood and increase the risk of heart disease and stroke," Dr. Kane said. "By understanding the mechanism—how this gene affects cholesterol regulation—we can diagnose those at risk earlier and choose better treatments for them."

The discovery is the fifth gene known to cause elevated cholesterol when it is defective. The gene's product is an enzyme called cholesterol 7-alpha hydroxylase (CYP7A1), and it is essential for the normal elimination of cholesterol. The enzyme initiates the primary conversion of cholesterol into bile acids in the liver.

The researchers hypothesized that a mutation that knocked out this gene would lead to an accumulation of cholesterol in the liver as the primary route of converting cholesterol to bile acids is blocked. The liver responds to excessive cholesterol by reducing the amount of receptors available to take up low density lipoprotein, or LDL—the "bad" cholesterol—from the blood. A mutation in the gene, they reasoned, would result in an accumulation of LDL.

The team also predicted higher triglyceride levels in the blood as well, because lower bile acid levels are known to lead to greater triglyceride production. Triglycerides, like LDL cholesterol, are major risk factors in atherosclerosis and other arterial disease. The scientists also predicted the presence of gallstones because inadequate bile acid levels would allow the cholesterol to crystallize into gallstones.

When the team identified their candidate patients, all their predictions were confirmed. Their search utilized a repository of DNA samples from more than 12,000 patients, along with their blood samples and clinical data which make up the Genomic Resource in Atherosclerosis of the UCSF Cardiovascular Research Institute (CVRI).

The team predicted the clinical effects of having a mutated CYP7A1 gene and then identified several hundred people who fit the profile. Using a sensitive technique to search for mutations in the DNA of these people, they found mutations in 11 people. Of 37 people in the family of one patient, nine carried the same mutation. Three were siblings with defects in both their maternal and paternal copies of the gene. Their cholesterol levels were above 300 mg/dl, nearly double their family's average, putting them at extreme risk for coronary heart disease. Two of the three brothers had elevated triglycerides and premature gallstone disease, as predicted.

Even family members with a mutation in just one of the two copies of the gene had significantly elevated cholesterol levels, the scientists found, equivalent to a heart attack risk more than 50% higher than average.

Taking into account that the original DNA sample was drawn from patients with cholesterol problems, the team was able to estimate that several hundred thousand people in the U.S. and Europe will be affected by defects in this gene.

The siblings with mutations in both copies of the CYP7A1 gene were, in effect, "human knockouts" for this gene. A powerful approach to determining how a particular gene functions is to knock out, or delete, both copies

As Predicted From Gene's Role

of the gene in mice and raise a line of mice lacking the gene. Such a mouse knockout has been developed for CYP7A1 but surprisingly, these mice do not exhibit the cholesterol problems predicted—and found—in people.

"The mouse model did not predict the significant increased cholesterol levels, but now that we have identified this disorder in patients, we hope that the new understanding of how LDL levels can become elevated will help prevent and treat atherosclerosis," said Clive R. Pullinger, PhD, research biochemist at the CVRI and lead author on the paper.

Dr. Pullinger identified the mutations in the suspected gene samples using a technique known as differential DNA melting, which pinpoints the mutated genes based on their abnormal mobility when the DNA is placed in an electrical field.

The research was funded by a number of institutions including NIH and the American Heart Association.

MIT Researchers closing in on RNA Splicing Code

MIT researchers have developed a computational method to predict which sequences of genetic material get spliced out, like outtakes of film on the cutting room floor, and which end up as the blueprint for life.

The discovery was reported on July 11 in *Science* by four MIT researchers led by Assistant Professor Christopher B. Burge.

The messenger RNA (mRNA) acts as a template for all the proteins that create a human being. This study represents one of the first times that computational methods have been used to successfully predict the function of molecular sequences in mRNA. This information could be used to predict which genetic mutations interfere with the splicing process by which mRNAs are created, potentially causing disease.

In and Out

Messenger RNA molecules typically contain strings of genetic material called exons, which code for proteins, and introns, which do not. Introns, like film outtakes, are removed from mRNA by a splicing mechanism that joins exons together. Surprisingly, the exons make up only a small percent of the genetic material in human cells. RNA splicing determines which segments, in the lengthy stream of genetic material that makes up a gene, end up being expressed and which do not.

This research was supported by grants from the Burroughs Wellcome Fund and the National Institutes of Health.

Reminder!

11TH NATIONAL CONFERENCE
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For more information go to:
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130-Year-Old Mysteries Solved:
How Nitroglycerin Works; Why Patients Develop Tolerance

For more than 130 years, doctors have prescribed nitroglycerin for relief of chest pain without a clear knowledge of how it actually worked. Now, not only have researchers from the Howard Hughes Medical Institute (HHMI) and Duke University Medical Center solved this age-old riddle, they have also shed light on the second major mystery surrounding nitroglycerin—why patients eventually develop a tolerance to the drug's effects.

Shortly after heart patients take nitroglycerin, the blood vessels supplying the heart muscle relax, allowing oxygen-rich blood to nourish the heart and relieve the pain. While it was known that nitric oxide—a breakdown product of nitroglycerin—plays a critical role in regulating blood vessel relaxation, scientists still did not know the mechanism by which nitric oxide is generated from the nitroglycerin molecule, which in fact shows little resemblance to nitric oxide.

The research team led by ASBMB member Jonathan Stamler, M.D., HHMI investigator at Duke, found an enzyme that not only breaks down nitroglycerin and releases a nitric oxide-related molecule, but whose action is suppressed in blood vessels made tolerant after repeated doses of nitroglycerin. While researchers in the past have searched for such an enzyme in different tissues, the Duke team found that the biochemical reaction that breaks down nitroglycerin takes place in mitochondria, a compartment within cells commonly known as the cell's "powerhouse." The enzyme is called mitochondrial aldehyde dehydrogenase (mALDH), and only in mitochondria can the nitric-oxide-related product of the enzyme get further processed to blood vessel-relaxing nitric oxide.

The results of the Duke scientists' research were published in the June 4 *Proceedings of the National Academy of Sciences (PNAS)*. The team's research was supported by HHMI. The results of this study "teaches us that mitochondrial aldehyde dehydrogenase is at least partially responsible for the bioactivation of nitroglycerin and is likely the target of nitroglycerin tolerance," wrote ASBMB member and Nobel Laureate Louis Ignarro, Ph.D., in an accompanying commentary in *PNAS*. "Moreover, by understanding the molecular mechanism of nitroglycerin bioactivation and tolerance, it may now be possible to design and develop novel nitrovasodilator drugs that do not cause tolerance."

Nitroglycerin is a common treatment for angina and heart failure. While the drug can be effective, it tends to lose it effectiveness over time, a situation that has for years frustrated physicians, who often take their patients off the drug for periods of time, leaving them at risk for angina and heart attacks.

According to Dr. Stamler, the key breakthrough in solving the puzzle came in the development of complex biochemical processes used to identify where the mALDH broke down the nitroglycerin. The Duke team screened alternative tissue types and surprisingly found that macrophages generated similar biochemical reactions. The team then subjected these macrophages to a long series of complex purifications and found that the key reaction took place in the mitochondria of the macrophages.

"By damaging mitochondria, nitroglycerin can actually damage the precious heart cells it is being given to protect."

—Dr. Jonathan Stamler

Protein biochemist Zhiqiang Chen, a post-doctoral fellow at Duke, designed the complicated processes responsible for this key breakthrough. With the knowledge that mitochondria appeared to be the center of the biochemical reactions, the researchers then looked at mitochondria within blood vessel cells and found that indeed, mALDH caused the nitric oxide to be released from the nitroglycerin.

"In general, cells don't work as well after being exposed to nitroglycerin," Dr. Stamler explained. "It appears that after several reactions, the enzyme is used up and over time, the mitochondria become totally depleted of active enzyme and are therefore unable to break down nitroglycerin. That is why patients eventually become tolerant to its effects. Additionally, by damaging mitochondria, nitroglycerin can actually damage the precious heart cells it is being given to protect."

Interestingly, according to Stamler, these findings shed light on many other disorders and diseases. "Our studies suggest that certain classes of drugs such as sulfonylureas used by diabetics, chloral hydrates used for sleep disorders and acetaminophen (Tylenol) inhibit mALDH activity," he said. "For that reason, heart patients who take nitrate drugs such as nitroglycerin may do better if they did not take those drugs."

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Plenary Lecture

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Scott D. Emr, *UCSD*

Lipid Traffic

PROTEIN MOTIFS REGULATING AMINOGLYCEROPHOSPHOLIPID TRAFFIC
*Dennis R. Voelker, *Natl. Jewish Res. Ctr.*

INTRACELLULAR CHOLESTEROL TRANSPORT
Laura Liscum, *Tufts Univ.*

REGULATION OF PHOSPHOLIPID FLIP AND FLOP ACROSS THE YEAST PLASMA MEMBRANE
Wylie Nichols, *Emory Univ. Sch. of Med.*

ENDOCYTOSIS AND SORTING OF GLYCOSPHINGOLIPIDS
Richard E. Pagano, *Mayo Clin. and Fndn.*

Lipid Enzymes—Structure and Function

REGULATION OF FATTY ACID BIOSYNTHESIS
*Charles O. Rock, *St. Jude Children's Res. Hosp.*

STRUCTURE AND MECHANISM OF PHOSPHOLIPASE A2 AT THE LIPID-WATER INTERFACE
Edward A. Dennis, *UCSD*

STRUCTURAL STUDIES OF MEMBRANE RECOGNITION
Michael L. Overduin, *University of Colorado HSC.*

ENZYMES OF PHOSPHATIDYLCHOLINE METABOLISM
Claudia Kent, *Univ. of Michigan Med. Ctr.*

Lipid Signaling

INSIGHTS INTO INOSITIDE MESSENGERS INVOLVED IN THE REGULATION OF MEMBRANE TRAFFICKING AND NUCLEAR FUNCTION
*John D. York, *HHMI, Duke Univ. Med. Ctr.*

REGULATION OF PHOSPHOLIPID METABOLISM BY ZINC
George M. Carman, *Rutgers Univ.*

SPHINGOSINE-1-PHOSPHATE—A PLURIPOTENT LIPID MEDIATOR
Sarah Spiegel, *Med. Col. of Virginia*

Lipid Metabolism—Genetic Diseases & Stress

BILE ACID BIOSYNTHESIS
*David W. Russell, *Univ. of Texas Southwestern Med. Ctr.*

MOLECULAR BASIS OF CONGENITAL GENERALIZED LIPODYSTROPHY
Abhimanyu Garg, *Univ. of Texas Southwestern Med. Ctr.*

THE NPC1 PERMEASE AND SUBCELLULAR LIPID TRANSPORT
Yiannis A. Ioannou, *Mt. Sinai Sch. of Med.*

THE ROLE OF STEAROYL CoA DESATURASES IN REGULATION OF LIPID AND CARBOHYDRATE METABOLISM
James M. Ntambi, *Univ. of Wisconsin, Madison*

**denotes chairperson*

More Information: ASBMB Meetings Office, 9650 Rockville Pike, Bethesda, MD 20814
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New Metabolic

Researchers from the Howard Hughes Medical Institute (HHMI) and Duke University Medical Center have identified a new class of metabolic switches, called G proteins, in yeast, which if found to be conserved in humans, could lead to the development of new drugs for treating diseases including diabetes, alcoholism, and heart disease.

The study, which was funded by the National Institutes of Health and the Burroughs Wellcome Fund, was coauthored by HHMI investigator and ASBMB member Joseph Heitman, M.D., Ph.D., and Toshiaki Harashima, Ph.D., with the Duke Center of Microbial Pathogenesis and HHMI at Duke.

G proteins are key controllers of the body's internal "switchboard" of metabolic pathways. They typically lie just inside the cell membrane, attached to "G protein-coupled receptors" (GPCRs) on the cell surface, which respond to external chemical signals such as hormones. Once such an external signal activates a receptor, it switches on its coupled G protein, which in turn triggers a cell response. G proteins control such cellular responses in tissues throughout the body, including the heart, lungs, adrenal glands, liver, brain and other organs. G protein malfunctions in humans can lead to symptoms associated with diabetes, alcoholism, cholera and whooping cough.

To date, scientists have reported approximately 450 genes for G proteins. Metabolic pathways involving the receptors for such G proteins are the targets of hundreds of drugs, including antihistamines, neuroleptics, antidepressants and antihypertensives. At least 50 percent of all drugs sold today target G protein-coupled receptors. However, the functions of many of these proteins are unknown. In humans, there are more than 1,000 types of G protein-coupled receptors in the brain, which indicates the great potential for drug discovery by studying GPCRs and their associated G proteins, said Dr. Heitman.

"This novel class of G proteins, which if proven to be conserved in humans, could play a role in allowing our cells and bodies to sense unique signals important in both health and disease," he explained.

The researchers' study focused on a

"Switches" Discovered

yeast G protein-coupled receptor called Gpr1 that is coupled with a G protein called Gpa2. Functionally, the Gpr1 receptor senses glucose in the yeast cells' environment and activates the coupled Gpa2 to launch a growth process in which the yeast cells elongate and produce filaments that extend away from the colony and into the growth medium to forage for nutrients.

G proteins are "heterotrimeric" complexes, meaning that they are composed of three different subunit proteins, called alpha, beta, and gamma — each of which plays a role in the transmission of the metabolic signal to the cell's machinery. Since Gpa2 is highly related to the alpha subunit, the researchers expected to find associated beta and gamma subunits — but they were not present. According to Dr. Heitman, the absence of these two subunits raised questions of whether the GPa2 functioned alone, or whether there existed as-yet-undiscovered classes of G protein subunits.

"Consider the analogy of a relay race," he said. "To run a relay you typically need four runners or swimmers. If any one is missing, the baton cannot be passed. So in this signaling pathway, who was passing the baton from the first runners to the last runner? Were they skipping a runner, or was there a novel runner that we didn't know about?"

Those questions led Dr. Heitman and his colleagues to identify three novel G protein subunits — two closely related subunits called Gpb1 and Gpb2, and a third called Gpg1.

The newly discovered subunits offer an example of completely unrelated proteins with similar biological functions, he stated. Proteins are made of strings of amino acids that once synthesized, fold into the complex globular shapes that make them into functioning enzymes. Proteins that perform similar functions typically share the same amino acid sequences. In this case, even though the Gpb1 and Gpb2 proteins function like G protein beta subunits, they still lack any known amino acid sequence similarity to beta subunits.

Using biochemical and genetic analyses, the researchers found that Gpa2 plays an activational signaling role, which means Gpa2 functions as a molecular gas pedal to turn the pathway on. On the other hand, Gpb1 and Gpb2 subunits play inhibitory signaling roles, which means these proteins function as molecular brakes to constrain signaling between the Gpa2 protein and another unknown target in the metabolic pathway. Also, the researchers found that the Gpg1 subunit appears to interact indirectly with Gpa2 subunit, through the Gpb1 or Gpb2 subunits.

Intriguingly, the researchers found that the Gpb1 and Gpb2 subunits contain very divergent repetitive sequences of amino acids in key sections of their structures, compared to G protein beta subunits; however once they fold into their working shape, they still function similarly. Such evolution of different molecules or structures to have similar function is known as "convergent evolution."

"Because these two completely different kind of repeat protein families fold into a similar structure, this suggests a striking example of convergent evolution with related structures. This further suggests there might be two structurally related, but sequence divergent families of heterotrimeric G proteins," said Heitman.

He and his colleagues will continue to study the structures of the newly discovered G proteins. They will also attempt to identify the molecular targets of the G proteins and study whether the proteins are conserved in multicellular organisms, such as insects, plants, and animals.

Yale Professor to Receive FASEB Excellence in Science Award

Joan A. Steitz, Henry Ford II Professor of Molecular Biophysics and Biochemstry at Yale University, has been selected to receive the 2003 FASEB Excellence in Science Award. This award is presented annually to a woman scientist for research that made significant contributions to the further understanding of a particular discipline. The award carries with it a $10,000 unrestricted research grant funded by Eli Lilly and Company, and transportation expenses to the 2003 Experimental Biology Meeting, April 11-15 in San Diego where Dr. Steitz will deliver a plenary lecture.

An ASBMB member who has served on the Society's Council, Dr. Steitz has made outstanding contributions to the field of molecular genetics. Her studies have defined the roles of small nuclear ribonucleoprotein particles in RNA processing in mammals. She has focused her research on the structure and function of these cellular complexes, which play a key role in some of the most basic biological processes that convert information in the DNA to the active protein molecules of the living cell.

The FASEB Award recipient earned her B.S. in chemistry from Antioch College in 1963. Significant findings emerged from her work as early as 1967, when her Harvard Ph.D. thesis examined the test-tube assembly of a ribonucleic (RNA) bacteriophage (anti-bacterial virus) known as R17. This work led to important early insights into how the protein and nucleic-acid components of viruses come together.

Currently, she leads the Molecular Genetics Program in the Boyer Center for Molecular Medicine and is a Howard Hughes Medical Institute investigator.

Life Sciences Institute Director Leaving Michigan

Dr. Jack E. Dixon, Minor J. Coon Professor of Biological Chemistry and Director of the Life Sciences Institute at the University of Michigan, has announced that he will be taking a new position in January 2003.

Dr. Dixon, who served as ASBMB President in 1996, has accepted the office of Dean of Scientific Affairs at the University of California, San Diego. He will be continuing his research on the protein phosphatases and bacterial pathogens and signal transduction interactions.

In a letter to the university's life sciences faculty, Dr. Dixon wrote, "This has been the most difficult decision of my professional career. I spoke with our new president, Mary Sue Coleman, to inform her of my decision. It was a particularly difficult phone call because of the respect and admiration I have for her and her new leadership efforts at the University.

"I plan to remain at Michigan until 2003 to participate in teaching two courses in the fall and give those people in my research group who cannot move to UCSD an opportunity to find new positions. I am also committed to helping the administration in the transition of its Life Science efforts."

Dr. Dixon said that while there were many factors that went into making his decision, "A very important factor was the fact that all of my previous scientific training was done on University of California campuses, and this was an opportunity to give something back to the university system that contributed so much to my development."

Also leaving the University of Michigan will be Dr. Dixon's spouse, Dr. Claudia Kent. She has announced that next summer she will be retiring from her position as Professor in the Department of Biological Chemistry at the University of Michigan. Dr. Kent is currently Co-Chair of ASBMB's 2003 Program Committee.

ASBMB Members Elected Fellows of American Academy

In addition to those mentioned in the June issue of *ASBMB Today,* we have learned of two more ASBMB members who were elected Fellows of the American Academy of Arts and Sciences. They are Bernard Agranoff, M.D, and Howard Gest, Ph.D.

Dr. Agranoff is a Professor of Biological Chemistry at the Mental Health Research Institute of the University of Michigan. Dr. Gest is Distinguished Professor Emeritus of Microbiology at the University of Indiana.

The American Academy of Arts and Sciences was founded in 1780 by John Adams, James Bowdoin, John Hancock and other scholar-patriots "to cultivate every art and science which may tend to advance the interest, honor, dignity, and happiness of a free, independent, and virtuous people." This year's new Fellows and Foreign Honorary Members will be welcomed at the annual Induction Ceremony at the Academy's headquarters in Cambridge, Massachusetts, on October 5.

Improved NCI Website to Study Genes

With the click of a mouse, researchers can quickly analyze information from thousands of genes stored in special databases over the Internet. But experts who utilize these databases face the same type of problems that greet many Web surfers, such as sites that are confusing and hard to navigate—or worse, information that is incomplete or non-existent.

To overcome these shortcomings, a group of researchers have designed a website that provides an easier and more accurate way to search for potential disease-causing genes. The new site, known as SAGE Genie, is available online (http//cgap.nci.nih.gov/SAGE) as part of the Cancer Genome Anatomy Project run by the National Cancer Institute (NCI).

"Now that most of the human genome has been sequenced, it is important to accurately determine exactly where these genes are expressed, but this information is often hard to use or not available," said Dr. Gregory Riggins of Duke University Medical Center, the lead author of a study on SAGE Genie that is to published in the *Proceedings of the National Academy of Sciences*. "We have simply improved a good way to study genes and made it available to everyone online."

The improvements are based on a highly respected technique for studying genes called serial analysis of gene expression, or SAGE, developed at Johns Hopkins. Although widely considered to be the most in-depth human gene-sequence profiling technique, even the most experienced gene hunters can have trouble navigating existing SAGE databases.

Researchers made several improvements as part of the upgrade. At Duke, a team led by Dr. Riggins went through nearly 7 million SAGE transcription tags to see which ones were the most reliable. Investigators at the Ludwig Institute for Cancer Research then developed a scoring method to alert users whether the tags were of high-quality or if they contained potential flaws.

Both teams helped to offset further errors, such as accounting for incomplete gene transcripts that can occur as experimental artifacts. Finally, specialists at the NCI developed a new site that incorporated these additions, providing a simplified interface that matches a particular transcript to where it is found in the body.

"This is very straight forward and user friendly," said Dr. Sandro de Souza of the Ludwig Institute for Cancer Research, Sao Paulo Branch. "It helps a large variety of scientists who want to check gene expression patterns to find a disease marker or target for treatment."

McGill University Awarded Five Major Health Training Grants

McGill University has been awarded major funding for five training programs by the Strategic Training Initiative in Health Research of the Canadian Institutes of Health Research (CIHR). It is predicted that 100,000 new health researchers will be needed by 2010 in Canada alone.

McGill's five successful applications (of a total of 51 awards nationwide) will receive more than $8 million (Canadian) in funding over the next six years.

The winning programs are:

The Montreal Centre for Experimental Therapeutics in Cancer, led by Dr. Gerald Batist, Chair of McGill's Department of Oncology. The Centre's program brings together researchers from 10 universities and other research institutes, with the ultimate aim of discovering and developing novel approaches to the prevention and treatment of cancer.

Training Program in Skeletal Health, led by Dr. David Goltzman of McGill's Faculty of Medicine and composed of researchers from six universities. The program is designed to give healthcare professionals the skills to address complex issues related to skeletal health. Diseases of the skeleton, such as osteoporosis and arthritis, are estimated to cost Canadian taxpayers $5 million in direct healthcare costs per year.

Training Centre in Integrative Biology of Infectious Diseases and Autoimmunity, led by Dr. Erwin Schurr of the University's Faculty of Medicine. The Centre aims to provide comprehensive training leading to the development of novel interventions for common human diseases. The training program will also look at issues of communication, ethics, intellectual property and technology transfer.

The Chemical Biology Training Program, led by Dr. David Thomas, Chair of McGill's Department of Biochemistry, and involving mentors from Biochemistry, Chemistry and Pharmacology and adjunct faculty from the biopharmaceutical industry. The program will provide young scientists with a wide range of skills for tackling research challenges posed by the rapid advances in genomics and proteomics.

The McGill University Cancer Consortium, led by Dr. Michel Tremblay, head of McGill's Cancer Centre, and grouping more than 30 laboratories pursuing clinical and basic research. The aim of the consortium's training program is to ensure continued improvement in cancer research, training and clinical services.

Researchers Identify New Skin Cancer Gene

British scientists have identified a gene involved in the deadliest form of skin cancer, in one of the first successes to emerge from the mapping of the human genome.

They found that a gene involved in controlling cell growth was mutated in about 70 percent of malignant melanomas, skin cancers that affect more than 60,000 people in the U.K. and U.S. alone.

"This discovery is important because it highlights the genetics of melanomas, and also because it opens up a window that we hope to explore for potentially developing a new therapeutic drug," said Dr. Andy Futreal, joint leader of the Wellcome Trust's Cancer Genome Project at the Sanger Institute, near Cambridge.

The gene, called B-RAF, shares much of its structure with another cancer-related gene called ABL, mutations of which are found in many leukemias, or cancers of white blood cells. A drug inhibiting the function of the ABL protein has had marked success in treating chronic myeloid leukemia.

"We are very positive about this because B-RAF and ABL ... are part of the same family of proteins. They have the same biological function," Sanger Centre Director Mike Stratton said.

"If you can find a molecule that inhibits activity in ABL, it is very plausible to find a molecule that inhibits activity in B-RAF."

But he stressed that although scientists in Cambridge had already begun screening small molecules for B-RAF inhibiting activity, the findings provided only an avenue for research, not a definite cure.

"We have to temper our optimism with a certain amount of caution," Stratton said. "Cancers are devious beasts. They are unpredictable, and they do not always respond in the way we would like them to."

by John D. Thompson, Editor

Will Pfizer/Pharmacia Deal Get Others Thinking Merger?

Pfizer, the world's largest drug company, expects to pull even further ahead of the pack, thanks to its $60 billion purchase of Pharmacia. The deal could well spark another wave of mergers in the industry, which is currently struggling to maintain its profitability.

Still, some question whether mergers will be the answer to the industry's growing list of problems. Expiring patents and a rush of generic competitors have eaten into the profitability of some of Pfizer's most lucrative products, such as Prozac. In America, states and private groups have taken to suing drug makers over excessive profits, and several companies are under investigation by the FTC for anti-competitive practices. And in Europe, public-health systems have aggressively moved to cut drug prices and, thanks to their virtual monopoly as buyers, have the power to force prices down.

The industry's biggest headache, though, may be how to boost productivity in research and development.

According to the Centre for Medicines Research (CMR), an industry think-tank in the UK, 31 new drugs were launched on the American market last year, compared with 52 a decade earlier. In order to maintain their profit growth, the giants of the industry need to create roughly three new drugs apiece a year. Since 2000, Pfizer and GlaxoSmithKline, two of the largest, have produced just three between them in the U.S.

While output slumps, the cost of producing new medicines rises. Last year the industry spent $44 billion on R&D, and a report from the Tufts Center for the Study of Drug Development shows that it now costs an average of $800 million to get a drug to market, twice as much as in 1987.

Much of this spending goes on clinical trials, the last stage of drug development, but according to Martyn Postle, at Cambridge Pharma Consultancy, up to 70% of the high cost of development is eaten up by drugs that do not even make it to market. A rough-and-ready rule of drug-making has it that for every 10,000 molecules screened in a given program, only one will survive to launch.

Ultimately, pharmaceutical firms are victims of their own success and the great expectations that accompany this. As Alastair Flanagan of Boston Consulting Group points out, it is not that they have become much worse at delivering new drugs, but rather that they have not become much better. That is exactly what investors hoped for after the last great wave of mergers in the industry, in the late 1990s.

Exelixis Announces Discovery of Two Proteins Involved in Alzheimer's Disease

Scientists at Exelixis, Inc., working in collaboration with Pharmacia Corporation, have discovered two proteins that play a role in the production of beta-amyloid, the main constituent of senile plaques associated with Alzheimer's disease. The two proteins identified, aph-1 and pen-2, are required for activity of the protein presenilin, a key component of gamma secretase, one of the two proteases responsible for the production of beta-amyloid. The discovery of these new proteins could lead to the discovery of novel small molecule drug treatments for Alzheimer's disease. These findings were published in the July 2002 issue of *Developmental Cell* in an article entitled, "aph-1 and pen-2 Are Required for Notch Pathway Signaling, Gamma-Secretase Cleavage of BetaAPP, and Presenilin Protein Accumulation."

Using genetics, functional genomics and model systems, scientists carried out a series of genetic screens in worms (*C. elegans*) to elucidate the biological pathways involved in Beta-amyloid production. These screens were based on the Notch signaling pathway, as gamma-secretase is known to play a dual role in cleavage both of Notch receptors and of the beta-amyloid precursor protein, BetaAPP. Through mutation and observation of the resultant phenotypic changes in *C. elegans*, the essential, conserved role of aph-1 and pen-2 in gamma-secretase activity was identified. Confirmation studies were performed in the fruit fly (*Drosophila*) and by demonstration that the human orthologs of aph-1 and pen-2 are functional in the *C. elegans* signaling context.

Australian Scientists Isolate Productive Rice Gene

Australian scientists have ended a 40-year search for a gene which they say could revolutionize rice cultivation.

The gene isolated by the scientists produces shorter, more productive varieties of rice, according to the government-backed Commonwealth Scientific and Industrial Research Organization (CSIRO).

Team leader Wolfgang Spielmeyer said isolating the gene would speed the process of creating new rice varieties and help identify "semi-dwarfing" genes in other cereal crops, such as wheat. "In terms of yield, the gene is probably the single most important gene in modern rice breeding," he stated.

The development of new varieties of rice with shorter stems, which produced record crop yields throughout Asia in the 1960s, was called the "green revolution" by scientists. But the gene responsible had not been isolated until now.

Funding for the CSIRO research to isolate the gene, called sd-1 after the term "semi-dwarfing," was funded by Graingene, an alliance of Australia's national wheat exporter AWB Ltd, CSIRO, and the Grains Research and Development Corp.

Tax Credits, Not Grants, Help Keep Small Companies Canadian

Unlike the United States, where research and development is generally funded through direct government contracts, Canada has seeded its cutting edge corporations with grants, subsidies, tax credits, and reimbursements that can shave the cost of R&D in half.

"We would be crazy not to" take advantage of Canada's tax breaks, said Gary Whipp, President and CEO of Nanox Inc., a Quebec City-based company in beta-testing of its nanocrystals. Since discovering its now-patented chemical process for making these nanomaterials in the mid-1990s, the company has received direct and indirect government support for its $660,000(U.S.) in research through collaborations with nearby Laval University, Canada's National Research Council, and federal and provincial tax credits.

Small companies spending heavily in R&D, he added, not only get tax credits against earnings, but actual reimbursements, "a check in the mail," during the startup phase.

"Here in Quebec City and in Montreal, companies that set up in the downtown areas that have been designated for growing the new economy get worker subsidies of up to $13,200 (Canadian) a year for up to 10 years, plus tax breaks for the first $132,000 (Canadian) of profit for five years, and for any international scientists the company hires," Whipp explained. "When you add all these things together, it's easy to do R&D here."

According to a 1997 Conference Board of Canada study of R&D tax treatment in the 25 main industrial countries, Canada came out second only to Italy in tax incentives. Since the early 1980s, it said, Canada's federal tax system—in combination with provincial incentives in Quebec and Ontario—has "the most generous tax incentives" among nations in the Organization for Economic Cooperation and Development.

Along with general and small business tax credits that range from 20-40% of expenses in Quebec and up to $1.32 million (Canadian) in expenses on the federal tax side, Canada also allows an immediate write-off for R&D capital costs, such as machinery and equipment, that can be fully deducted in the year incurred. Additionally, in high-tax Quebec, new companies are eligible for a tax holiday of up to five years. These tax breaks are key to Canada's efforts to keep its cutting edge industries and compete with the United States and Europe.

In the U.S., funding is mostly through direct government contracts, rather than tax write-offs, according to Marlene Bourne, an analyst with InStat/MDR, a consulting firm that specializes in high-tech industries.

"From an R&D standpoint, there's no tax credit at the national level and most state credits are on a case-by-case basis, usually aimed at keeping big companies in place so they don't lose jobs," she said. As a result, she added, small companies don't get the breaks, and funding has to come directly through contracts with some division of the government.

Molecular Biology Times Two

Rebecca and Susan Kahane are identical twins with nearly identical interests: Field hockey, helping children, karate, and molecular biology.

Molecular biology may sound like an extraordinary pursuit for teenagers, but these sisters are anything but ordinary. The 17-year-olds, both seniors at Walter Johnson High School in Bethesda, Maryland, are high achievers whose interest in science arose in a ninth grade honors biology class and had them doing after-school research in National Institutes of Health (NIH) labs.

Becky and Susie, as they like to be called, were participants in a Howard Hughes Medical Institute (HHMI)-supported Student and Teacher Program at NIH. This program enables high school students to receive academic credit for conducting biomedical research, with NIH scientists as mentors and advisors.

Susie, Becky and 18 other Maryland high school students presented their research findings at a symposium in May, at HHMI headquarters.

Becky works at the National Institute of Child Health and Development's molecular growth regulation laboratory. She is studying the role of two transcription factors—interferon regulatory factor 4 (IRF-4) and interferon consensus sequence binding protein (ICSBP)—in the normal development of blood cells and their potential roles in blood disorders such as leukemia.

"ICSBP is a transcription factor whose activities are believed to be disturbed in chronic myelogenous leukemia (CML)," Becky explains. "Mutant mice in which the ICSBP gene is disrupted develop a CML-like disease characterized by an increased number of granulocytes and an impaired production of macrophages. We believe that a closely related protein—IRF—may also play an important role in macrophage and granulocyte development."

To test this hypothesis, she introduced IRF-4 into ICSBP knockout mice and found that IRF-4 also controls myeloid cell differentiation. She plans further experiments to identify the molecular mechanism by which these two transcription factors control target genes. "That should help us learn more about how myeloid cell growth and differentiation are regulated," she explains.

"Becky was very quick to learn highly sophisticated techniques, and she obtained useful results," says Keiko Ozato, an NIH researcher who heads the lab where Becky works.

Working in the laboratory of molecular pharmacology at the National Cancer Institute, Susie has been helping develop a knockout mouse whose mitochondrial topoisomerase gene has been inactivated. Topoisomerases are a class of enzymes essential for normal cellular activity. "One goal of this project is to gain a better understanding of mitochondria, which have been linked to aging and several genetic diseases," she explains.

Both are academic award winners. Becky was a finalist for the National Presidential Scholar Medal, which is based on SAT scores, while Susie won a National Merit Scholarship. They expect to end up at different colleges, although both have been accepted at the University of Maryland. Susie also was accepted at Columbia University, and Becky was wait-listed at the University of Pennsylvania, her first choice. At press time, they had not made their final decisions.

Neither twin has yet decided whether to pursue a research career. "If I stay in research, I'm interested in studying cancer," says Becky. "But I'm also interested in public health, in working with people, and possibly teaching. I will probably go into some health area, but I'm not sure it will be scientific research."

This article by Jennifer Beth Donovan appeared on the website of the Howard Hughes Medical Institute and is reprinted with permission.

British Nobel Laureates Blame Europe for Brain Drain to U.S.

Six Nobel Laureates have criticized the European Union's (EU) science policy and urged reforms and a doubling of research funds to stem the brain drain to the United States.

"Brain drain—young talented scientists leaving their countries—is making itself felt in most EU countries," the laureates and several other European scientists said in a letter to EU leaders preparing to hold a summit in Seville, Spain.

The EU should at least double current investment in research and development if it is serious about achieving its stated goal of creating "the most competitive knowledge-based economy in the world by 2010," the scientists said in a letter obtained by Reuters.

The Nobel Laureates called the current EU goal, increasing spending on research and development to 3% of EU gross domestic product by 2010 from 2% now, insufficient.

The scientists called EU spending plans "inadequate even to put a brake on the process of relative back-sliding of European scientific capability, let alone if one wants to catch up with and overtake the United States."

Many European scientists are attracted to the funds and facilities in the United States, which has generated the largest national share of Nobel science laureates since the 1950s. The Nobel Prize is the most prestigious prize for scientific work and is worth about $1 million (U.S.).

Citing reports from the Organization for Economic Cooperation and Development and the EU Commission, the laureates said the EU was falling behind the U.S. and Japan.

They said EU spending on research and development was one-tenth of the amount spent on agriculture, a gap that "conveys a strange view of the potential and the future of the European Union," their letter said.

The laureates said the EU should focus on basic research to generate knowledge and invest in young scientists as well as international "centers of excellence," including EU candidate countries.

They also suggested creating a European Science Council, modeled on the more transparent U.S. system with open academic peer-review, rather than letting EU bureaucrats in Brussels evaluate scientific projects needing funds.

The Nobel signatories were 1992 French Physics laureate Georges Charpak, 1984 Italian Physics laureate Carlo Rubbia, 1982 British Chemistry laureate Aaron Klug, and three winners of the Medicine Prize, Sweden's Bengt Samuelsson (1982), Italy's Rita Levi-Montalcini (1986) and Belgian Christian de Duve (1974), an ASBMB member.

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.

Ann Lynn Benko
Penn State University College of Medicine

Greg P. Bertenshaw
Penn State University

Ming Bi
Texas Tech University Health Sciences Center

Bruce Doll
Penn State University College of Medicine

Regina M. Graham
Tulane University

Natacha L. Hausler
Texas Christian University

Sarah L. Johnston
Massey University

Robert M. Jones
Tulane University

Nathaniel J. Szewczyk
University of Pittsburgh

ASBMB Members Named Royal Society Fellows

Three ASBMB members are among the 58 new Fellows elected by the Royal Society of Canada, the Canadian Academy of the Sciences and Humanities. In keeping with the motto of the Society, "different paths, one vision," these newly elected Fellows, while coming from diverse backgrounds and disciplines, all are dedicated to achieving excellence in their endeavors, and thus enhancing Canada's competitiveness on a global basis.

Fellowship in the Royal Society of Canada is considered Canada's most prestigious academic accolade. "These distinguished individuals have accomplished work of truly outstanding quality," said Howard Alper, President of the Royal Society of Canada. "They add enormous value to the extraordinary resource of talent and experience that constitutes the Society."

The ASBMB members elected Fellows of the Royal Society's Academy of Science are:

Carol E. Cass, Professor and Chair, Department of Oncology, University of Alberta.

Richard Rachubinski, Professor and Chair, Department of Cell Biology, University of Alberta.

Cecil Yip, Professor and Vice-Dean, Research, University of Toronto.

This year's new Fellows will be inducted to the Society in a ceremony at Rideau Hall, the Governor General's residence in Ottawa, on Friday, November 22.

CiteTrack:
A Free Email-alerting Service that Finds Articles You Might Have Missed

In the January issue, we 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! At that time 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.

When HighWire interviewed scientists about their needs for information retrieval and access, one of the major points was that researchers and their labs could scan only a few dozen journals among a lab team, in terms of examining them for important articles. One lab reported on an informal time-limited study in which they found 30 articles related to the lab's work in their "usual" journals; but when they looked broadly across many, many other journals they found another 30 articles that were related and would have been overlooked.

HighWire's new portal has a solution to this problem: "CiteTrack," a free alerting service that can alert you on articles that match your interests, by automatically looking across all new content in Medline every day, and all of the new full-text in over 340 HighWire-based journals every day. You can focus on your core journals, and let CiteTrack track hundreds and thousands of other journals for you.

If CiteTrack finds a match with a term or author you've specified, you will get an email the same day the article is published. The email gives you the full author/title/citation to the newly-published article, plus a hyperlink to get you right to it.

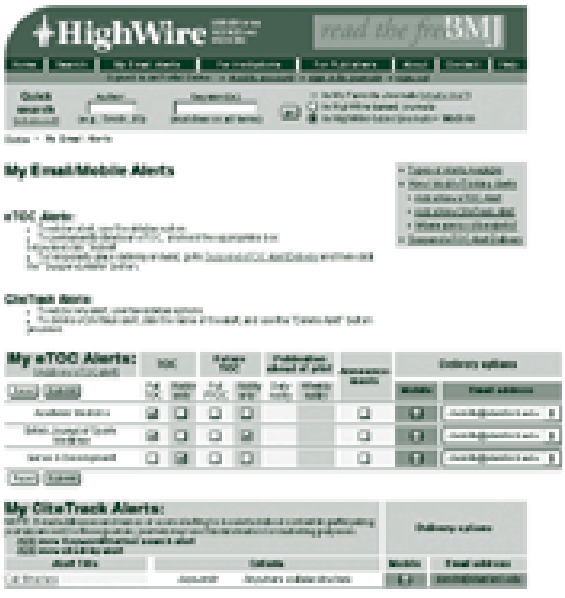
You can register as many CiteTrack alerts as you'd like, each with a different set of keywords and/or authors. You can also be alerted when articles of interest to you are cited, and see who cited them, perhaps citations to your own articles! You can tell CiteTrack to look only in particular journals (perhaps the ones in your journal club), in journals that publish in particular topics, in all 340+ HighWire-based journals' full-text, or across all of HighWire plus all of Medline.

In the future, you'll be able to tell CiteTrack that you are interested in certain topics, defined by detailed subject categories – and have CiteTrack tell you whenever new content is published in your favorite categories. This will allow you to match your general interests, without having to figure out all the possible keywords and authors that determine those interests. You'll be able to receive a daily or weekly list of articles published, the table of contents for a "virtual journal" that matches just your interests.

How to Set Up CiteTrack Alerts

Just click on the My Email Alerts link on the HighWire home page at http://highwire.stanford.edu. From the My Email Alerts page you can create an alert by author, words in the title or abstract, or text anywhere in an article. The My Email Alerts page also shows you all your email tables of contents alerts ("eTOCs"), and will soon allow you to sign up to have content delivered to your Palm/PDA. Figure 1 shows the summary of alerts you will get on

Figure 1, below



the My Email Alerts page; if you look for the links to "ADD" an alert you'll see how to create a new alert. Figure 2 shows how easy it is to add an alert once you've clicked on the ADD link from the previous page: you just fill out a form as if you were going to do a search! In fact, this is the way CiteTrack works: it does a search for you, and whenever it retrieves something it hasn't retrieved before, it emails you. (The list of topics is abbreviated in Figure 2.)

Figure 2

If you are not a registered user of the HighWire portal or haven't signed in when you click on My Alerts, you'll see a link to register or sign in. Registration takes only a minute or two; its fast and free. And once you've registered, other new features discussed in this series become available to you, such as "My Favorite Journals" described in the May issue.

Next month we'll look at new techniques to further refine your search, whether you are new to a field and looking for just a few key articles, or when your search retrieves far too many results to examine.

Genes and Insurance: The 'Forbidden' Questions on Genetic Testing

How much do you drink? Do you smoke? Do you take part in any dangerous pastimes? Questions like these are familiar to anyone who has recently applied for life insurance in Britain. However, insurance companies in the United Kingdom are currently prohibited from asking questions they may find even more helpful about genetic tests, which could reveal whether applicants have genetic mutations which could put them at a high risk of developing certain diseases.

Now, with funding from the Wellcome Trust's biomedical ethics program, a team based in Cardiff, Wales, is working on research to help decide what use, if any, such tests might be to insurance companies. The team seeks to gather evidence on the potential impact of genetic testing on insurance costs, and the interaction between genetic testing and insurance buying.

The team comprises: Dr. Lindsay Prior, Reader in Sociology in the School of Social Sciences at Cardiff University; Professor Peter Harper, Professor of Medical Genetics at the University of Wales College of Medicine (UWCM); Dr. Jonathan Gray, Consultant in Medical Genetics (Cancer) at UWCM; and Professor Angus Macdonald, Professor of Actuarial Mathematics at Heriot-Watt University in Edinburgh, Scotland.

Dr. Prior explained: "The question is, how do people perceive the risk, and what do they do about it? This is an important issue for patients, whose lives it directly affects, and for clinicians, who fear that the insurance industry's attitude may deter people from having tests, as well as for the insurance industry which fears adverse selection."

For the first stage of the research, Dr. Prior and the team are extracting anonymous data on families affected by certain inherited diseases which develop in adult life. These range from Huntington's disease to conditions that lead to colon cancer.

Using the anonymous data, the researchers will construct mathematical models to determine what scope there is for adverse selection, and what effect this may have on insurance claims, and therefore premiums.

The second part of the study will involve asking a sample of adults from the families about their views and behavior towards buying insurance. "From this information, we should be able to determine whether people can adversely select against insurance companies, and if they actually do," said Dr. Prior.

The final stage of the research will involve interviewing representatives from the insurance companies themselves to gain an understanding of the problem from their point of view.

The team's findings is intended to influence the policy to be introduced by the UK government, when the current moratorium on the use of genetic test results by insurers ends in October 2006.

Calendar of Scientific Meetings

SEPTEMBER 2002

Molecular Targets for Dietary Intervention in Disease

September 19-22 • Iowa State University, Ames, Iowa
Contact: Growth Factor and Signal Transduction Conferences
Ph: 515-294-7978; Fx: 515-294-2244; Email: gfst@iastate.edu;
Website: http://molebio.iastate.edu

7th International Symposium on Dendritic Cells

September 19-24 • Bamberg, Germany
Contact: Prof. Dr. Alexander Steinkasserer
Ph: ++49-9131-853-6725; Fx: ++49-9131-853-5799;
Email: steinkasserer@derma.imed.uni-erlangen.de
Website: http://www.dc2002.de/

American Society for Bone and Mineral Research 24th Annual Meeting

September 20-24 • San Antonio, Texas
Contact: ASBMR Business Office
Ph: 202-367-1161; Fx: 202-367-2161;
Email: ASBMB@dc.sba.com; Website: http://asbmr.org

The Role of Institutional Rules, Guidelines, and Education in Promoting the Responsible Conduct of Research

September 23-24 • Philadelphia, PA
Website: http://www.rowsciences.com/ORIconference/home.html

OCTOBER 2002

European Conference on Computational Biology 2002 in conjunction with the German Conference on Bioinformatics 2002

October 6–9 • Saarbruecken, Germany
Email: eccb.organizers@bioinf.uni-sb.de
Website: http://www.eccb2002.de

Metabolic Engineering IV: Applied System Biology

October 6-11 • Il Ciocco, Castelvecchio Pascoli Tuscany , Italy
Contact: United Engineering Foundation; Ph: 212-591-7836
Fx: 212-591-7441; Email: engfnd@aol.com
Website: http://www.engfnd.org
Registration: http://www.engfnd.org/2ay.html

Symposium on Phenotyping Mouse Cardiovascular Function and Development

October 10-11 • NIH Campus, Bethesda, Maryland
Abstract submissions are welcome.
Contact: Judy Corbett, Ph: 301-496-4910,
Email: corbettj@nhlbi.nih.gov;
Website: www.nhlbi.nih.gov/meetings/mouse

9th Midwest Platelet and Vascular Biology Conference

October 11-13 • Washington University School of Medicine, St. Louis, MO
Abstract and registration due August 15, 2002
Website: http://www.biochem.wustl.edu/mwpc9/index.html

Federation of Analytical Chemistry and Spectroscopy Societies

October 13–17 • Providence, Rhode Island
Contact: FACSS National Office; Website: http://www.facss.org

The 18th International Conference on Arginine and Pyrimidines

October 13-17 • Giza, Cairo, Egypt
Biennial conference on all aspects of biochemistry and genetics of uptake and metabolism of arginine and pyrimidines.
Contact: Ahmed T. Abdelal, Georgia State University
Email: aabdelal@gsu.edu; Website: http://www.cas.gsu.edu/icap

The Applications of Proteomics

October 16–18 • Lille-Villenueve d'Ascq, France
Contact: French Society for Electrophoresis and Proteomic Analysis; Tel.: 33-3-20-43-40-97;
Email: hubert.hondermarck@univ-lille1.fr
Website: http://www.sfe-ices.org/

18th Asilomar Conference on Mass Spectrometry

October 18–22 • Asilomar, Pacific Grove, CA
Contact: American Society for Mass Spectrometry
Ph: 505-989-4517; Email: office@asms.org;
Website: http://www.asms.org;

Fourth HUGO Pacific Meeting and Fifth Asia-Pacific Conference on Human Genetics

October 27–30 • Pattaya, Chonburl, Thailand
Contact: Tel.: 66-2-8892557-8; http://www.mu-st.net/hugothai/

NOVEMBER 2002

AAPS Annual Meeting and Exposition

November 10-14 • Toronto, Ontario, Canada
Contact: AAPS Meetings; Fx: 703-243-9532 Email: Meetings@aaps.org

First Human Proteome Organizational (HUPO) Congress

November 21–24 • Versailles, France
Contact: http://www.hupo.org

3rd Conference of the International Coenzyme Q10 Association

November 22-24 • Metropole Hilton, London, UK.
Contact: Gian Paolo Littarru; Ph: +39 071 220 4674/4319
Email: littarru@unian.it Website: www.CoenzymeQ10.org

DECEMBER 2002

13th International Conference on Genome Informatics

December 16–18 • Tokyo, Japan
Email: giw@ims.u-tokyo.ac.jpWebsite: http://giw.ims.u-tokyo.ac.jp/giw2002/

JANUARY 2003

18th Enzyme Mechanisms Conference

January 4-8 • Galveston Island, Texas
Contact: Andrea Scott; Ph: 979-845-9165; Fx: 979-845-9452
Email: ascott@mail.chem.tamu.edu
Website: http://www.chem.tamu.edu/enzyme

FEBRUARY 2003

Miami Nature Biotechnology Winter Symposium

February 1-5 • Radisson Deauville Resort, Miami Beach
Contact: Sandy Black, Executive Director
Ph/Fx: 423-253-3876; Email: sblack@miami.edu
Website: http://www.med.miami.edu/mnbws

MARCH 2003

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

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

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

AUGUST 2003

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

Department Heads Take Note:

ASBMB Offers Free Membership to New Ph.D.s

ASBMB is now offering a free one-year Associate membership to all students who have, within the past year, earned a Ph.D. degree in the molecular life sciences or related areas.

ASBMB implemented this program as a way to recognize the significant accomplishment of earning the Ph.D., and to provide new Ph.D.s with something tangible and of economic value. Membership in ASBMB brings with it a free subscription to the online versions of the *Journal of Biological Chemistry* and *Molecular and Cellular Proteomics*, as well as subscriptions to *The Scientist* and the Society's magazine, *ASBMB Today*, discounts on other publications, and a host of other benefits.

The Society is asking department chairs to provide ASBMB with the names and addresses of each new Ph.D. recipient from their institutions. Upon receipt of this information, we will write the new Ph.D.s to congratulate them on their accomplishment and offer the free one-year membership in ASBMB. Names and addresses of the new Ph.D.s should be sent to:

Kathie Cullins
Membership and Subscriptions Manager
American Society for Biochemistry
& Molecular Biology
9650 Rockville Pike
Bethesda, MD 20814
Email: asbmb@asbmb.faseb.org

This is an ongoing project; please advise us whenever a student in your department earns the Ph.D., so that we can make this free membership offer to him or her.

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