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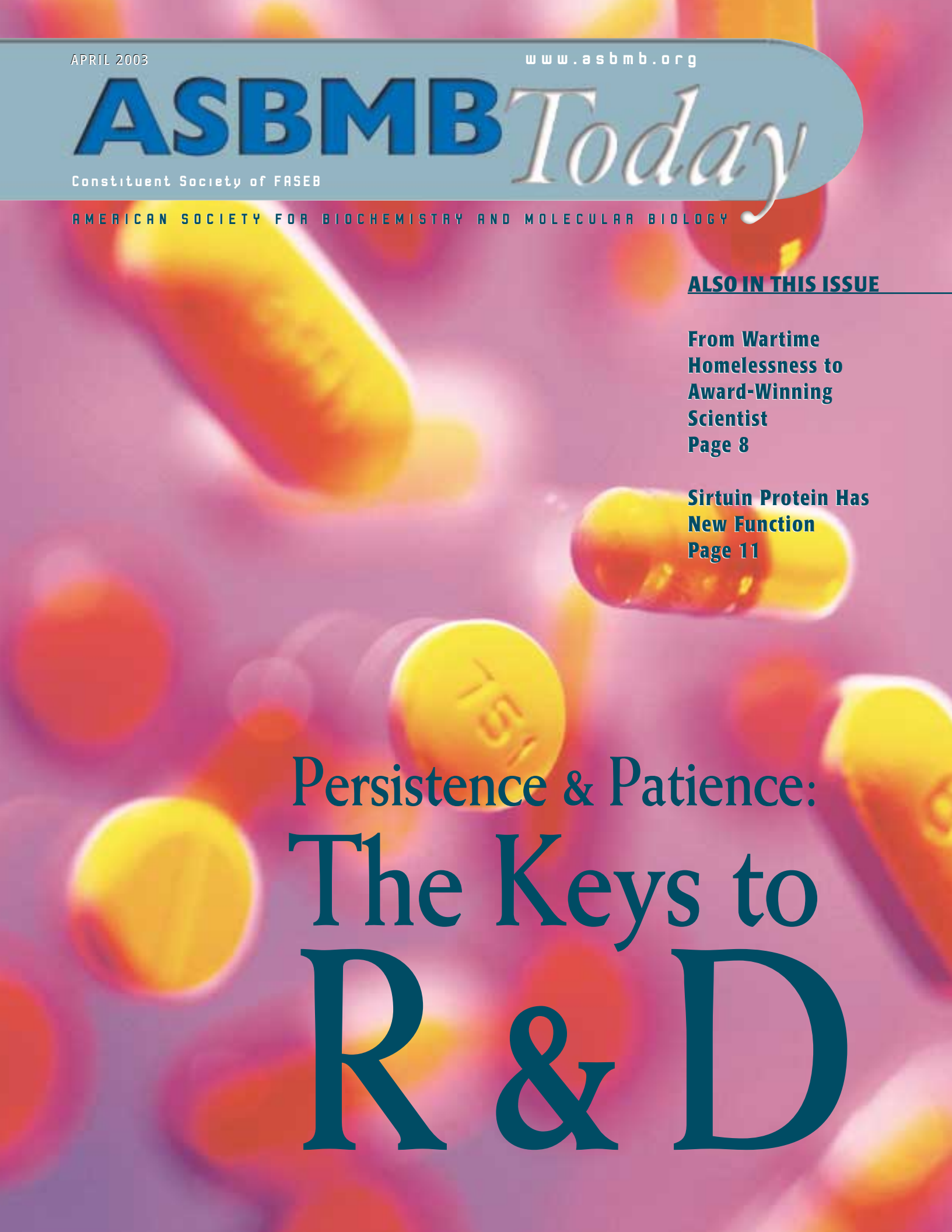

ALSO IN THIS ISSUE

Persistence & Patience: The Keys to R & D

Proteomic Solutions in Cellular and Developmental Biology and Medicine

Stowers Institute For Medical Research
Kansas City, Missouri
May 2–4, 2003

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Stowers Institute for Medical Research

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See page 2 for more information on this meeting

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ASBMB Today

AMERICAN SOCIETY FOR BIOCHEMISTRY AND MOLECULAR BIOLOGY

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Comments

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Announcing Special Symposia

The ASBMB has announced its support for Special Symposia and Joint Meetings of 2-4 days in length beginning in the Fall 2004. The ASBMB Meetings Committee, chaired by Dr. George Carman, Rutgers University, recently presented the proposal to the ASBMB Council for approval. The proposal was approved and a solicitation for proposals, including guidelines for submissions and review were composed. ASBMB President Bettie Sue Masters then appointed Dr. Roy Soberman, Massachusetts General Hospital, Harvard Medical School, as Chairman of the Small Meetings Advisory and Evaluation Subcommittee.

"Small meetings will allow the ASBMB to highlight specific areas of research that may be in an early (ascendant) phase of interest and importance that might not otherwise be highlighted," said Dr. Carman. "Despite the revised format of the national meeting, which emphasizes the linear aspect of concepts, and a 'small meeting theme,' the environment and focus at small meetings is different and more intimate, and is increasingly a preferred venue for scientific interaction," he continued.

The ASBMB Council has already approved co-sponsoring a Special Symposium in 2003 with the Stowers Institute for Medical Research in Kansas City, Missouri, May 2-4. The Proteomic Solutions in Cellular and Developmental Biology and Medicine meeting will try to move beyond developing technologies for protein separation, analysis of composition and post-translational modifications, and analysis of protein-protein interactions. The organizers of the meeting intend to promote discussion of how best (i) to use proteomic approaches to address biological problems and (ii) to analyze the data from proteomic analyses and effectively integrate it with results of more traditional, "hypothesis-driven" research.

Dr. Masters explains, "This is a new experiment for ASBMB in attempting to explore the frontiers of biomedicine and in engaging our members in interacting with other fields and groups to answer the problems of biology. We intend to co-sponsor a number of other meetings over the next several years as we continue to assess the success of such an approach."

ASBMB Special Symposia

Have an idea for a small meeting? Submit a proposal to the ASBMB!

The American Society of Biochemistry and Molecular Biology announces its support for Special Symposia and Joint Meetings of 2-4 days in length beginning in the Fall 2004. Proposals should be 3-4 pages in length, and focused on topics that are not routinely addressed by an ongoing meeting series at other venues. For details of the proposal requirements and evaluation, please see the website:

www.asbmb.org/meetings

Submit proposals to:
ASBMB Meetings Office
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ASBMB

Persistence and Patience: The Keys to Success in R&D

The following is based on an article about ASBMB member Dr. Cecil Pickett which was published in Continental*, the in-flight magazine of Continental Airlines.*

Since March 2002, the 57-year-old biochemist has led the Schering-Plough Research Institute (SPRI), the worldwide research and development arm of Schering- Plough Corp. in Kenilworth, N.J. As president of a company tasked with finding new medicines to bring to the market, he rarely succeeds. And that's expected.

"The success rate for compounds in Phase One research [the early safety-testing stages] becoming a product is about 10 percent," Dr. Pickett says. "Successes in this business are rare." And, he adds, the average time required to yield a successful new product, from conception to market, is 12 years. Beyond the requisite skill and scientific discipline, it's a job that takes persistence and patience. For Dr. Pickett, it's a way of life—and the nature of science.

Dr. Pickett grew up in Canton, Ill., a small town near Peoria. His father was a farmer and later a factory worker at an International Harvester farm machinery plant. His mother, a housewife, raised him and his eight brothers and sisters. The second oldest of a brood who all grew up to be successful in their chosen fields, Dr. Pickett was the only family member who graduated from college. Acting on a strong desire to go to California, he enrolled at the University of California, Berkeley, and later transferred to California State University, Hayward. He paid his way through school by working full-time at a variety of jobs, including fractionating blood products in a commercial laboratory. After earning a bachelor's degree in biology, he secured a fellowship at UCLA, where he obtained a doctorate in biology and did post-graduate work. "I've always had a love for science as far back as I can remember. It's the only thing I ever wanted to do," says Dr. Pickett.

It was "doing science" that led him to leave academia for Merck & Co. in 1978. It was an unusual move; in the late '70s, few research biologists were leaving campuses for corporations. But Dr. Pickett had been inspired by an article he read in *The Journal of Biological Chemistry*. The author was Dr. P. Roy Vagelos, a well-known biochemist who was president of Merck Research Laboratories and later CEO of Merck & Co. On Dr. Pickett's arrival in the corporate-world, Vagelos gave him a simple mandate: Set up a strong research program, but always keep the objectives of the company in mind. "That gave me a lot of license," he recalls happily. It also, provided the blueprint upon which to build a career.

Dr. Pickett pursued his research in drug metabolism at the same time that he was being given more administrative and scientific over-sight responsibility. In 1988, he was appointed head of research at the Merck-Frosst laboratories in Montreal. It was a post that gave him international experience, as well as a longer look at the big picture. "It gave me a sense of the overall business because I sat on an executive committee that oversaw all Merck business in Canada," he says. His work there was also a high point in his career with the discovery of the asthma drug Singulair.

That success brought him to the attention of Schering-Plough, where he was lured in 1993 with the position of executive vice president of discovery research. His main task was to find new pharmaceuticals. "Drug discovery," he explains, "is basically starting with an hypothesis and a specific molecular target—a biochemical target, an enzyme, a receptor—involved in a disease process, and discovering an inhibitor, an antagonist or agonist to that particular molecular target that will have activity to that particular disease."

Dr. Cecil Pickett

The job is as painstaking and complex as it sounds and Dr. Pickett identifies his good old-fashioned work ethic as a key to his performance. "I was raised in the Midwest. I came from a large family, by no means wealthy, but was able to work my way through school and achieve some level of success. I have a strong work ethic; no nonsense," he says. "You have to strongly believe in that and communicate that to the research laboratories." Most important, he adds, you must truly enjoy what you do.

Continued on p. 6

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ARC-853	Phosphatidylcholine,L-α-1-palmitoyl-2-linoleoyl [linoleoyl 1-14C]	10 µCi	$699
ARC-854	Phosphatidylcholine, L-α-1-palmitoyl-2-oleoyl [oleoyl 1-14C]	10 µCi	$469
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ART-859	Sphingosine D-threo [3-3H]	50 µCi	$719
ART-778	Sphingosine, D-erythro-[3-3H]-1-phosphate	10 µCi	$1199
ARC-1048	Sulphatide [stearoyl 1-14C]	50 µCi	$1299
ARC-1492	N,N,N-Trimethylsphingosine, [N-methyl-14C]	10 µCi	$599
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Success in R&D continued

Continued from p. 4

As head of drug discovery, Dr. Pickett tripled the size of the organization's chemistry group, expanded nearly all the therapeutic areas, and built what he calls scientific excellence in the biology sphere. Under his leadership, the company also entered a new scientific area—exploring central nervous system disorders—and moved to the forefront in implementing new technology.

"Schering-Plough was one of the first pharmaceutical companies that integrated genomics and combinatorial chemistry into drug discovery," he says with pride. But technological development notwithstanding, looking back on his nine years heading the drug discovery organization, the scientist is most proud of the focus and work ethic of the team he built and of the development of three drugs: Zetia (for lowering plasma cholesterol), which was recently approved in the U.S.; Noxafil (posaconazole), a treatment for fungal infections; and Sarasar, for the treatment of leukemia and solid tumors.

"We're at the golden age of discovering novel therapies, based on a molecular understanding of disease."

— Dr. Cecil Pickett

His impressive list of accomplishments led to his promotion to head Schering-Plough R&D. Upon the occasion of that appointment, Schering-Plough's chairman and chief executive officer, Richard Jay Kogan, commented, "Dr. Pickett's impressive record of scientific accomplishment and his strong research and managerial capabilities bring valuable benefits to Schering-Plough. I'm confident that under his leadership the important research progress being achieved by our scientists will continue."

SPRI is currently researching a novel compound it hopes will be able to block the ability of HIV to enter cells. Despite the size of the tasks at hand, Dr. Pickett views the job no differently from his first assignment nearly 25 years ago: to produce novel drugs that are beneficial to human health and that will drive the growth of the company.

Dr. Pickett's formula for managing a successful R&D organization is fourfold: recruit and retain outstanding people; create an environment of open communication where ideas are heard and debated and people feel empowered to contribute to the mission; prioritize resources and program issues; and build a sense of urgency.

To keep himself grounded, even in his newest role heading a 3,500 person, $1.3 billion organization, Dr. Pickett supervises his own laboratory, something he says is rare among high-ranking R&D executives. "Tackling fundamental questions helps me think through broader questions as they relate to our research and development activities," he says. "That's my major criticism of many people who head R&D organizations – they've lost touch with the science that they're responsible for."

Dr. Pickett's achievements have not gone unrecognized outside of the Schering setting. He was elected to the Institute of Medicine of the National Academy of Sciences for his research in how genes that encode drug-metabolizing enzymes are activated by foreign chemicals. He was honored as the winner of the 2001 Chemical Industry Institute of Toxicology Centers for Health Research Founders' Award. The award is given to a distinguished scientist who has significantly advanced scientific understanding. Dr. Pickett also serves on the Food and Drug Administration (FDA) Science Board, the National Cancer Policy Board for the Institute of Medicine, and the advisory board of the director of the National Institutes of Health.

When Dr. Pickett was recently named by *Fortune* magazine as one of the 50 most powerful black executives in America, he deflected the designation's importance, except to say that perhaps being a role model could be helpful for people. "It's only important if it has an impact on careers of younger scientists," he explained, "particularly minority scientists, who are under-represented, not only in our industry but in academic institutions."

For all he has accomplished, Dr. Pickett sees better things ahead. "I think we're at the golden age of discovering novel therapies, based on a molecular understanding of disease," he says. "The Human Genome Project certainly helps that a lot. I think we'll realize discoveries over the next 10 to 20 years where you'll have novel therapies that can impact diseases like Alzheimer's disease, schizophrenia, Parkinson's disease, and various neurological diseases where there's no outstanding treatment today."

It's that promise that keeps him going. "It's extremely rewarding to think that you can actually discover something in the laboratory that can be useful in human medicine, that can really improve the life of an individual," he says. "All it takes is persistence. And a lot of failure."

Receptor Could Be Target for Cancer Therapy

Blocking prostaglandin might restore immune response to tumors

Tumor cells have evolved a crafty scheme for protecting themselves from the killing power of the host immune system; in part, they disable the immune response. New studies from a group of Vanderbilt University Medical Center investigators implicate a receptor for prostaglandin E2 (PGE2) in this phenomenon of tumor-induced immune suppression.

The findings, published in the March 1 *Journal of Clinical Investigation*, suggest that drugs that block the PGE2 receptor, called EP2, might restore the immune system's tumor-killing capacity.

"In two different transplantable tumor models in mice, it looks like the EP2 receptor is a key mediator of the tumor's immunosuppressive action," said ASBMB member Richard M. Breyer, Ph.D., Associate Professor of Medicine and Pharmacology.

The team of investigators, including Dr. Breyer, Dr. David P. Carbone, Ingram Professor of Cancer Research at the Vanderbilt-Ingram Cancer Center, and graduate student Li Yang, injected colon and lung cancer cells into two groups of mice—normal mice and mice lacking the EP2 receptor (EP2 knockout mice). Tumors were smaller in the EP2 knockout mice, and these mice survived for longer periods of time compared to control mice.

"Not having an EP2 receptor appears to slow cancer growth and improve survivability," Dr. Breyer said. The researchers tracked the EP2 receptor effect to a difference in immune system function—the EP2 knockout mice appeared to mount an effective tumor-killing immune response; the control mice did not.

Dr. Breyer's focus on the EP2 receptor stems from his long-standing interest in the biological effects of prostaglandins, a family of locally acting hormones produced by the cyclooxygenase (COX) enzymes. COX enzymes are the targets of aspirin and other non-steroidal anti-inflammatory drugs, which work to relieve pain and inflammation by blocking the production of prostaglandins.

The connection between COX and cancer was made in the early 1990s, Dr. Breyer said, when researchers noted that people who took aspirin on a regular basis had a 40 to 50 percent drop in the relative risk of developing colorectal cancer. Raymond N. DuBois, Mina Cobb Wallace Professor of Gastroenterology and Cancer Prevention, and colleagues subsequently found high levels of one of the COX enzymes (COX-2) in cancerous colon tissue and demonstrated that blocking the enzyme could stop colon cancer cell growth.

An international trial established the effectiveness of the COX-2 inhibitor Celebrex in reducing the number of pre-cancerous polyps in individuals with familial adenomatous polyposis. Multiple trials are now underway testing COX-2 inhibitors for cancer prevention and treatment. COX inhibitors may not be ideal anti-cancer drugs, Dr. Breyer said, because they block the production of all prostaglandins. "Some of these prostaglandins could have beneficial effects," he said. "We were interested in discovering which prostaglandins are participating in the tumor-promoting effect, and more importantly, which prostaglandin receptors."

> ***"Not having an EP2 receptor appears to slow cancer growth and improve survivability."***
>
> **— Dr. Richard Breyer**

It was known that tumor tissue produces the prostaglandin PGE2, he said. And since his laboratory had already engineered mice lacking the EP2 receptor, one of the four known receptors for PGE2, it made sense to look at tumor growth in these mice. Indeed, following injection of colon or lung cancer cells, the EP2 knockout mice grew smaller tumors and lived longer than control mice, suggesting that PGE2 works through the EP2 receptor to promote cancer growth.

Because they suspected a difference in immune system response, the investigators compared the function of various types of immune cells. A series of experiments demonstrated that white blood cells called T cells were normal in number and function in both wild-type and EP2 knockout mice. The investigators found differences though, in the function of dendritic cells, special immune system cells that stimulate the production of tumor-killing T cells. In tumor-bearing normal mice, the number of dendritic cells was reduced. But in EP2 knockout mice, the number of dendritic cells was increased, as would be expected in animals mounting an immune response, Dr. Breyer noted.

Dendritic cells police the body for intruders (like tumor cells) and "present" tumor cell proteins to T cells, stimulating them to become killer T cells that can seek out and destroy the infringing tumor cells. The investigators showed that EP2 knockout mice, but not wild-type mice, produce these killer T cells in response to tumor cells. When the EP2 receptor is active, as it is in normal mice, Dr. Breyer said, it

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From Wartime Homelessness

As a small child, Mario R. Capecchi wandered homeless through Trento, Italy, after the Nazis put his mother in a concentration camp. Now, Dr. Capecchi is a world-renowned, award-winning scientist.

In May, Dr. Capecchi, Distinguished Professor of Human Genetics and Biology, Co-Chair of the University of Utah Department of Human Genetics, and an Investigator for the Howard Hughes Medical Institute, will return to Trento under happier circumstances. He will receive a cash prize for winning the 2003 Pezcoller Foundation-AACR (American Association for Cancer Research) International Award for Cancer Research.

But his travels will not stop in Italy. After receiving the award in Trento, Dr. Capecchi will go to Israel to accept the 2002/03 Wolf Prize in Medicine, Israel's top honor in medical research. He'll share the Wolf Prize with two other distinguished researchers—Dr. Oliver Smithies of the University of North Carolina and Dr. Ralph R. Brinster of the University of Pennsylvania.

Dr. Capecchi and Dr. Smithies, working independently, developed techniques for targeted gene mutation in mammals, enabling researchers to create strains of mice with mutations in virtually any gene. Dr. Brinster developed a way to modify genes in mice embryo by injecting the eggs with RNA.

The techniques developed by these three have given researchers powerful tools for investigating human biology and its misregulation in disease, according to the Wolf Prize jury.

"These methods have enabled the development of models for a wide variety of diseases including hypertension, degenerative neurological diseases and cancer," the jury said.

In its citation for his work, the Pezcoller Foundation-AACR Board of Directors said Dr. Capecchi has "changed the face of modern biology."

"The generation of models of human cancer in mice, stemming from your work, has made an enormous impact on cancer research by elucidating the molecular mechanisms involved in tumorigenesis and allowing new therapeutic strategies to be tested in laboratory animals," the directors said.

Announcement of the awards had Dr. Capecchi poring over a map of Northern Italy.

During the Second World War, he wandered the country for four years until his mother, who had been incarcerated by the Nazis, found him in a hospital after the war. Trento was one of the cities the young Capecchi spent time in during that period. In a sense, his trip to Italy to accept the cash prize from the Pezcoller Foundation will bring him full circle from his childhood. But the award, he hopes, signifies that other scientists have benefited from his research.

"Dr. Capecchi's work has influenced countless researchers worldwide in the quest to understand diseaseand may lead to major breakthroughs in fighting life-threatening disease."

— Dr. A. Lorris Betz

Dr. Mario Capecchi

"It's gratifying to have people from around the world recognize our work," he said. "Hopefully, it means that they're using the technology we've developed and finding it beneficial, too."

A. Lorris Betz, M.D., Ph.D., University of Utah senior vice president for health sciences and dean of the medical school, said the awards recognize the "fundamental importance" of Dr. Capecchi's discoveries.

"Dr. Capecchi's work has influenced countless researchers worldwide in the quest to understand disease and may lead, one day, to major breakthroughs in fighting life-threatening disease," Betz said.

Raymond F. Gesteland, Ph.D., U of U vice president for research and distinguished professor of genetics and biology, called Dr. Capecchi "a treasure."

"These prizes awarded to Mario Capecchi, and others, justly praise the

To Award-Winning Scientist

revolutionary technology that has provided a most powerful tool for modeling human disease and for understanding the complexity of our genes," Dr. Gesteland said.

Many scientists would have rejected the possibility that one gene, among 20,000 to 30,000, could be individually targeted in a living animal. But Dr. Capecchi's and others' success is a tribute to the eternal optimism of scientists, added Dr. Gesteland.

The Wolf Prize was established in 1978 by Dr. Ricardo Wolf, a German-born inventor, "for achievements in the interest of mankind and friendly relations among people, irrespective of nationality, race, color, religion, sex or political view." The prize is awarded each year in four of five scientific fields: agriculture, chemistry, mathematics, medicine, and physics. A prize in the arts also is awarded.

To date, 204 scientists and artists from 20 countries have received Wolf Prizes. Each carries a $100,000 cash award.

The AACR and Pezcoller Foundation established their award in 1997 to honor a scientist who has made "significant contributions to understanding cancer and whose ongoing work holds promise for future outstanding contributions." The award carries a 75,000 euro cash prize, equivalent to over $82,000 U.S.

In addition to these latest honors, Dr. Capecchi has received the 2001 Albert Lasker Award for Basic Medical Research, the Kyoto Prize in Basic Science, the General Motors Corporation Alfred P. Sloan Jr. Prize for Outstanding Basic Science Contributions to Cancer Research, and last year, the 2001 National Medal of Science from President Bush.

Dr. Capecchi will accept the Pezcoller Foundation-AARC International Award for Cancer Research at a March symposium in Toronto, where he'll also give a lecture. In May, he will travel to Trento to receive the cash prize from the Pezcoller Foundation, then to Israel where he'll receive the Wolf Prize from the President of Israel, Moshe Katsav, in a ceremony scheduled for May 11.

APS Award Winner To Lecture at EB 2003

The American Physiological Society's 2003 Lectureship and Distinguished Lectureship Award winners for 2003 will be speaking at EB 2003 in San Diego. Among them will be ASBMB member Jeffrey I. Gordon, Professor and Head of the Department of Molecular Biology and Pharmacology at Washington University, St. Louis.

Dr. Gordon, who was awarded the Horace W. Davenport Distinguished Lectureship (Gastrointestinal Section), will deliver his lecture, "Living With Microbes: An Inside View," on April 13.

Recipients of the Distinguished Lectureships are chosen by the 12 APS Disciplinary Sections as outstanding contributors and representatives of the best research within their field. Awardees actively participate in the Experimental Biology meeting presenting their lectures and meeting with graduate and postdoctoral students during the meeting.

Montreal Neurological Institute Researcher Finds Normal Nerve Cells Can Mimic Viruses

Montreal Neurological Institute researcher Dr. Wayne Sossin, an ASBMB member, has discovered that nerve cells can bypass the cell's normal protein-making machinery in the same way that viruses do when they infect a cell. In a study published in *Nature Neuroscience*, Dr. Sossin and colleagues describe the first example of regulated IRES (internal ribosome entry site) usage after a physiological stimulus in neurons.

When a virus infects a cell, its goal is to make more virus particles. To do this, a virus takes over the cell's protein making machinery (the ribosome), so that the cell essentially becomes a viral protein factory. It does this by using an internal ribosome entry site (IRES); which shuts down and bypasses the normal mechanisms that regulate binding of messenger RNAs to ribosomes. While many viral messenger RNAs are known to possess an IRES, few normal cellular RNAs do. Abnormal IRES regulation has been correlated with two human diseases, multiple myeloma and Charcot-Marie-Tooth disease. This is the first time that scientists have demonstrated that normal nerve cells can use an IRES to produce large quantities of protein under physiological conditions.

> ***"This new discovery reveals an unexpected regulatory role of the IRES in nerve cells."***
>
> **— Dr. Nahum Sonenberg**

Dr. Sossin and colleagues made their discovery in a study of egg laying in the sea slug Aplysia. During egg laying, protein production of the egg laying hormone (ELH) increases dramatically. He and his colleagues discovered that the ELH messenger RNA contains an IRES. They demonstrated that after egg laying, nerve cells producing ELH switch from the normal cellular mechanism of protein production to one that uses the IRES. This switch allows for massive amounts of ELH protein to be produced at the expense of other cellular proteins, mimicking what a virus does when it infects a host cell.

"Egg laying is an important investment for an animal, thus when stimulated to do so, it wants to get it right," explained Dr. Sossin. "In order to do this, the cell must make a lot of ELH protein in a short period of time to signal the release of eggs. One way to do this is to temporarily stop making other proteins and concentrate on making one particular protein, in this instance, the ELH."

"The new discovery of Dr. Sossin reveals an unexpected regulatory role of the IRES in nerve cells. This finding could have important implications for understanding the learning and memory processes in the brain," explained Dr. Nahum Sonenberg, Department of Biochemistry at McGill University, who first discovered the IRES in poliovirus in 1988. Other non-pathological uses of IRES regulated protein production could include production of hormones or growth factors.

Dr. Sossin's paper, An Activity-dependent Switch to Cap-independent Translation Triggered by eIF4E Dephosphorylation, can be viewed on-line at *Nature Neuroscience*.

Dr. Wayne Sossin, a scientist at the Montreal Neurological Institute, is an Associate Professor of Neurology and Neurosurgery and Anatomy and Cell Biology at McGill University. Dr. Sossin obtained his bachelors degrees in Biology and Computer Science in 1984 from Massachusetts Institute of Technology. He completed his Ph.D. in 1989 at Stanford University and conducted his postdoctoral research at Columbia University. Dr. Sossin's research has led to several fundamental principles of protein processing and packaging in neurons. He is the author of more than 40 scientific publications

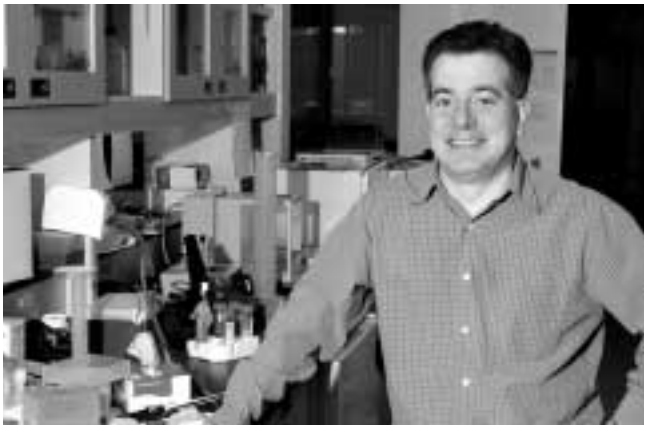


Photo courtesy of Montreal Neurological Institute

Dr. Wayne Sossin discovered that nerve cells can bypass the cell's normal protein-making machinery.

Sirtuin Protein Has New Function; May Play Role in Extending Lifespan

Scientists from Johns Hopkins and the University of Wisconsin have discovered that a protein called Sir2, which is found in nearly all living cells, has a newly discovered function that might help explain how calorie restriction can increase lifespans for some animals, the scientists say. Their report appeared in the December 20 issue of *Science*.

A number of laboratories have shown that restricting total calorie intake extends the lifespans of organisms ranging from yeast to laboratory animals. Others have shown that this effect requires Sir2's protein family, called sirtuins, and increased cellular respiration, which is the process of using oxygen to convert calories into energy.

Studying bacteria, the Johns Hopkins-Wisconsin team has discovered that sirtuin controls the enzyme that converts acetate, a source of calories, into acetyl-CoA, a key component of cellular respiration.

"Sirtuins are highly conserved across species, but this is a never-before-described ability of the protein," says Jef Boeke, Ph.D., Professor of Molecular Biology and Genetics at Johns Hopkins' Institute for Basic Biomedical Sciences. "If sirtuins modify this enzyme in other organisms, turning on production of acetyl-CoA, it could help explain why restricting regular sources of calories—sugars and fats—leads to extended lifespan in many kinds of organisms."

Identified in all living creatures, including single-celled organisms like bacteria and yeast, sirtuin proteins previously were known to play an important role in keeping regions of chromosomes turned off. By modifying the histone proteins that keep DNA tightly coiled, sirtuins prevent certain regions of chromosomes from being exposed to cells' DNA-reading machinery.

Dr. Jef Boeke

Sirtuin's new role in bacteria involves the same modification as its interaction with histone—removing an acetyl group, a "decoration" added to a protein's sequence (like phosphate)—but the targeted protein is involved in producing energy, not controlling chromosomes.

Normally, cells can survive by using many different molecules as sources of energy—potent sources like fats or sugars, or even relatively energy-poor molecules like acetate.

However, ASBMB member Jorge Escalante-Semerena and Vincent Starai of the University of Wisconsin created a strain of bacteria missing its sirtuin protein and noticed that it couldn't live on acetate. Boeke had previously noticed that yeast without sirtuin had the same problem, so the researchers dug deeper.

> ***"If sirtuins modify this enzyme in other organisms, turning on production of acetyl-CoA, it could help explain why restricting regular sources of calories leads to extended lifespan."***
>
> **Dr. Jef Boeke**

They discovered that the sirtuin protein in bacteria is a crucial modifier of an enzyme known as acetyl-CoA synthetase, which converts acetate into acetyl-CoA in a two-step process. Acetyl-CoA then can directly fuel the citric acid cycle, the central energy-producing step in cellular respiration.

"This is a completely new target for the sirtuin protein," said Dr. Boeke, who has been studying "transcriptional silencing"—sirtuin's previously known role—for some time. "Converting acetate isn't the cell's only way of making acetyl-CoA, but when acetate is the major energy source, it's crucial. Now we have to check for this role in other organisms."

The Wisconsin researchers found that sirtuin activates the first step of acetate's conversion, and Dr. Boeke and Johns Hopkins' Dr. Robert Cole and Dr. Ivana Celic figured out that sirtuin does so by removing an acetyl group from a lysine in the enzyme's active site.

While bacteria and yeast are both single-celled critters, yeast are much more closely related to animals, including humans, than are bacteria. If the yeast version of sirtuin also modifies the newly identified target, that would more likely reflect the protein's role in animals and would more formally link the protein to lifespan extension, at least for yeast. The effect of calorie restriction on the lifespan of bacteria has not been established.

How Enzyme Uses Oxygen to

When it comes to visual entertainment, three-dimensional viewing can be quite eye-opening. So, too, in science, where a recent finding involving University of Iowa researchers used three-dimensional imaging to understand how a bacterial enzyme can take oxygen from air and use it to convert certain molecules into useful chemicals.

Specifically, the scientists saw that naphthalene dioxygenase, a bacterial enzyme, can bind oxygen (to iron) in a side-on fashion and add it on to naphthalene, a hydrocarbon molecule. The discovery is a result of the first three-dimensional imaging of naphthalene dioxygenase, a member of the family of enzymes called Rieske dioxygenases. The findings could help lead to the development of microorganisms that can clean up toxic and cancer-causing waste in the environment and to the development of novel drugs.

"The more we know about how enzymes catalyze reactions, the better able we are to modify them—to improve or stop reactions, as desired," said S. Ramaswamy, Ph.D., University of Iowa (UI) Professor of Biochemistry and one of the study's authors.

"The question was: how does the enzyme actually work at the molecular level?" said ASBMB member David Gibson, Ph.D., UI Professor of Microbiology and one of the study's authors, whose previous research led to the discovery of the Rieske dioxygenase family of enzymes.

That seemingly straightforward question required seven years of collaborative work between the UI and researchers in Sweden, and included assistance from the UI Center for Biocatalysis and Bioprocessing.

Dr. Ramaswamy and Dr. Gibson began research related to this investigation when Dr. Ramaswamy was a faculty member in the molecular biology department at the Swedish University of Agricultural Sciences in Uppsala, Sweden. The paper's lead author is Dr. Andreas Karlsson, who was a graduate student of Dr. Ramaswamy's at the Swedish University and currently works for Aventis in Paris.

"People always thought that side-on binding of oxygen to iron existed, but no one had ever seen it in this enzyme or any other catalyst," said Dr. Ramaswamy, whose contribution to the project focused on how oxygen specifically binds to iron in the enzyme. Side-on refers to the visualized orientation of oxygen as it binds to iron.

The team used X-ray crystallography to determine the three-dimensional structure of the enzyme and then embarked on a series of experiments designed to take snapshots of the enzyme as it catalyzed the reaction, Dr. Gibson explained.

In all, the team had to analyze information from nearly 400 crystals in order to focus on five particular snapshots that led to the finding. The approach was revealing.

"Those five three-dimensional snapshots were the most relevant in understanding this side-on mechanism," Dr. Ramaswamy said. "Although we could not watch the reaction occur, the snap-

NHGRI Launches Project to Sequence Cattle Genes

The National Human Genome Research Institute (NHGRI) has approved spending $50 million to sequence all the genes in cattle. The work will be done in Texas, at the Baylor College of Medicine and Texas A&M University.

The NHGRI, which has sponsored projects to sequence the human genome as well as the collection of genes in mice, fruit flies and other animals, said it would put up half the money if the remaining $25 million could be raised from other sources.

Texas Governor Rick Perry said the state would pay $10 million and work to raise another $15 million, adding that the project promised long-term benefits for human health and the biotechnology industry, as well as enormous gains for the beef and dairy industries.

The bovine genome is similar in size to the genomes of humans and other mammals, with an estimated size of 3 billion base pairs. Understanding cattle genetics could help the beef and dairy industries and might offer insights into human disease, too.

"By comparing the human genome with the genomes of different organisms, we can better understand the structure and function of human genes and thereby develop new strategies in the battle against human disease," NHGRI Director Dr. Francis Collins said in a statement. "The more genomes we have, the more powerful this tool becomes."

Produce Useful Chemicals

Dr. David Gibson and Dr. S. Ramaswamy used X-ray crystallography to determine the three-dimensional structure of naphthalene dioxygenase enzyme.

shots allowed us to see key points of the process."

Dr. Gibson likened the improved view to being able to "walk inside a molecule," just as one can walk inside a house and see the layout. By seeing how things are arranged within a molecule, scientists can better predict how to make changes to the structure and thus create desired reactions.

The researchers said the particular finding of their investigation suggests that other oxygen-using enzymes may also use a side-on binding mechanism. Thus, the study approach and results likely will impact how scientists investigate other enzymes of interest.

Scientists use a "lock and key" analogy to describe enzyme actions. In this study, naphthalene dioxygenase (enzyme) is a lock and naphthalene (substrate) is a key. For a reaction to occur between the two, the lock and key need to be complimentary.

"The thought was that there was one key and one lock, but now we are finding out that there can be many keys, or substrates, because we have the ability to go in and make a change to the lock, or enzyme," Dr. Gibson said.

"We can use this knowledge to engineer enzymes to do reactions and target other substrates in an effort to create new products or prevent other products from being created," Dr. Ramaswamy added.

For example, noted Dr. Gibson, naphthalene dioxygenase is a key component in the development of the environmentally benign blue dye Indigo. In addition, a related Rieske dioxygenase synthesizes a key precursor in the production of Crixivan, an inhibitor of the AIDS virus.

The research team also included Juanito Parales, UI research assistant in microbiology; Rebecca Parales, Ph.D., UI research scientist in microbiology, and Hans Eklund, Ph.D., a faculty member at the Swedish University of Agricultural Sciences.

House Votes to Ban Human Cloning

By Peter Farnham, ASBMB Public Affairs Officer

The House of Representatives voted February 27 to ban all forms of human cloning, whether reproductive or therapeutic. The expected vote took place following an afternoon of debate and after a substitute bill that would have allowed therapeutic cloning was handily defeated.

The Human Cloning Prohibition Act of 2003 had been introduced early in February by Representative Dave Weldon (R-FL), a practicing physician who had introduced a similar bill in the last Congress. That bill also passed the House handily, but a companion bill was never brought to a vote in the Senate.

The House debate hinged on whether the legislation should ban so-called "therapeutic" cloning—cloning solely for the purpose of research to produce stem cells. There was no support in the House for allowing reproductive cloning—cloning for the purpose of producing a child. An amendment to the Weldon bill was introduced by Rep. Jim Greenwood (D-PA) that would ban reproductive cloning, but allow therapeutic cloning to continue. The Greenwood substitute was defeated by a margin of 231-174, approximately the same as in the last Congress when it lost by 249-178.

ASBMB President Bettie Sue Masters said of the House vote, "We at ASBMB are very concerned that the Weldon bill was approved so hastily, without the benefit of hearings to develop the knowledge base on the issues associated with somatic cell nuclear transfer. Modern biomedical science is making discoveries each day that will lead to improvements in the health of the American people in the coming years. It's especially sad to see the House of Representatives decide to close off this promising research avenue. We are hopeful that the Senate will take a different course."

The Weldon bill is echoed by one introduced in the Senate by Senator Sam Brownback (R-KS) and co-sponsored by Senator Mary Landrieu (D-LA) and 21 other senators. It was introduced immediately following a Senate Commerce Subcommittee hearing on human cloning chaired by Senator Brownback. The Commerce Committee does not have jurisdiction over the bill; the hearing served as a forum for Senator Brownback to make his case.

The Brownback bill has much less support in the Senate than Weldon's enjoys in the House. Senator Brownback had introduced a similar bill in the last Congress, but it never came to a vote as it was clear that opponents had at least 50 votes to prevent its passage (although not the 60 required to end a filibuster or override an expected presidential veto if the bill had passed).

On February 5, the Human Cloning Ban and Stem Cell Research Protection Act of 2003 was introduced in the Senate. The bill's sponsors include Senators Orrin Hatch (R-UT), Dianne Feinstein (D-CA), Arlen Specter (R-PA), Edward Kennedy (D-MA), Tom Harkin (D-IA), and Zell Miller (D-GA). The bill bans human reproductive cloning, but permits nuclear transplantation under strict guidelines.

This measure includes a number of oversight provisions and protections to assure that nuclear transplantation is conducted safely and ethically. They include a 14-day limit on the development of a product produced through nuclear transplantation; review by an ethics board; informed consent requirements for the donors eggs; a prohibition on the purchase or sale of eggs (beyond what is described only as "reasonable payments"); separation of *in vitro* fertilization labs from labs performing nuclear transplantation; a prohibition on exporting an unfertilized blastocyst produced through nuclear transplantation to any country that does not prohibit human reproductive cloning; and civil penalties for anyone who intentionally violates these provisions.

Senator Orrin Hatch

Reading a letter from former First Lady Nancy Reagan endorsing the bill. She wrote: ". . . there are so many diseases that can be cured, or at least helped, that we can't turn our back on this. We've lost so much time already. I can't bear to lose any more."

Senator Hatch read a letter by former First Lady Nancy Reagan endorsing the bill. She wrote: ". . . there are so many diseases that can be cured, or at least helped, that we can't turn our back on this. We've lost so much time already. I can't bear to lose any more."

A press conference following the introduction of the legislation was

ASBMB President Bettie Sue Masters

"We at ASBMB are very concerned that the Weldon bill was approved so hastily, without the benefit of hearings to develop the knowledge base on the issues associated with somatic cell nuclear transfer. Modern biomedical science is making discoveries each day that will lead to improvements in the health of the American people in the coming years. It's especially sad to see the House of Representatives decide to close off this promising research avenue. We are hopeful that the Senate will take a different course."

attended by Senators Hatch, Feinstein, Specter, advocates for patients, and actor Kevin Kline, an activist in the area of juvenile diabetes.

Senator Specter said he was confident the legislation would garner at least 50 votes—enough to ensure that "those who want to stop science will not have the votes in the Senate." He also discussed a bill he plans to introduce to permit federal funding for the derivation of additional stem cell lines from unused embryos at fertility clinics. The Senator noted that there are more than 100,000 embryos at IVF clinics that will be discarded if unused.

ASBMB member Dr. David Baltimore, President of the California Institute of Technology, who attended the press conference, noted that the approximately 70 existing stem cell lines, which President Bush has approved for potential federal funding, include only about a dozen that are usable. He summarized the scientific value of nuclear translation, and said that we need to engage more scientists in this research; dollars to support the research; and "careful, thoughtful regulation."

Senator Arlen Specter

"Those who want to stop science will not have the votes in the Senate."

No member of congress or senator in at least the last two congresses has supported reproductive cloning, and all legislation introduced on the subject has explicitly banned cloning to produce a child. The issues are related to both safety and ethics. Regarding safety, only a few animals of a half dozen or so species have been successfully cloned, and it is highly likely that most of these have defects that are not readily apparent. The first animal cloned, the sheep Dolly, was euthanized last month at the age of six. Dolly was suffering from arthritis, seldom seen in sheep under 12 years of age, as well as other problems that made euthanasia the most humane option. Of course, euthanasia would not be an option for a human child born with similar birth defects. If cloning experiments with other mammalian species are any indicator, birth defects either gross or subtle are highly likely in the few cloned human children that would survive to term.

But there are also ethical concerns. There is concern about eugenics—trying to somehow "perfect" the human species through selective breeding, with all the resonance this concept brings with it from the Nazi era in the 1930s and 40s. Second, the nature of "humanness" comes into play. Is a cloned person a human in the same sense as non-clones are? Assuming this question is answered, would a cloned individual suffer psychological damage, knowing he or she was a genetic duplicate of one or more (perhaps dozens) humans? Of course, many of the same arguments were made against the concept of "test-tube babies" in the 1970s, as well as other advances such as surrogate motherhood, *in vitro* fertilization, and the taking of fertility drugs.

While virtually all members of Congress oppose reproductive cloning on one or more of these grounds, so-called therapeutic cloning gets tossed into the mix by many of the opponents of reproductive cloning. The specter of embryo farms, where embryos would be raised for their organs to be used as spare parts is constantly raised by cloning opponents. And of course, the attempt to connect somatic cell nuclear transfer to the anti-abortion movement is a widely-disseminated objection. To opponents, these objections outweigh the enormous potential therapeutic cloning has for combating some of the great scourges humanity has faced for millennia. Even more unfortunately, the intransigence of cloning's opponents on the issue of therapeutic cloning will likely keep a ban on reproductive cloning from becoming law this year. This could mean that unscrupulous individuals could clone a human baby because there was no law preventing them from doing so. This would very likely be a tragedy for the child, and would start the world on the so-called "slippery slope" cloning opponents say they fear most.

Jill Adleberg, FASEB Office of Public Affairs, also contributed to this story.

Leanness, Not Diet, May Be Key to Long Life

Could it someday be possible for people to stay slim, avoid type 2 diabetes, and live longer while eating whatever they want. A new study led by Joslin Diabetes Center researchers brings scientists one step closer to turning this scenario, now just a dream for the estimated 60 million overweight American adults, into a reality.

The study, conducted in laboratory animals, raises the possibility that new drugs can be developed to make fat cells in the body less sensitive to insulin. Perhaps one day humans, like the genetically altered mice studied, may be able to eat whatever they want and still stay slim and live longer.

The researchers, headed by ASBMB member C. Ronald Kahn, M.D., at the Joslin Diabetes Center, experimented with mice that had been genetically altered to have no insulin receptor in fat. These FIRKO mice were able to eat all they wanted and remain lean. In fact, even when they were stimulated to overeat, they failed to gain any extra weight. Even more important, these mice lived longer than brother/sister controls that ate the same amount of food but did not have this genetic knockout. Matthias Bluher, M.D., of Joslin, and ASBMB member Barbara B. Kahn, M.D., of Boston's Beth Israel Deaconess Medical Center's Department of Medicine, participated in the study. Both institutions are affiliated with Harvard Medical School, where Dr. Ronald Kahn is the Mary K. Iacocca Professor of Medicine and Dr. Barbara Kahn is Professor of Medicine.

Researchers Barbara B. and C. Ronald Kahn found that lack of insulin in mice helped keep them slim.

Why did the mice stay slim? The mice in the study had fat that could not respond to insulin. "Since insulin is needed to help fat cells store fat, these animals had less fat and were protected against the obesity that occurs with aging or overeating. They also were protected against the metabolic abnormalities associated with obesity, including type 2 diabetes," Dr. Ronald Kahn said.

"In this interesting mouse model, a reduction in fat mass, achieved without caloric restriction, significantly extends lifespan. These exciting results demonstrate how the NIH investment in fundamental research continues to generate new insights with major implications for preventing and treating diabetes and obesity," said Dr. Judith Fradkin, who heads the Endocrinology and Metabolic Diseases Division of the National Institute of Diabetes and Digestive and Kidney Diseases, part of NIH which funded the study.

Scientists know that how long an organism lives depends on many factors, including genetics, hormone signaling, body weight, body fat content and environmental factors such as food or caloric intake. It also has been known for some time that caloric restriction increases longevity in various organisms, ranging from yeast to mammals. What was not clear was if diet restriction increased longevity directly or whether the longevity was due to the associated leanness.

In their study, the researchers found FIRKO mice at all ages had a 50% to 70% reduction in fat mass, despite the fact that they ate normally—or even more than the controls. Moreover, they were protected against obesity and its related metabolic disorders, including type 2 diabetes, which affects at least 17 million Americans and is associated with obesity in at least 80 percent of cases.

The researchers found both male and female FIRKO mice on average had a lifespan increase of 18 percent or 134 days—from 753 to 887 days. Furthermore, the researchers found that at 30 months of age, when 45% to 54% of control mice had died, that more than 80% of FIRKO mice were still alive.

While the researchers do not know if the same outcome would occur in other mammals or humans, the findings in the FIRKO mice study provide hope. "Perhaps one day if we are able to find a drug to reduce or block insulin action in fat cells in humans, we might be able to prevent obesity, as well as type 2 diabetes and other metabolic diseases," Dr. Ronald Kahn said. "And who knows, they might also live longer too."

Suppressing Immune System Reverses Otherwise Untreatable Blood Disease

Treatment with two medications that suppress the immune system, rituximab and cyclophosphamide, appears to have cured one woman of an otherwise untreatable case of the blood disease known as thrombotic thrombocytopenic purpura (TTP). The findings support the theory that TTP is an autoimmune disease, and not only provide insight into diagnosis and treatment, but also reveal clues about blood clotting and autoimmune diseases in general.

"In this particular patient who did not respond to standard therapy, immunosuppression seems to have been successful," says Morey A. Blinder, M.D., Associate Professor of Medicine and of Pathology and Immunology at Washington University School of Medicine in St. Louis. "These results are promising for others suffering from similarly resistant cases of TTP."

Dr. Blinder led the study, in conjunction with ASBMB member J. Evan Sadler, M.D., Ph.D., Professor of Medicine and of Biochemistry and Molecular Biophysics. Their findings appeared in the January 21 issue of the journal *Annals of Internal Medicine*.

TTP is a blood disorder that affects an estimated 3,000 Americans each year, most of whom are women of childbearing age. Prior to the early 1980s, the prognosis was grim: The risk of dying from complications of the disease such as heart attack or stroke was as high as 90 percent. And because the disease is so rare, it continues to be misdiagnosed and untreated.

Today, most patients who are diagnosed accurately with TTP are successfully treated with plasmapheresis, in which an individual's blood is swapped for healthy blood in a daily process similar to dialysis for kidney failure. But plasmapheresis does not target the underlying problem, which is believed to be similar to autoimmune diseases such as lupus, in which the immune system attacks a person's own tissues. Therefore, even with daily plasmapheresis, the disease returns in about 25% of patients.

In 2000, Dr. Sadler's team, in collaboration with investigators at the University of Washington in Seattle, identified a protein in the bloodstream called von Willebrand factor-cleaving protease and found that it either is missing or abnormal in people with TTP, presumably as a result of disruption by the immune system. Without it, the protein called von Willebrand factor is not regulated and therefore sticks to itself, forming large clumps, or blood clots, that often lead to stroke or heart attack.

"The discovery of this protein really helps us understand the mechanism of blood clotting in general and how important von Willebrand factor is," said Dr. Blinder. "Also, we hope to use this knowledge to develop a definitive test for TTP so that it can be more easily diagnosed and more effectively treated. It also may be possible to genetically engineer the protein for infusion, similar to the use of insulin for diabetes."

To prevent the immune system from destroying or disrupting this essential cleaving protease, the Washington University team tested two drugs already shown to suppress the immune system. In October 2001, after 19 months of relapsing disease despite extensive plasmapheresis, the team gave one 42-year-old woman with severe TTP two drugs – rituximab and cyclophosphamide, both known anti-cancer drugs. Her symptoms and blood levels improved and continue to be stable to date.

"This may not be a public health issue like AIDS or breast cancer, but the fact that first this disease was almost always life-threatening and now may be curable is really important," says Dr. Blinder. "And now that we're really beginning to understand the disease itself, it will help us diagnose and treat TTP and will provide insight into blood clotting and how immune diseases work in general."

Scientific Publishers Issue Statement Concerning Restrictions on Publication

By Peter Farnham, Public Affairs Director

Authors and editors from some of the world's top scientific journals and publishing houses issued a document February 15 acknowledging the potential problem involved in the publication of data in scientific papers that might be construed as helping the development of materials used for terrorism. They discussed at length the dilemma that not only are such data usually very important for the development of our basic understanding of immunologic and microbiological mechanisms, but often are milestones in the development of new clinical therapies. The entire document was published in the February 21 issue of *Science* , page 1149.

The editors and authors characterized the document as a discussion of "outcomes" of the group's January 10 discussion, not a formal recommendation.

The statement was an outgrowth of a meeting held the day before at the National Academy of Sciences. That meeting of scientists, publishers, security experts, and government officials was co-hosted by the Academy and the Center for Strategic and International Studies, after being initially suggested by the American Society for Microbiology. The day-long meeting focused on many of the most important issues associated with the publication of life sciences research in an era when bioterrorism is a serious and proven threat.

On the day following the Academy meeting, a group of editors and authors convened to discuss a possible statement on the subject. They issued a document that makes four points:

1. The scientific information published in journals carries special status, and confers unique responsibilities on editors and authors. We must protect the integrity of the scientific process by publishing manuscripts of high quality, in sufficient detail to permit reproducibility. Without independent verification—a requirement for scientific progress—we can neither advance biomedical research nor provide the knowledge base for building strong biodefense systems.

2. We recognize that the prospect of bioterrorism has raised legitimate concerns about the potential abuse of published information, but also recognize that research in the very same fields will be critical to society in meeting the challenges of defense. We are committed to dealing responsibly and effectively with safety and security issues that may be raised by papers submitted for publication, and to increasing our capacity to identify such issues as they arise.

3. Scientists and their journals should consider the appropriate level and design of processes to accomplish effective review of papers that raise such security issues. Journals in disciplines that have attracted numbers of such papers have already devised procedures that might be employed as models in considering process design. Some of us represent some of those journals; others among us are committed to the timely implementation of such processes, about which we will notify our readers and authors.

4. We recognize that on occasions an editor may conclude that the potential harm of publication outweighs the potential societal benefits. Under such circumstances, the paper should be modified, or not published. Scientific information is also communicated by other means: seminars, meetings, electronic posting, etc. Journals and scientific societies can play an important role in encouraging investigators to communicate results of research in ways that maximize public benefits and minimize risks of misuse.

Cancer Therapy continued...

Continued from p. 7

participates in suppressing the immune response that produces killer T cells. The studies suggest that blocking the EP2 receptor would be a useful strategy to improve immune system killing of tumor cells, said Dr. Breyer.

Because previous studies from other groups had linked PGE2 to angiogenesis, the growth of new blood vessels, the investigators also explored this possibility in the EP2 knockout mice. They found no difference in the number of tumor blood vessels or the levels of blood vessel growth factors in normal and EP2 knockout mice. Dr. Breyer suspects that other PGE2 receptors may be involved in promoting tumor blood vessel growth.

Other contributors to the studies include Noboru Yamagata, Rajwardhan Yadav, Suzanne Brandon, Regina L. Courtney, Dr. Jason D. Morrow, Yu Shyr, Ph.D., Dr. Mark R. Boothby, and Sebastian Joyce, Ph.D. The research was launched under the auspices of the National Institutes of Health-funded Research Center for Pharmacology and Drug Toxicology, directed by Morrow. It was also supported by other NIH grants and by the Vanderbilt-Ingram Cancer Center.

Robert Linhardt Receives ACS Award For Research on Heparin

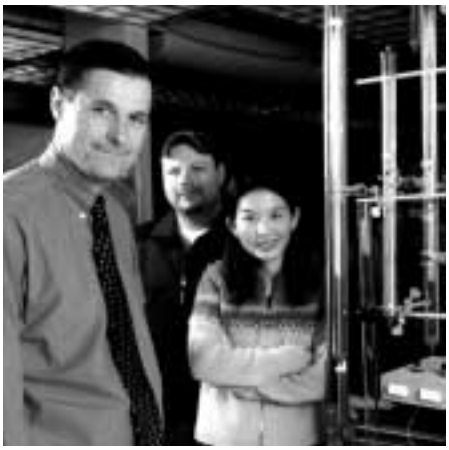
ASBMB member Robert J. Linhardt, Professor of Chemistry and Chemical Engineering at the University of Iowa, was honored March 25 by the world's largest scientific society for his achievements in understanding and improving pharmaceuticals based on carbohydrates, in particular the clot inhibitor heparin. He received the 2003 Claude S. Hudson Award in Carbohydrate Chemistry from the American Chemical Society at its national meeting in New Orleans.

"Carbohydrates have a lot of unique properties," said Dr. Linhardt. "In addition to being important to diet, they're also necessary whenever cells communicate with each other, for example. So they can make very powerful drugs, and heparin is one of them."

Researchers discovered heparin in 1916, learning the body produced it naturally to provide a slick lining for blood vessels. It's used today to keep blood flowing through artificial kidney and heart machines and to inhibit growth of blood clots in patients at risk for heart attack or stroke.

Heparin piqued Dr. Linhardt's interest 20 years ago as "an unsolved mystery of nature," he said. The drug is not one carbohydrate but a collection of millions, and researchers knew little about their specific structures, activities and roles in the body. He decided to study them and, by doing so, try to make a simpler, more selective version of the drug in the laboratory.

With his multidisciplinary team of carbohydrate chemists, biologists, medicinal chemists and pharmacologists, Dr. Linhardt eventually discovered one of what is now known as low-molecular-weight heparins. It is among the five such products currently prescribed by doctors.



Dr. Robert Linhardt with lab colleagues

"Low-molecular-weight heparins are a little more selective, but the real advantage is their cost efficiency," he said. Because they can be administered as daily shots rather than constantly dripped through a patient's IV solution, "they save hospital costs and keep a person functional."

Dr. Linhardt is now working on synthesizing a derivative structure of heparin, enabling pharmaceutical companies to manufacture the drug rather than harvest it from animal tissue.

He received his undergraduate degree from Marquette University in 1975 and his Ph.D. from Johns Hopkins University in 1979. He is a member of the ACS divisions of carbohydrate, organic and medicinal chemistry as well as the biotechnology division.

The Claude S. Hudson Award in Carbohydrate Chemistry is sponsored by the National Starch and Chemical Co.

Summer Workshop
Science and Social Responsibility
Preliminary Announcement

From **June 20-June 23** an intensive workshop on science and social responsibility will be offered at The Hastings Center, Garrison, N.Y. (45 miles north of New York City). The purpose of the workshop is to help respond to a widespread call for a more active participation by young bench scientists [research scientists] in discussion and action on social, ethical, and political issues in the life sciences.

The aim of the workshop will be to examine the various issues that have arisen in recent years; the role scientists have played in public discussion and debate—and could play in the future; and to help create a fresh network of scientists who can begin working with those of a similar interest.

The workshop will be co-sponsored by the European Molecular Biology Laboratory, The Department of Social Medicine of the Harvard Medical School, and The Hastings Center. The workshop will be open to scientists from all countries.

Funds are available to pay either full or partial transportation, food, and accommodation costs. While applications from older researchers will be accepted, preference will be given to those under the age of 40. In order to help us plan the workshop it will be necessary to have some preliminary information from those who might be interested in taking part and would like to receive a full application packet.

Toward that end, please send us a letter [e-mail or regular mail] (a) describing your present research work and interests as a research scientist, (b) previous experience in dealing with issues of science and social responsibility (and any special interests you may have in that respect), and (c) whether you will need full or partial financial support. There will be no tuition or other charges for the workshop itself. Meal and accommodation expenses will be approximately $600, but there will be no fee for the workshop itself.

Send your letter to: Daniel Callahan, Director, International Program, The Hastings Center, 21 Malcolm Gordon Road, Garrison, N.Y. 10524. Phone: 845-424-4040; fax: 845-424-4545; e-mail: callahan@thehastingscenter.org.

New York and Seattle Researchers to Receive Perl-UNC Neuroscience Prize

The University of North Carolina at Chapel Hill has named Dr. Linda Buck and Dr. Richard Axel, an ASBMB member, co-recipients of the third annual Perl-UNC Neuroscience Prize.

Dr. Buck is a member of the Basic Sciences Division at the Fred Hutchinson Cancer Research Center in Seattle and Affiliate Professor at the University of Washington. Dr. Axel is University Professor of Biochemistry and Molecular Biophysics at Columbia University. Both scientists are Howard Hughes Medical Institute investigators.

The prize carries a $10,000 award and is given to recognize a seminal achievement in the field of neuroscience. Previous awardees were Dr. David Julius from the University of California at San Francisco and Dr. Roderick MacKinnon from Rockefeller University.

"This year's Perl Prize is awarded to Dr. Axel and Dr. Buck in recognition of their discovery of the family of olfactory receptor proteins. Until their pioneering work, almost nothing was known about how specialized nerve cells in the olfactory epithelium of the nose differentially respond to the myriad odors that humans and animals can distinguish," said Dr. William Snider, Director of the UNC Neuroscience Center and head of the selection committee for the prize.

The discovery of a family of approximately 1,000 odorant receptors has made it possible to understand how olfactory receptor neurons respond to odors and how information about odors is conveyed to the brain, said Dr. Snider. The discovery has vastly expanded the sub field of neuroscience devoted to understanding the sense of smell.

The Perl-UNC Neuroscience Prize is named for Dr. Edward R. Perl, Sarah Graham Kenan Professor of Cell and Molecular Physiology at the UNC School of Medicine. His work in pain mechanisms has been highly influential. Thirty years ago, he was the first to prove that a particular class of nerve cells (now called nociceptors) responds exclusively to stimuli that are perceived as painful. His work has had a decisive impact on modern pain research, and these cells are now targets of intensive efforts to find drugs that block their function.

Dr. Richard Axel

Dr. Linda Buck

The award will be presented by Dr. Jeffrey Houpt, Dean of the School of Medicine, May 2 on the UNC campus.

Virology Pioneer Harold Ginsberg

Harold S. Ginsberg, a microbiologist who contributed fundamental research findings to the fields of virology and infectious disease, died in Woods Hole, Massachusetts, from pneumonia on February 2 at the age of 85.

Dr. Ginsberg, an ASBMB member since 1964, is perhaps best known for characterizing adenoviruses, work he began in the late 1950s at what is now Case Western Reserve University. He eventually described their structure, replication and their role in causing infections such as atypical pneumonia, pharyngitis and acute respiratory disease.

Dr. Ginsberg was a member of the National Academy of Sciences and received numerous scientific awards. He published more than 200 scientific papers and contributed to several books, including the widely-used textbook, Microbiology (Lippincott, Williams & Wilkins).

He lived in Woods Hole and in Washington, DC, with his wife of 53 years, Marion Reibstein Ginsberg. He is also survived by four children: Benjamin, Peter, Ann and Jane; eight grandchildren and one brother, Joseph.

NIGMS-Funded RNA Research Named 'Breakthrough of the Year'

Science magazine has declared advances in understanding molecules called "small RNAs" as the top scientific achievement of 2002. This "Breakthrough of the Year" research was funded by the National Institute of General Medical Sciences.

Once thought to be mere foot soldiers that carry out DNA's orders, RNA molecules are now known to play a significant role in controlling gene expression and other cellular activities. NIGMS grantees whose discoveries are included in the Science Breakthrough of the Year include Dr. Andrew Fire of the Carnegie Institution of Washington in Baltimore, Md.; Dr. Craig Mello of the University of Massachusetts Medical School in Worcester; Dr. Gregory Hannon and Dr. Shiv Grewal of Cold Spring Harbor Laboratory in New York; Dr. Martin Gorovsky of the University of Rochester in New York; and Dr. C. David Allis of the University of Virginia Health System in Charlottesville.

Two other NIGMS-funded research areas were named among *Science* magazine's top 10 achievements for 2002: research on TRP (transient receptor potential) ion channels that allow us to taste spicy hot and minty cool sensations, and advances in a technology called cryoelectron tomography, which makes it possible to view cellular structures in three dimensions.

ASBMB Member Named to NAGMS Council

ASBMB members Dr. Shelagh M. Ferguson-Miller and Dr. Theodora E. Joan Robinson, were among three new members recently appointed to the National Advisory General Medical Sciences (NAGMS) Council by HHS Secretary Tommy G. Thompson. Dr. Ferguson-Miller is University Distinguished Professor and Chair in the Department of Biochemistry and Molecular Biology at Michigan State University. Dr. Robinson is Dean, Morgan State University.

Also named to the council was Dr. Yu-li Wang, of the University of Massachusetts Medical School.

The council, which meets three times a year, is composed of leaders in the biological and medical sciences, education, health care, and public affairs. Its members, who are appointed for four-year terms, perform the second level of peer review for research and research training grant applications assigned to the National Institute of General Medical Sciences (NIGMS). Council members also offer advice and recommendations on policy and program development, program implementation, evaluation and other matters of significance to the mission and goals of NIGMS.

NIH Grant Announcements

NIGMS and other NIH components have announced the Academic Research Enhancement Award, which stimulates research at educational institutions that provide baccalaureate or advanced training for a significant number of research scientists but that have not been major recipients of NIH support.

For details, see: http://grants1.nih.gov/grants/guide/pa-files/PA-03-053.html

NIGMS and other NIH components have announced Exploratory/Developmental (R21) Bioengineering Research Grants (EBRG). These grants will support innovative, high-risk/high-impact bioengineering research in new areas that are lacking preliminary testing or development. This research can explore approaches and concepts new to a particular substantive area; research and development of new technologies, techniques, or methods; or initial research and development of data upon which significant future research may be built.

For details, see: http://grants1.nih.gov/grants/guide/pa-files/PA-03-058.html

by John D. Thompson, Editor

Britain Unveils Plan for Partnerships Linking Science, Technology

The British Government has announced a sweeping new initiative in the United States aimed at promoting research and development, and commercial partnerships across the Atlantic. The Global Partnerships program, spearheaded by InvestUK in partnership with Trade Partners UK, was unveiled in February during the American Association for the Advancement of Science Annual Meeting in Denver. Representing a shift in economic development policy, Global Partnerships addresses specific market demand that will allow British and U.S. businesses to co-develop technologies or products through transatlantic partnership before committing to direct investment.

"We developed the Global Partnerships program in response to the need for knowledge driven companies, particularly in biotechnology and information technology, to establish a presence in the UK in a challenging economic climate," said Alastair Newton, Director of Invest.UK/USA. "For U.S. entrepreneurs, a successful transatlantic alliance can reduce risk, shorten time to market, and set the foundation for expansion into the European market. We expect the formation of new partnerships to play a significant role in future wealth and job creation in both the U.S. and the UK."

The Global Partnerships program incorporates the expertise of three arms of the British Government in the U.S., Invest.UK, Trade Partners UK and the UK's Science and Technology Network. All will be working closely to identify and advise clients in the U.S.

Now rolling out on a global basis, in its first six months the U.S. pilot program yielded more than 20 partnership projects despite the downturn in the business cycle. The announcement at the AAAS conference in Denver marked the official national launch of the program.

Glaxo Loses Paxil Patent Case

A U.S. District Court judge has ruled that TorPharm Pharmaceuticals' generic version of the anti-depressant Paxil does not infringe on a patent held by Britain's GlaxoSmithKline (GSK). Judge Richard Posner ruled that a generic version of Paxil from Canada's privately held Apotex did not infringe GSK's patent on Paxil. GSK, Europe's biggest pharmaceutical company, said it would appeal. The British firm had claimed that anhydrate converts naturally and during tablet-making to the more stable hemihydrate form, but the judge found hemihydrate was not present in Apotex's product in sufficient amounts to infringe GSK's patent.

The case in Chicago is one of two over Paxil patents due to be heard in the United States this year. GlaxoSmithKline also is suing Apotex and other generic companies over patent issues in Philadelphia, where the firm has its U.S. research headquarters. No trial date had been set as of early March.

Paxil sales reached $3.25 billion worldwide last year, representing nearly 10 percent of group sales according to Reuters. Two-thirds of the sales were made in the U.S.

GSK claims patent protection on Paxil through 2006. It also argues it has separate exclusivity under the Hatch-Waxman Act valid until September 19, 2003, that will prevent Apotex from selling its copycat drug before then.

In a bid to minimize the threat to Paxil, GSK is promoting a new controlled-release version of the medicine, called Paxil CR, that is protected by separate patents and already accounts for 31 percent of new U.S. Paxil prescriptions. GSK adopted a similar strategy for its leading antibiotic, Augmentin, when generic versions of that drug were launched.

Milk Production Gene Identified

MTT Agrifood Research Finland and the University of Liège, Belgium, have worked together successfully in locating a gene that regulates total yield and protein and fat content of milk.

The scientists found a variation, in the growth hormone receptor gene in the bovine chromosome 20, which is associated with a major effect on milk yield and composition in Ayrshire, Holstein, and Jersey cows. This is the second time that a clear quantified association has been demonstrated between a single gene and bovine milk production. The MTT group is currently fine-mapping the genes that affect cows' susceptibility to mastitis. This is of interest to cattle breeders, since traits sensitive to environmental effects, such as disease resistance, are difficult to improve by conventional methods, and for economic and welfare reasons the eradication of mastitis is an important goal for dairy cattle breeders.

For Drug Deals, Think Small

Biotech observers pondering 2003's first major acquisition, February's $2.4 billion purchase of Sunnyvale, California-based Scios, may wonder if this is the opener for a new round of biotech merger activity.

There may be a lot of mergers, but they are unlikely to be on the scale of the Johnson & Johnson/Scios deal according to Forbes. In that deal, J&J acquired a ready-made hot item, Natrecor, a treatment for heart failure. Since Natrecor's approval a year ago, Scios' shares have more than doubled in value.

Johnson & Johnson has a unique strategy for mergers. Where Pfizer makes big buys and then squeezes the maximum in savings from them, J&J buys for revenue growth. Scios will remain under the control of its current management, while Johnson & Johnson's large, skilled sales force will focus on pushing Natrecor sales farther and faster. Expectations are that the drug could bring in as much as $500 million per year.

More mergers will be seen in the biotech sector soon, but they will involve biotechnology companies that are running out of money. According to Biotechwatch.com, which runs a proprietary database of biotech companies, more than 158 biotech firms have one year's worth of cash in the bank or less. That means deals such as OSI Pharmaceuticals' acquisition of Cell Pathways for $32 million in stock. Cell Pathways had almost run out of cash, but it has one marketed product, for treating chemotherapy side effects. It also has a drug that is being tested in late-stage clinical trials and another in the early stages of development. However, as OSI's Chief Executive Colin Goddard noted, "In this kind of environment, a company running out of money simply can't execute."

Transkaryotic's New CEO Plans to Scale Back

Transkaryotic Therapies CEO Richard Selden has been replaced by Michael J. Astrue, who has served as general counsel at both Transkaryotic and Biogen. Astrue announced plans to reduce the number of drugs the Cambridge, Massachusetts-based biotech is developing to three, and to cut one-third of its 450-person workforce.

Transkaryotic will continue work on developing Replagal, for a rare disorder called Fabry disease; a treatment in midstage clinical tests for another rare disorder, Hunter's disease; and one other medication yet to be identified.

In January, an FDA advisory panel decided that clinical studies on Replagal did not provide strong evidence that it worked. Even worse, the panel said that the data for a rival Genzyme's Fabryzyme, supported that product's effectiveness. That was interpreted as giving Fabryzyme, the inside track for a six-year term of exclusivity under orphan drug laws.

Analysts expect that if Genzyme gets orphan designation for Fabryzyme, Transkaryotic is unlikely to get Replagel to market any time soon. That would limit Replagel's sales to the less lucrative European market, where it is already approved.

Transgenic Cotton a Winner in India

In India, genetically modified cotton produces crops that are 80% larger than conventional varieties, farm trials from 2001 have found. Results from last year's commercial harvest were similar, although less spectacular, says the Indian biotech industry.

GM crops will be especially useful in tropical developing countries, says agricultural economist Matin Qaim of the University of Bonn in Germany. "Population growth and limited farmland mean that we need yield advantages," he says. Qaim and his colleague David Zilberman looked at 157 typical cotton farms in three Indian states.

Farmers grew Bt transgenic cotton alongside two non-GM varieties. Bt plants carry a gene for a toxin from bacteria that makes them resistant to bollworm caterpillars, to which cotton farmers typically lose about half of their crop. Bt cotton gave 80% higher yields, and used almost 70% less pesticide, than conventional varieties. The GM seed costs four times as much as normal cotton, but the yield improvements mean that the crop is worth five times as much, according to Qaim.

Others deny that Bt cotton is better. Afsar Jafri, deputy director of the Research Foundation for Science, Technology and Ecology, a New Delhi-based conservation group, has been quoted as stating, "I have personally conducted a study in two states, and have found a drastic failure of transgenic Bt cotton."

American Universities Operating Fewer Industry Trials

Academia is conducting fewer and fewer industry-sponsored trials in the U.S. according to CenterWatch, the independent clinical trials monitor. Academic health centers, it found, conducted just 36% of industry-sponsored trials in 2001, down from 50% in 1996 and 71% in 1991. Whereas academic health centers once looked to industry trials as a major source of revenue, increased funding from NIH and potential conflicts with industrial sponsors make the liaisons less attractive.

Academic researchers often find the sponsor's budget too low to cover study costs, and there are growing complaints that the studies being offered have lost their scientific appeal. A recent review of research at the University of Minnesota found that many industrial studies do not meet academic standards. Of the 354 clinical research proposals evaluated by the university's Research Services Office, only 62% were acceptable to investigators and the institution, according to the journal *Academic Medicine*.

Nature Medicine quoted Marcia Angell, former editor of the *New England Journal of Medicine*, as saying the changes in the academic health centers approach are part of a backlash against the strings that are traditionally attached to industry money. "They've accepted contracts in which companies had total control over the data. Sometimes the sponsor helped write the studies," she says. "That has caused a lot of concern. I think the academic medical centers are beginning to say, 'No, we went too far.'"

CenterWatch's president, Ken Getz, confirmed the sea change, declaring, "In some way the academic institutions have been struggling for a while, in part because industry-sponsored research has been seen as tainted."

Industry also appears to have found the relationship increasingly dissatisfying. Over the past 10 years, drug companies have favored private clinical research organizations over the more bureaucratic academic health centers when seeking clinicians to test new drugs. The centers' internal review boards tend to be slow, whereas sponsors face limited opposition from clinical research organizations in retaining control of data and editing journal submissions. Some of the inefficiencies at academic centers stem from oversight systems designed to protect patients, says William Rodriguez, chief medical editor of Veritas Medical, a website that directs patients to clinical trials.

One result of this trend was a decision by the 85-member University Health system Consortium, to drop plans to coordinate large multi-center trials. *Nature Medicine* quoted the consortium's senior director, Karl Matuszewski, as saying "For the last five years, we've seen the ascension of the for-profit CROs and we found that we just couldn't compete with them." University administrators have said that many AHC clinical trial programs do not always meet industry's needs.

2003 National Science Olympiad

The nation's future scientists and engineers are likely among the 2500 young people that will be visiting Ohio State University to compete May 9-10 in the 2003 National Science Olympiad Tournament.

The National Tournament is an annual gathering comprised of students from around the nation who have risen to the top in academic competition and have been recognized as outstanding students of science.

The Science Olympiad tournaments are rigorous academic interscholastic competitions that consist of a series of individual and team events. These challenging and motivational events are balanced between the various science disciplines of biology, earth science, chemistry, physics, computers, and technology. They include events requiring knowledge of science facts, concepts, processes, skills, and science applications. In addition, there will be open house activities featuring science and mathematics demonstrations and activities conducted by professors and scientists at the host institution. To get to the national event, student teams in middle and high schools have to win their state Olympiads. There are now over 14,000 K-12 schools participating from all 50 states and Ontario.

The Science Olympiad is an international nonprofit organization devoted to improving the quality of science education, increasing student interest in science and providing recognition for outstanding achievement in science education by both students and teachers. These goals are accomplished through classroom activities, research, training workshops and the encouragement of intramural, district, regional, state and national tournaments.

For more information, visit www.soinc.org.

HIGHWIRE

Keeping Track of All Those Searches

In early 2001, *ASBMB News* introduced the new "portal" site from Stanford's HighWire Press, which allows you to search all of Medline plus 340 journals' full-text at once. 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

This month we take a step back from all the search and discovery features we've covered over the previous 13 articles in this series. In this article we look at how you can keep track of the different searches you've tried as you're exploring a new topic, and how you can most easily review them and refine them. Because subject/topic searching is an exploration process, rather than a direct "go to the article with this citation" process, you will often have a large number of "trial and error" searches. Along the way some will have been very productive and you might want to return to those and refine them. The HighWire portal supports this.

There are two links on every search result page that you will find handy when you want to review and refine your searches: Search History; and Rephrase My Search.

Search History

The Search History tool shows you a list of all the searches you've done in the past two hours, from most recent to oldest. It lists the search criteria, and the search result size, as shown in the example here. You can click to bring a search result back (the "resubmit" button), or modify the search criteria (the "rephrase" button).

Rephrase My Search

The Rephrase tool will take the criteria you used in a search, and fill in the Advanced Search form with those criteria. You can then change the criteria —by adding or removing keywords, by changing date ranges, etc.—to refine your search after seeing what result you get. You might, for example, decide to change from the "all words" option to the "phrase" option, requiring that articles have a phrase exactly matching your criteria. Or you might see that your result has a lot of chaff in it and add a "NOT <keyword>" on the search terms.

Give these simple tools a try as you explore subject/topic searches.

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

Evolution Boosted Anti-Cancer Prowess of a Primordial Gene

Arf gene became more effective in stemming cell growth when it joined forces with p53

Researchers at St. Jude Children's Research Hospital have looked back in evolutionary time and identified what may be a gene that was once only moderately effective in slowing down cellular reproduction, until it linked up with a more efficient set of genes to create a powerful anti-cancer response.

The gene, called Arf, was already known to have cancer-suppressing activity. Arf responds to cancer-causing environments by activating the well-known tumor suppressor gene, p53. In turn, p53 activates a battery of other genes to stop cell growth or, in extreme cases, to trigger cell death in response to a variety of harmful conditions, such as DNA damage or activation of oncogenes (cancer-causing genes). In fact, loss of Arf or p53 is a common event in many human cancers.

But the new results suggest that Arf plays a role far older in evolutionary terms than its more familiar job of stimulating p53 to prevent cancer. The St. Jude findings suggest that Arf originally evolved to slow the cell's metabolism and growth by limiting production of ribosomes. Ribosomes, made up of RNA (de-coded DNA) and proteins, guide the production of all other cellular proteins according to the genetic code. The new work shows that Arf interferes with production of the RNA components of ribosomes in order to exert some control of protein production and cell growth.

Researchers Dr. Charles Sherr and ASBMB member Dr. Martine F. Roussel

"About 80 percent of a cell's RNA is tied up in ribosomes," said ASBMB member Dr. Charles Sherr, of the Genetics & Tumor Cell Biology Department at St. Jude and a Howard Hughes Medical Institute investigator. "In fact, producing ribosomes is practically what cells do for a living. It's their major energy-consuming activity. So it makes sense that any limitation on ribosome production would slow cell growth."

His team believes that Arf counteracts excessive growth-promoting stimuli by interfering with ribosome production. But inhibiting ribosomal production isn't a particularly efficient way to control cell growth. "On the other hand, p53 activates many growth suppressive genes," Dr. Sherr said. "So, Arf appears to have become more efficient because, by evolving a way to activate p53, it was able to extend its reach and inhibit many more cellular responses apart from ribosome synthesis."

Dr. Sherr is senior author of a report on these findings published in the February 2003 issue of *Molecular Cell*. Other authors of the study include Dr. Masataka Sugimoto, Dr. Mei-Ling Kuo, and ASBMB member Dr. Martine F. Roussel, all of whom are St. Jude investigators.

The group studied the role of Arf in controlling ribosomal RNA production using a variety of mouse cells. The effects were then examined by inserting Arf genes into harmless viruses used to infect the cells, and by tracking the levels of newly synthesized RNA in the cells under various experimental conditions. The exact mechanism by which Arf interferes with ribosomal RNA synthesis remains unclear and is a subject for future research, according to Dr. Sherr.

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.

Zhuan Fen Cheng
University of Miami, School of Medicine

Amy Haas
Medical College of Wisconsin

Kuo-Hsiang Tang
University of Wisconsin, Madison

Career Opportunities

POSTDOCTORAL POSITIONS

Postdoctoral positions (3) available to study the effects of HIV, its therapeutics, and selected toxins on cardiac, skeletal muscle, and hepatic mitochondrial DNA replication and mitochondrial structure and function. The laboratory uses myocardial-targeted transgenic mice and cell culture models to address scientifically based and clinically relevant questions about mitochondrial defects in AIDS. Excellent, collegial working environment exists. Laboratory possesses state-of-the-art facilities. Projects include (1) defining the effects of selected HIV proteins on mitochondrial function, (2) defining the effects of inhibition of DNA polymerase gamma on cardiac structure and function, and (3) determining the individual and combined effects of HIV and its therapeutics on cardiac and hepatic function (4) defining the role of hepatic mitochondrial function in lactic acidemia in AIDS (5) defining the combined effects of cardiotoxins on the development of cardiomyopathy (6) defining the events of mitochondrial nucleoside import and metabolism. Salary support is competitive and based on candidate's experience and institutional guidelines. Potential for faculty appointment exists for successful postdoctoral candidates. Candidates must possess a Ph.D. (or equivalent advanced degree), have a strong background in biochemistry, cell and/or molecular biology. Please send C.V. and list of references.

William Lewis, M.D., Professor
Department of Pathology
Emory University School of Medicine
Woodruff Memorial Research Building
1639 Pierce Drive
Atlanta, GA 30322
Email: wlewis@emory.edu
Phone: 404 712 9005

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NEW FACULTY POSITIONS

Department of Pharmacology, Toxicology, and Therapeutics
University of Kansas Medical Center

The Department of Pharmacology, Toxicology, and Therapeutics is initiating an expansion by inviting applications at all ranks for tenure-track faculty positions. We anticipate 2 new hires annually for 5 years. Preferred candidates will show evidence of currently funded research in areas which will compliment existing strengths in the department and the medical center. Departmental emphasis for the first hires is on toxicology and xenobiotic disposition (ADME). Broader areas of strength in the medical center include cancer, neuroscience, reproductive biology, and renal pathophysiology, and a growing effort in clinical pharmacology. A competitive startup package and appropriate space will be offered, bolstered by the construction of a new 200,000 sq. ft. research building. Standard support facilities are present, including biotechnology and transgenics, and we have just opened a state of the art brain imaging center. Applications will be reviewed as they are received until the positions are filled. Anticipated appointment date is as early as July 1, 2003. Applicants should provide a C.V. and names of three references to:

Curtis D. Klaassen, Ph.D.
Chairman, Dept. of Pharmacology, Toxicology, and Therapeutics
University of Kansas Medical Center
3901 Rainbow Boulevard
Kansas City, KS 66160-7417
Email: cklaasse@kumc.edu

The University of Kansas Medical Center is proud to be an Equal Opportunity/Affirmative Action Employer.

FACULTY POSITION IN PHARMACOLOGY

Wilkes University, School of Pharmacy

Applications are invited for a 9-month tenure-track faculty position at the Assistant/Associate level. The successful candidate will participate in the training of professional pharmacy students as members of the team of scientists and clinicians responsible for the four-semester sequence of courses in pharmacotherapy. The applicant will be asked to develop professional electives and a modest research program. Minimum requirements are a Ph.D in Pharmacology or a closely related discipline and the ability to communicate clearly and effectively. The pharmacologist should be expert in neuropharmacology and comfortable teaching physiology. Application materials should include a letter of interest, a full curriculum vitae, and the names, addresses and telephone numbers of three individuals who may be contacted for a confidential reference. Preference will be shown to those with an undergraduate degree in pharmacy.

Complete applications should be sent to: Dr. Arthur H. Kibbe, Chair, Department of Pharmaceutical Sciences, School of Pharmacy, Wilkes University, Wilkes-Barre, PA 18766, E-mail: kibbe@wilkes.edu

Wilkes University is an Equal Opportunity/Affirmative Action Employer.

Calendar of Scientific Meetings

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

9th National Symposium on Basic Aspects of Vaccines

April 30–May 2 • Bethesda, Maryland
Contact: Conference Secretariat; Walter Reed Army Institute of Research; Dept of Membrane Biochemistry
503 Robert Grant Ave, Room 2A24; Silver Spring, MD 20910
Ph: 301-319-9462 fx: 301-319-9035
e-mail: symposium@na.amedd.army.mil
Website: http://wrair-www.army.mil/symposia/dmbsym.htm

MAY 2003

Proteomic Solutions in Cellular and Developmental Biology and Medicine

May 2–4 • Stowers Institute, Kansas City, Missouri
Contact: Kelly Gull; Ph: 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
Contact: Gulshan Singh
Ph: 515-294-7978; Fx: 515-294-2244; E-mail:pbmb@iastate.edu
Website: http://molebio.iastate.edu/-gfst/phomepg.html

4th International Symposium on Hormonal Carcinogenesis

June 21-25 • Palau de la Musica, Valencia, Spain
Contact: Tandria Price/Dr. Jonathan J. Li
University of Kansas Medical Center
Ph: 913-588-4744; Fx: 913-588-4740; Email: tprice@kumc.edu
Website: http://www.kumc.edu/hormonecancers.

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: 301-634-7145; Fx: 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

Biology of Molecular Chaperones Mechanisms and Regulation of Chaperones

August 30–September 4 • Tomar, Portugal
Contacts: Dr. Josip Hendekovic or Caroline Walford
Ph: + 33 388 76 71 35; Fx: + 33 388 36 69 87
Website: http://www.esf.org/esf_euresco
Please quote 2003-15 in any correspondence

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

NMR in Molecular Biology
EuroConference on Structural Genomics: From Gene to Structure as viewed by NMR

September 5–10 • Obernai (near Strasbourg), France
Contact: Dr. Josip Hendekovic or Anne-Sophie Gablin
Ph: + 33 388 76 71 35; Fx: + 33 388 36 69 87
Website: http://www.esf.org/esf_euresco
Please quote 2003-14 in any correspondence

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/

JUNE 2004

American Society for Biochemistry and Molecular Biology Annual Meeting and 8th IUBMB Conference

June 12-16 • Boston, Massachusetts
Contact: Kelly Gull; Ph: 301-634-7145; Fx: 301-634-7126
Email: kgull@asbmb.faseb.org; Website: www.asbmb.org/meetings

AUGUST 2004

12th International Conference on Second Messengers and Phospoproteins

August 3-7 • Montreal, Canada
Contact: smp2004@eventsintl.com
Website: www.secondmessengers2004.ca

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.

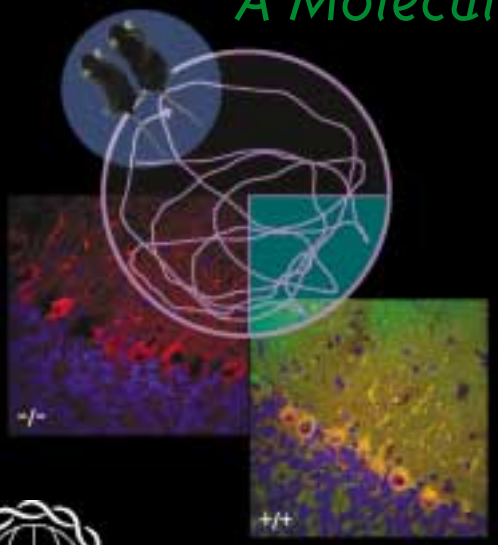
The Society is asking department chairs to provide ASBMB with the names and addresses of each new Ph.D. recipient from their institutions. Upon receipt of this information, we will write the new Ph.D.s to congratulate them on their accomplishment and offer the free one-year membership in ASBMB. Names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

IUBMB/ASBMB 2004

"A Molecular Exploration of the Cell"



June 12 – 16

Boston, MA

American Society for Biochemistry and Molecular Biology Annual Meeting and 8th IUBMB Conference

Organized by:

John D. Scott, HHMI, *Vollum Institute*
Alexandra C. Newton, *UCSD*
Julio Celis, *Danish Cancer Society*, and
the 2004 ASBMB Program Planning Committee

Award Lectures

ASBMB-Merck Award
ASBMB-Avanti Award in Lipids
ASBMB-Amgen Award
William C. Rose Award
Herbert A. Sober Lectureship
Schering-Plough Research Institute Award
Howard K. Schachman Public Service Award

For further information:

ASBMB
9650 Rockville Pike
Bethesda, MD 20814
Tel: 301-634-7145
Fax: 301-634-7126
Email: asbmb@asbmb.faseb.org
http://www.asbmb.org/meetings

Meeting I: Molecular Recognition and Catalysis
Organizer: Jack E. Dixon, *UCSD*

Meeting II: Cellular Organization and Dynamics
Organizer: Harold A. Stenmark, *Norwegian Rad. Hosp.*

Meeting III: Genomics, Proteomics and Bioinformatics
Organizers: Charlie Boone, *Univ. of Toronto* and
Michael Snyder, *Yale Univ.*

Meeting IV: Integration of Signaling Mechanisms
Organizer: Kjetil Tasken, *Univ. of Oslo, Norway*

Meeting V: Molecular and Cellular Biology of Lipids
Organizer: Dennis Vance, *Univ. of Alberta*

Meeting VI: Protein Structure, Catalysis and Dynamics
Organizer: Susan Taylor, *UCSD*

Meeting VII: Protein Dynamics and Turnover
Organizer: William J. Lennarz, *SUNY at Stony Brook*

Meeting VIII: Regulation of Gene Expression and Chromosome Transactions
Organizer: Joan W. Conaway, *Stowers Inst. for Med. Res.*

Meeting IX: Signaling Pathways in Disease
Organizers: Alexandra Newton, *UCSD* and
John D. Scott, *HHMI, Vollum Inst.*

Meeting X: The Future of the Profession
Organizer: J. Ellis Bell, *Univ. of Richmond*