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"TRANSLATING THE GENOME"

Opening Lecture—FRITZ LIPMANN LECTURESHIP

"Ion Channels"
Roderick MacKinnon, *The Rockefeller Univ.*

Public Affairs Lecture

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Organized by Dennis R. Voelker, *Natl. Jewish Med. Res. Ctr.*

Meeting IV: Biological Catalysis
Organized by Tadhg Begley, *Cornell University*

Meeting V: Metabolism—Pathways and Regulation
Organized by Luciano Rosetti, *Albert Einstein Col of Med.*

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Meeting VIII: Protein Synthesis, Folding and Turnover
Organized by Cecile M. Pickart, *Johns Hopkins Bloomberg Sch. Pub. Hlth.*

Meeting IX: Nucleic Acid Structure, Function and Processing
Organized by Michael Dahmus, *UC, Davis*

Meeting X: Membrane Assembly Interaction and Transport
Organized by Stephen H. White, *UC, Irvine*

Meeting XI: The Future of the Profession
Organized by A. Stephen Dahms, *California State Univ. System Biotechnology Program*

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ASBMB Today

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features

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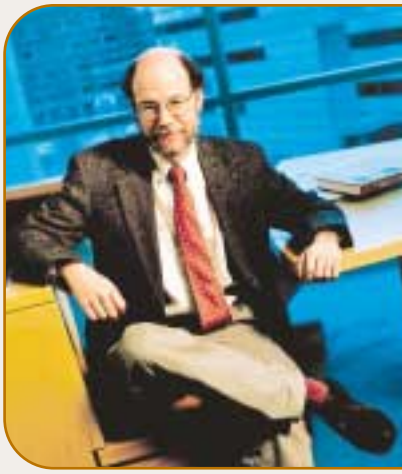

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ASBMB 2003 Meeting

Roderick MacKinnon, Howard Hughes Medical Institute (HHMI) Investigator and Professor, Laboratory of Molecular Neurobiology and Biophysics, Rockefeller University, and recipient of the 2003 Fritz Lipmann Lectureship, will be the opening keynote lecturer at the ASBMB Annual Meeting, April 11-15, in San Diego.

The Lipmann Lectureship was established by friends and colleagues of Fritz Lipmann. Dr. MacKinnon will be the eighth recipient of this honor. Previous awardees include Ulrich Hartl, James E. Rothman, Helmut Beinert, Wayne A. Hendrickson, Joan A. Steitz, Steven Fesik, and Heidi Hamm. The recipient receives a plaque, stipend, and all expenses to attend EB 2003 and present the lecture.

"Ion Channels" is the title of Dr. MacKinnon's lecture, and ion channels is a topic which he is eminently qualified to address. In 1998, through the use of X-ray crystallography his laboratory established the structure of the potassium ion channel, in recognition of which he received the 1999 Albert Lasker Basic Medical Research Award.

Better Understanding Ion Channels

Dr. MacKinnon's research addresses the atomic basis of electrical signaling in living cells. Initially his laboratory used mutational and electrophysiological analyses to show that potassium channels are tetramers of identical subunits and that a specific segment of amino acids – which he and his colleagues called the potassium channel signature sequence – is conserved in all potassium channels throughout nature and forms the selectivity filter. Having reached the limits of information that his initial techniques could provide, he next went on to address the mechanisms of ion selectivity and conduction at the atomic level through X-ray crystallography of potassium and chloride ion channels.

MacKinnon's laboratory has determined the structures of the two known valence selective ion channels, potassium and chloride channels. In their first major breakthrough they showed that potassium channels feature an "inverted teepee-shaped" pore that protrudes through the cell membrane and forms a pore that holds multiple potassium ions during their transmembrane passage. Through the use of monoclonal antibody fragment mediated crystallization they have advanced the resolution to provide an atomic description of potassium coordination in breath-taking detail. The selectivity filter, comprised of the very signature sequence amino acids

Tell Us What You Think

We appreciate receiving letters that are suitable for publication from ASBMB members regarding issues of importance or commenting on articles appearing in *ASBMB News*. Letters should be sent to the editor, John Thompson, at the address found at left. Letters must be signed and must contain the writer's address and telephone number. The editor reserves the right to edit all letters.

Will Open With Lecture on Ion Channels

defined in Dr. MacKinnon's laboratory many years earlier, creates a unique sequence of cages that delicately hold potassium ions *via* carbonyl oxygen atoms, much in the same manner that water molecules hold potassium in the hydrated state.

Having understood the ion selective pathway, the next major question concerned how potassium channels open and close in a process referred to as gating. "Although in previous work we had solved the structure of the potassium channel, we still did not understand this gating mechanism—how it opens and closes," says Dr. MacKinnon in discussing his team's determination of how potassium channels open to allow potassium ions to flow through the cell membrane, a process that is crucial in many biological processes, including the rhythmic beating of the heart and the generation of nerve impulses.

Dr. MacKinnon and his colleagues addressed the problem of gating by first identifying a potassium channel that they could open in the crystal. For this purpose they chose a ligand-gated potassium channel, in which calcium binding causes the gate to open. The researchers used X-ray crystallography again to obtain snapshots of the structures. They then compared the opened calcium activated potassium channel to their previously determined closed potassium channel.

Comparison of the two structures — KcsA and MthK potassium channels — revealed how the teepee-shaped pore opens. "These pores both have helical-shaped alpha-helices that line their inner surfaces," he reported. "We could see that the equivalent helices in KcsA ran straight, whiles those in MthK were bent outward by a little more than 30 degrees. So this difference allowed us to recognize that we were looking at a hinge that opens the pore."

Their study revealed that almost all potassium channels have the amino acid glycine in the critical hinge region. The flexibility of the glycine amino acid enables the hinge to work. "All potassium channels in nature have this canonical pore, which is composed of four identical subunits," said Dr. MacKinnon. "And there is a high degree of sequence conservation among these channel proteins, so we know that this mechanism is going to be similar throughout potassium channels."

Recently Dr. MacKinnon and his colleagues determined the structure of a chloride ion channel. "Nature uses a fundamentally different architecture to conduct the anion chloride as compared to the cation potassium. But it is clear that within the very different architectures, similar physical principles – helix dipoles, backbone atoms, partial charges, multiple ions - are used. It is very beautiful."

When asked about the applications of his work for future therapies, Dr. MacKinnon emphasizes that the findings from his laboratory are very basic observations that allow us to understand how cells produce electrical signals. He notes that ion channels – the electric signal generators of life – are crucial to health and disease and hopes that his work will someday find application.

About Dr. Roderick MacKinnon

A native of Massachusetts, Dr. MacKinnon was drawn to science from childhood by his love of solving puzzles and his fascination with the natural world. He received a B.A. degree in biochemistry from Brandeis University in 1978 and an M.D. from Tufts University in 1982. Choosing to pursue a career in basic research, he returned to Brandeis in 1986 for postdoctoral studies. In the laboratory of Christopher Miller, his undergraduate mentor, he began work on the biophysical aspects of ion channel function, focusing on the protein selective for potassium ions, and continued these studies at Harvard Medical School, where he joined the faculty in 1989.

Dr. Roderick MacKinnon

Dr. MacKinnon moved to Rockefeller University in 1996 to focus his efforts on determining the atomic structures of ion channels. He is currently professor and head of the Laboratory of Molecular Neurobiology and Biophysics and investigator in the Howard Hughes Medical Institute. It was here that his laboratory established the structure of the potassium ion channel in 1998, a finding that led to his receipt of the Albert Lasker Basic Medical Research Award.

Lasker Awards Honor Discoverers

This year's Lasker Award for Basic Medical Research honors two ASBMB members who discovered the universal molecular machinery that orchestrates the budding and fusion of membrane vesicles, a process that cells use to organize their activities and avert the biochemical anarchy that would result if all of their contents commingled. By 1970, Dr. George Palade had published his classic work showing that proteins travel between cellular compartments, but the molecular basis for this phenomenon was unknown. Using a biochemical and genetic approach, respectively, Dr. James E. Rothman, Chair of the Cellular Biochemistry and Biophysics Program at the Sloan-Kettering Institute, and Dr. Randy W. Schekman, Professor in the Division of Biochemistry and Molecular Biology, University of California, Berkeley, transformed this descriptive field into one of detailed molecular clarity.

The cellular trafficking system explains how pancreatic cells release insulin, how nerve cells communicate, how embryos liberate growth factors to stimulate organ development, and how viruses infect.

The cellular trafficking system elucidated by Dr. Rothman and Dr. Schekman explains how pancreatic cells release insulin, how nerve cells communicate, how embryos liberate growth factors to stimulate organ development, and how viruses infect. Alterations in these pathways explain a plethora of pathological processes, including the most common form of diabetes and the lethal effects of bacterial diseases such as botulism and tetanus.

When the two began their work, scientists knew that mammalian cells bustle with transport activities. Containers called vesicles ferry proteins from one site to another. These vesicles pinch off, or bud, from one membrane and merge, or fuse, with the next. Multiple types of vesicles shuttle cargo to different sites, and each must somehow find its correct destination among the many possibilities. Secreted proteins, for instance, travel from a compartment called the endoplasmic reticulum (ER) to the cell surface by way of a structure called the Golgi. Together, the specific membrane fusion events maintain the identity of cellular compartments, yet foster communication with each other and the outside. Controlling these maze-like interactions is essential because mixing the cell's contents would spur disaster. For example, enzymes intended to chew up food would instead munch important cellular machinery. The cell then would be unable to orchestrate its activities, and chaos would prevail.

Although this general picture was clear by the mid-1970s, the details remained obscure. No one understood, for example, how cells made vesicles from membranes, how vesicles knew where to go, or how they fused with their target membranes.

Both Dr. Rothman and Dr. Schekman aimed to track down the molecular machinery that performed these crucial trafficking functions, but they chose different initial strategies.

Dr. Rothman decided to dismantle the pathway and reconstitute it from its components in a test tube; success at building up the entire process from its parts would indicate that he had fished out the vital elements. Similar so-called biochemical strategies had boasted victories in the arena of complicated, multi-step biological activities, including the mechanism of DNA replication and protein synthesis.

Dr. Randy Schekman

Dr. Schekman selected a genetic scheme, in which researchers prod cells to reveal constituents that participate in a particular pathway. The aim was to obtain mutants that can't perform a certain function; the genes mutated in these cells presumably play essential roles in the process of interest. This strategy, too, had triumphed in eluci-

'America's Nobel'

The Lasker Award for Basic Medical Research is regarded as "America's Nobel." Every year since 1992 the Nobel has been awarded to a scientist who had previously received a Lasker Award. Last year, Dr. Leland Hartwell and Sir Paul Nurse, who shared the Lasker Award in 1998, received the Nobel Prize.

# of Universal Molecular Machinery

dating the mechanism by which cells divide, for example. Both approaches provide a way to find single components of complex systems, which can then be probed further.

Each tactic produced significant contributions of its own, and reinforced findings from the other. Together, the advances unmasked the machinery and means by which cells transport proteins, yielding unanticipated insight into fields that span the physiological gamut.

Brave New Worlds

When the two began their work in the late 1970s, some scientists raised their eyebrows; others yawned. Dr. Schekman, a biochemist and microscopist, had developed the idea of using yeast genetics to identify cellular trafficking components. Grant reviewers trounced his first proposal because he had no experience with yeast. They thought that he underestimated the difficulty of working with membranes, and doubted whether yeast had a robust secretion system anyway. Dr. Rothman encountered skepticism as well. Most scientists thought his approach would fail because compartments that exchange delivery vesicles in the cell tend to lie close together, and they believed that vesicles found their targets in large part due to this proximity.

Despite the doubts of others, the combined work of Dr. Schekman and Dr. Rothman unveiled the key machinery and mechanisms of membrane trafficking. This process is vital for countless physiological events, and when it malfunctions, illness occurs. In type II diabetes, for example, cells can't ingest glucose from the blood—

Dr. James E. Rothman

even in the presence of adequate amounts of insulin—because molecules that normally reside on the cell surface and import the sugar are stranded in vesicles inside. Some patients are already using insulin-sensitizing drugs that restore fusion so the transport molecules can reach the surface and slurp the glucose that's just out of reach.

Knowing the mechanism of protein secretion in yeast has allowed scientists to use these microbes as protein factories. Yeast genetically engineered to secrete human insulin currently produces about 25% of the world's insulin supply and all of the Hepatitis B antigen used for vaccination. Medical applications based on new information about trafficking extend much further. Drugs that shift the balance between neurotransmitter uptake and export might someday provide novel therapies for cognitive and mood disorders. Recent studies suggest, for instance, that regulation of membrane fusion is altered in schizophrenia.

Dr. Rothman and Dr. Schekman's legacy has permeated a vast number of physiological disciplines, including neurobiology, endocrinology, virology, and embryology, and promises to expand its impact further. Happily, the doomed projects that began 25 years ago have defied their initial prognoses.

Lasker Award Honors Rockefeller University's James Darnell

"Special Achievement in Medical Science" recognizes a groundbreaking researcher, influential writer and mentor.

James E. Darnell Jr., M.D., an ASBMB member and pioneering researcher in the field of gene regulation who has nurtured the careers of over 100 young, talented scientists, has been honored with the 2002 Albert Lasker Award for Special Achievement in Medical Science.

A member of the National Academy of Sciences, Dr. Darnell joined Rockefeller University in 1974 and is the university's Vincent Astor Professor and head of the Laboratory of Molecular Cell Biology.

"For more than 40 years, Jim Darnell has had a major impact on American science," said Nobel Laureate Phillip A. Sharp, Ph.D., in his letter nominating the Rockefeller scientist for the Lasker honor. "He has played a unique role as a scientist, author and educator over this time and is uniquely qualified to receive this award."

Dr. Darnell's many scientific achievements include the discovery of a pathway by which "molecular cues" on the surface of a cell signal the genes in that cell's nucleus to take specific actions. These signals are sent in reaction to changes in the cell's external environment in the body. As a result of the signals, the genes may express RNA for a specific hormone or other protein, or halt gene expression or activation. Such communications contribute to the survival of cells and indeed the entire organism.

The cell-signaling route discovered by Dr. Darnell, the JAK-STAT pathway, "provides the clearest example of signaling from the cell surface to genes in the nucleus. Studies of this pathway also yield important new insights into the biology of specific human cancers including multiple myeloma and head and neck tumors," added Dr. Sharp, Institute Professor and founding Director of the McGovern Institute for Brain Research at the Massachusetts Institute of Technology.

Dr. James E. Darnell Jr.

Besides advancing scientific understanding of the factors regulating activation or expression of genes in animal cells as models for human biology, Dr. Darnell has fostered the development of over 100 scientists, most of whom today are now professors or directors of major laboratories at institutions throughout the world.

Dr. Darnell was the "originating author and wrote approximately half of *Molecular Cell Biology*," said Dr. Sharp about the textbook which was first published in 1986 with co-authors Harvey F. Lodish, Ph.D., and David Baltimore, Ph.D. "It is fair to say that this book, together with *Molecular Biology of the Cell* by Bruce Alberts, Ph.D., James D. Watson, Ph.D., and others, provided teachers of biology throughout the world with material to teach a thoroughly modern course based, for the first time, on modern experimental biology, just as was traditionally the case with chemistry and physics."

"It is no exaggeration to say that Jim is one of three or four most notable contributors to the molecular understanding of animal cell physiology," Dr. Sharp noted. His research has been basic to understanding how normal cells grow and become specialized, e.g., how instructions in genes get copied into messenger RNA (mRNA) and expressed at the right time and at the proper rate.

Dr. Darnell's research supplied much of the evidence for the now generally accepted scientific concept that all RNA is formed by extensive "molecular carpentry." His studies first with ribosomal and transfer RNA, molecules that assist in coding mRNA to make protein, showed that both these molecules are chemically "processed" (chemical groups are added after synthesis and a long initial product is cut into usable pieces) before their use in the cell's cytoplasm.

His studies on pre-mRNA from the DNA virus, adenovirus, paved the way for the Nobel Prize-winning discovery of RNA splicing in mRNA formation by Dr. Sharp, Dr. Richard Roberts and their colleagues.

Perhaps the most far reaching results from Dr. Darnell's laboratory began with research in the early 1980s that culminated in 1992 with the mapping of the first complete "signal transduction" pathway: the JAK-STAT signaling pathway. His group discovered that a set of dual function proteins, which they named STATs for Signal Transduc-

ers and Activators of Transcription remain quiescent in the cell until circulating polypeptides bind to specific receptors on the surface of the cell.

Specific STATs then are activated, pair up and travel to the nucleus to activate appropriate genes. For example, some STATs switch on a group of interferon-responsive genes when interferon contacts cells. Interferon, a cytokine used in anti-cancer and anti-viral therapy to halt or slow proliferation of cancer cells or viruses, is sometimes used in combination with chemotherapy. This discovery has promoted a flurry of research into the ways cells receive signals to become and remain specialized, to respond to growth factors and to deal with infection.

"For more than 40 years, Jim Darnell has had a major impact on American science."
—Nobel Laureate Phillip Sharp, Ph.D.

The Lasker Award recipient's lab also has shown that the persistent activation of a protein called Stat3 can, by itself, cause normal cells to behave like cancer cells. Scientists previously knew that Stat3 was often activated in various human cancer types, including lymphomas, leukemias, breast cancer and a high percentage of head and neck cancers, but Dr. Darnell and his colleagues showed for the first time that persistent Stat3 activation could contribute directly to the development of tumors.

During the last 20 years, Dr. Darnell also has studied the coordinated control of sets of genes that are expressed mainly in liver cells. By studying the proteins responsible for liver-specific gene activation, he discovered a group of proteins that was also found to switch on specific genes very early in animal embryonic development.

Currently, he and his colleagues at Rockefeller University are exploring the molecular mechanisms by which STATs activate genes and why persistently active Stat3 contributes to cancer.

Protein Chemistry and the Development of Allosterism: Jeffries Wyman

An Analysis of the Titration Data of Oxyhemoglobin of the Horse by a Thermal Method

(Wyman, J., Jr. (1939) *J. Biol. Chem.* **127**, 1-13)

Jeffries Wyman (1901-1995) was born in West Newton, Massachusetts into a prominent Boston family. After receiving a classical education at Noble and Greenogh's School, a preparatory school in Boston, he entered Harvard College. A great uncle, C.C. Felton, had been President of Harvard, and his grandfather, Jeffries Wyman, had been a distinguished Harvard Professor of Natural History and Comparative Anatomy and founder of the Peabody Museum as well as a founding member of the National Academy of Sciences. During Wyman's undergraduate years at Harvard, he studied philosophy and became interested in biology only toward the end of his undergraduate years. After receiving his degree, he stayed at Harvard for another year taking additional courses in thermodynamics and physical chemistry, both of which would significantly contribute to his career preparation. During his undergraduate years, he also developed what became a lifelong friendship with John T. Edsall, the author of a previous *Journal of Biological Chemistry* (JBC) Classic (1).

Wyman and Edsall left Harvard for Cambridge University together to study biochemistry. The biochemistry department at Cambridge was chaired by F. Gowland Hopkins, author of another JBC Classic (2), and provided excellent opportunities for students to conduct research and take courses in biochemistry. While Edsall remained at Cambridge for a year before returning to Harvard to complete the M.D. degree, Wyman transferred to University College, London to work with Archibald Vivian Hill, the preeminent physiologist. Hill was working on a variety of biological problems including a description of oxygen binding by hemoglobin. It was Hill's work on hemoglobin that led to his description of the Hill coefficient to describe the oxygen binding to hemoglobin and that has subsequently been used as a measure of cooperativity. Hill showed that for hemoglobin the coefficient, n, = 2.8 whereas for myoglobin, $n = 1$. His assumption in the interpretation was that hemoglobin was a monomeric protein and that a value of $n > 1$ indicated that the protein was aggregated. (It was G.|S. Adair, also the author of a previous JBC Classic (9), who correctly measured the molecular weight of hemoglobin, recognized it was a tetramer, and correctly interpreted the oxygen binding by hemoglobin as a cooperative process.) Although much of Wyman's later work was focused on hemoglobin and cooperative oxygen binding, he worked with Hill on the thermodynamics of muscle action, not hemoglobin.

After completing his research in London, Wyman returned to Harvard as an Instructor in Zoology. Edsall too returned to Harvard. The two friends were rejoined. Even though Wyman was in the biology department in the College, he and Edsall both worked together with Edwin J. Cohn, Chairman of the Department of Physical Chemistry at Harvard Medical School. With Cohn, author of another JBC Classic (3), whose major interest was the physical chemistry of proteins, Wyman worked on a variety of problems including dielectric measurements of amino acids, peptides, and proteins. The paper reprinted here as a JBC Classic describes the titration of oxyhemoglobin and identification of the ionizable groups. Wyman argued that titrations of the different ionizable groups in proteins could be characterized by their different heats of dissociation. Titrations were conducted at different temperatures between pH 4 and pH 10. He concluded that groups that ionize up to pH 5.5 are carboxyl groups, those between pH 5.5 and pH 8.5 are the imidazole groups of histidine, and those ionizing above pH 8.5 are either the amino or the guanidino groups of lysine or arginine, respectively. Wyman also concluded that a change in pK of the imidazole groups of a few histidine residues occurs on oxygenation of hemoglobin and accounts for the well known Bohr effect. These assignments are in agreement with determinations by other methods, so the conclusions of the work are not in themselves particularly insightful. The approach, however, reflects a notable understanding of basic thermodynamics and its application to complex problems of protein chemistry. Wyman began to teach his own course in biophysical chemistry at Harvard. He was later joined by Edsall. and together they published their classic textbook, *Biophysical Chemistry*, Volume 1 (7). They had planned a second volume, but it was never published.

Jeffries Wyman

Wyman's work, like that of most American scientists, was interrupted by World War II as attention turned to the war effort. Wyman joined the Woods Hole Oceanographic Institution, which was a major contractor for the Navy. He worked on submarine detection by echo ranging and the tactical use of smoke screens, which required considerable understanding of meteorology and atmospheric conditions.

A Classic from the *Journal of Biological Chemistry*

FOLLOWING IS ONE IN A SERIES OF CLASSIC *JBC* PAPERS THAT WILL BE PUBLISHED IN *ASBMB TODAY* AS WE PREPARE FOR THE *JOURNAL OF BIOLOGICAL CHEMISTRY*'S CENTENNIAL CELEBRATION IN 2005. (SEE WWW.JBC.ORG FOR A COMPLETE LIST OF CLASSICS)

After spending four years in Paris, Wyman held a series of positions elsewhere in Europe and the Middle East including several years in Cairo as Direc After the war, Wyman published a review of hemeproteins that is one of his classic papers (4). He had by then begun to formulate ideas about how conformational changes in proteins could lead to changes in functional properties. His first report on this subject, which was later called allosterism, was published in 1951 (5). About that time, Wyman decided not to continue his career as a university professor and accepted the newly created position as science attaché at the United States Embassy in Paris. He was to be responsible for the development of scientific activities in France, Italy, and Belgium. While he was in Paris, Wyman continued to extend his thoughts about cooperativity in molecular interactions, which led to the classic paper published with Jacques Monod and Jean-Pierre Changeux, for which he is probably best known, the model for allosteric transitions (6). The "plausible model" came to be known as the "concerted" or the "MWC" model, for Monod, Wyman, and Changeux. It was proposed that proteins that exhibit cooperativity can exist in only two conformational states, and the equilibrium between these two states is modified by binding of a ligand, oxygen in the case of hemoglobin. The model, which has stood the test of time, can explain quantitatively the behavior of many allosteric proteins.
tor of the Middle East Science Cooperation Office of UNESCO. He worked in Rome for 25 years at the Institute Regina Elena where he continued to develop his ideas on protein conformational states until his death in 1995.1

Robert D. Simoni, Robert L. Hill, and Martha Vaughan

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10. Virtually all the biographical information for this Classic introduction was taken from Ref. 8.

Three Share 2002 Nobel for

The 2002 Nobel Prize in Physiology or Medicine has been awarded jointly to a trio of scientists, two of whom are ASBMB members. Sydney Brenner, Director of Research and President, Molecular Sciences Institute, Berkeley, California; H. Robert Horvitz, HHMI Investigator and Professor, Department of Biology, Massachusetts Institute of Technology; and John E. Sulston, Wellcome Trust Sanger Institute, Cambridge, England. Dr. Brenner and Dr. Horvitz are both ASBMB members. The award was in recognition of their discoveries concerning genetic regulation of organ development and programmed cell death.

This year's Nobel Laureates in Physiology or Medicine have made seminal discoveries concerning the genetic regulation of organ development and programmed cell death. By establishing and using the nematode Caenorhabditis elegans as an experimental model system, possibilities were opened to follow cell division and differentiation from the fertilized egg to the adult. The Laureates have identified key genes regulating organ development and programmed cell death and have shown that corresponding genes exist in higher species, including man. The discoveries are important for medical research and have shed new light on the pathogenesis of many diseases.

Dr. Brenner established *C. elegans* as a novel experimental model organism. This provided a unique opportunity to link genetic analysis to cell division, differentiation and organ development and to follow these processes under the microscope. His discoveries laid the foundation for this year's Prize.

Dr. Sulston mapped a cell lineage where every cell division and differentiation could be followed in the development of a tissue in *C. elegans*. He showed that specific cells undergo programmed cell death as an integral part of the normal differentiation process, and he identified the first mutation of a gene participating in the cell death process.

Dr. Horvitz discovered and characterized key genes controlling cell death in *C. elegans*. He has shown how these genes interact with each other in the cell death process and that corresponding genes exist in humans.

Programmed cell death

Normal life requires cell division to generate new cells but also the presence of cell death, so that a balance is maintained in our organs. In an adult human being, more than a thousand billion cells are created every day. At the same time, an equal number of cells die through a controlled "suicide process," referred to as programmed cell death.

The seminal breakthrough in our understanding of programmed cell death was made by this year's Nobel Laureates. They discovered that specific genes control the cellular death program in the nematode C. elegans. Detailed studies in this simple model organism demonstrated that 131 of totally 1090 cells die reproducibly during development, and that this natural cell death is controlled by a unique set of genes.

The model organism *C. elegans*

Dr. Brenner realized, in the early 1960s, that fundamental questions regarding cell differentiation and organ development were hard to tackle in higher animals. Therefore, a genetically amenable and multicellular model organism simpler than mammals, was required. The ideal solution proved to be the nematode *Caenorhabditis elegans*. This worm, approximately 1 mm long, has a short generation time and is transparent, which made it possible to follow cell division directly under the microscope.

He provided the basis in a publication from 1974, in which he broke new ground by demonstrating that specific gene mutations could be induced in the genome of *C. elegans* by the chemical compound EMS (ethyl methane sulphonate). Different mutations could be linked to specific genes and to specific effects on organ development. This combination of genetic analysis and visualization of cell divisions observed under the microscope initiated the discoveries that are awarded by this year's Nobel Prize.

Mapping the cell lineage

Dr. Sulston extended Dr. Brenner's work with *C. elegans* and developed techniques to study all cell divisions in the nematode, from the fertilized egg to the 959 cells in the adult organism. In a publication from 1976, he described the cell lineage for a part of the developing nervous system, and showed that the cell lineage is invariant, i.e., every nematode underwent exactly the same program of cell division and differentiation.

As a result of these findings Dr. Sulston made the seminal discovery that specific cells in the cell lineage always die through programmed cell death and that this could be monitored in

Genetic Regulation Discoveries

©Paul Fetters for HHMI

Dr.Robert Horvitz

the living organism. He described the visible steps in the cellular death process and demonstrated the first mutations of genes participating in programmed cell death, including the nuc-1 gene. Sulston also showed that the protein encoded by the nuc-1 gene is required for degradation of the DNA of the dead cell.

Cell Identification of "death genes"

Dr. Horvitz continued Dr. Brenner's and Dr. Sulston's work on the genetics and cell lineage of *C. elegans*. In a series of elegant experiments that started during the 1970s, he used *C. elegans* to investigate whether there was a genetic program controlling cell death. In a pioneering publication from 1986, he identified the first two bona fide "death genes," ced-3 and ced-4. He showed that functional ced-3 and ced-4 genes were a prerequisite for cell death to be executed.

Later, he showed that another gene, ced-9, protects against cell death by interacting with ced-4 and ced-3, and also identified a number of genes that direct how the dead cell is eliminated. Dr. Horvitz showed that the human genome contains a ced-3-like gene. We now know that most genes that are involved in controlling cell death in C. elegans, have counterparts in humans.

Valuable for many research disciplines

The development of *C. elegans* as a novel experimental model system, the characterization of its invariant cell lineage, and the possibility to link this to genetic analysis have proven valuable for many research disciplines. For example, this is true for developmental biology and for analysis of the functions of various signaling pathways in a multicellular organism. The characterization of genes controlling programmed cell death in *C. elegans* soon made it possible to identify related genes with similar functions in humans. It is now clear that one of the signaling pathways in humans leading to cell death is evolutionarily well conserved. In this pathway ced-3-, ced-4- and ced-9-like molecules participate. Understanding perturbations in this and other signaling pathways controlling cell death are of prime importance for medicine.

Disease and programmed cell death

Knowledge of programmed cell death has helped us to understand the mechanisms by which some viruses and bacteria invade our cells. We also know that

Dr. Sydney Brenner

Wellcome Trust Sanger Institute

Dr. John E. Sulston

in AIDS, neurodegenerative diseases, stroke and myocardial infarction, cells are lost as a result of excessive cell death. Other diseases, like autoimmune conditions and cancer, are characterized by a reduction in cell death, leading to the survival of cells normally destined to die.

Research on programmed cell death is intense, including in the field of cancer. Many treatment strategies are based on stimulation of the cellular "suicide program." This is, for the future, a most interesting and challenging task to further explore in order to reach a more refined manner to induce cell death in cancer cells.

Using the nematode *C. elegans* this year's Nobel Laureates have demonstrated how organ development and programmed cell death are genetically regulated. They have identified key genes regulating programmed cell death and demonstrated that corresponding genes exist also in higher animals, including man. In *C. elegans*, the fertilized egg cell undergoes a series of cell divisions leading to cell differentiation and cell specialization, eventually producing the adult organism. All cell divisions and differentiations are invariant, i.e. identical from individual to individual, which made it possible to construct a cell lineage for all cell divisions. During development, 1090 cells are generated, but precisely 131 of these cells are eliminated by programmed cell death. This results in an adult nematode (the hermaphrodite), composed of 959 somatic cells.

Osaka University

Aiming to Live Locally, Grow Globally

Since its foundation in 1931, Osaka University has supplied Japanese society with a great number of women and men of high talent. Now, the university's goal is to become a "university of world caliber" by fulfilling its motto "Live Locally, Grow Globally."

In the twenty-first century as information technology develops at a tremendous speed, globalization is advancing into all areas of our lives, bringing competition and cooperation on a global scale. For Japan to maintain its status as an advanced nation in this age of rapid change, the university believes that it must cultivate men and women capable of producing cultural and scientific results that will benefit the six billion people living on this planet.

In the words of Osaka University President Tadamitsu Kishimoto, "As we enter the twenty-first century, it becomes increasingly important for people to think on their own about what they want to and can achieve in this world. Merely graduating from a good university or getting a

Osaka University President Tadamitsu Kishimoto is currently Japan's leading scientist in the field of life science, specifically in immunology, and has made fundamental contributions to the understanding of cytokine functions through a series of studies on IL -6, its receptor and transcription factors. His discovery of gp130, a signal transducer in the IL-6 family of cytokines, has revealed the molecular mechanism of the functional redundancy of cytokines.

good job does not guarantee one's future. How you think and act with your education and in your profession will make a tremendous difference in your life. We want young people everywhere to break away from the protective shells of their own countries and actively explore other lands, see globalization first hand and make international friendships through real-life experiences."

First Priority Is Structural Reform

"Osaka University has long been dedicated to educating students to become citizens rich in both culture and dignity," said Dr. Kishimoto. "Now, it must also focus on providing society with persons who are not only highly skilled, but well rounded and practical. To achieve this, students must be allowed to study in departments and take fields outside the faculty they belong to. In other words, it is necessary to create a better environment for both students and faculty members to enjoy their campus life and dedicate themselves to research and educational activities."

Cooperation and co-prosperity with local communities is the second goal of the university's mission. The university has plans to build a third campus at Nakanoshima, in the heart of downtown Osaka. The new campus will offer opportunities for intellectual information exchanges, education services and research activities to the citizens of Osaka and people from all over the country and the world.

Growing Globally

The third goal for Osaka University is to "Grow Globally." It is now preparing to employ educational and research systems that comply with the international standards adopted by first-rate colleges and universities all over the world.

"The university will open its doors to more international members in all its faculties, not just those concerned with language education," said Dr. Kishimoto. "We want to encourage world-class scholars to join research activities at the university and promote holding many more international conferences and symposia."

Students from 63 countries currently studying at Osaka University come from Asia, North America and Europe. The university also encourages Japanese students to attend overseas colleges and universities for study in order to gain a global perspective.

Japan's Center for Excellence

The Center of Excellence (COE) was launched in 1995 by the Japanese government to promote new scientific research for the twenty-first century. It

Professor Kuboi Ryoichi, in his laboratory in the Graduate School of Engineering Science's Department of Chemical Science and Engineering, works with an international group of researchers to elucidate the mechanism of the stress-responsive, self-organizing system that living matter uses to evolve and maintain life.

Dr. Shigekazu Nagata, a Professor in Osaka University Medical School, also heads a group in the Integrated Biology Laboratories, Graduate School of Frontier Science, that is working on molecular mechanism and physiological roles of apoptosis. Dr. Nagata's laboratory has identified a death factor and its receptor that controls apoptosis, and showed that deregulation of apoptosis can break mammalian homeostasis, leading to cancer and autoimmune diseases. His group also elucidated the signal transduction of the death-factor-induced apoptosis by identifying specific proteases (caspases) and DNase (caspase-activated DNase).

Professor Murooka Yoshikatsu, in the Department of Biotechnology, gives researchers from Inodonesia instructions for a genetic experiment. Indonesia is just one of many nations worldwide from which students come to Osaka,

aims to create superior research centers that "promote the most advanced and creative academic research," and only global themes are accepted for research at COE.

Of the 839 projects that were submitted between 1995 and 2000, only 32 were adopted. Six were from Osaka University. They were:

- How Genetic Information is Transformed into Individual Life
- Hopes for Industrial Innovation Using Superconductivity
- Top Runner in Immunology Research
- Super Five Senses—Development of a Brain-like Sensor
- Hi-tech for Research and Development in the Next Generation
- Uncovering the Molecular Mechanisms of Incurable Diseases

Frequently Cited Researchers

ISIHighly Cited.com is a gateway to highly influential scientists and scholars worldwide. The designation "Highly Cited researcher," and inclusion in ISIHighly Cited.com is an unusual honor.

Three of the top seven Highly Cited researchers in 2001 were from Osaka University. They are: Osaka University President Tadamitsu Kishimoto in Molecular Biology and Genetics; Professor Shigekazu Nagata, also in Molecular Biology and Genetics; and Professor Masaya Tohyama in Neuroscience.

Professor Toshio Hirano, of the Department of Molecular Biology, was named a Highly Cited researcher in 2000.

Innovative Faculties Serve People of Osaka

Osaka Imperial University was inaugurated as the sixth imperial university in Japan in 1931. It started with two faculties: medicine and science. The School of Engineering was added as a third faculty two years later. Osaka Imperial University changed its name to Osaka University in 1947. In 1949, as a result of the government's education system reform, Osaka University started its postwar career with five faculties: science, medicine, engineering, letters and law. Although it is a national university, Osaka University was established in response to the requests of local industrial circles and citizens. This is reflected in the many faculties that were founded through the financing of voluntary contributors.

Unique and innovative faculties, graduate schools and research institutes have been established one after another. They include the School of Engineering Science, the first of its kind in a national university, which is situated between the Schools of Engineering and Science, and the School of Human Sciences which covers psychology, sociology and education. In 1993, Osaka University Hospital was relocated from Nakanoshima in Osaka City to the Suita campus. This move

Dr. Naoyuki Taniguchi, Professor and Chairman of the Department of Biochemistry, Graduate School of Medicine, is an internationally renowned researcher in the fields of glycobiology, and reactive nitrogen and oxygen species. He serves as a member of the JBC Editorial Eoard and was the President of the 74th Annual Meeting of the Japanese Biochemical Society in 2001. Dr. Taniguchi will be the Secretary General of the IUBMB Congress in 2006 in Kyoto. For his outstanding contributions to glycobiology, he became the first Japanese researcher to receive the International Glycoconjugate Organization Award in 2001 (See ASBMB News, December 2001, Vol. X, No. 7, Members in the News).

completed the implementation of the university's plan to integrate all major facilities into the two campuses.

Research institutes were also established in rapid succession. In addition to the Research Institute for Microbial Diseases and the Institute of Scientific and Industrial Research which existed before World War II, the Institute for Protein Research, the Institute of Social and Economic Research, and the Welding Research Institute (the current Joining and Welding Research Institute) were set up, respectively separated from their parent faculties. Added to these institutes were Nationwide Joint-Use Facilities, Intra-University Joint-Use Facilities, and the Research Center for Materials Science at Extreme Conditions, which was recently built to develop new industrial materials. In total, there are 25 centers, research facilities and laboratories in operation at Osaka University today.

April of this year saw the establishment of the Graduate School of Frontier Biosciences which is dedicated to advancing the frontiers of life science. Its chairman, Dr. Toshio Yanagida, is one of the top scientists in the field of nanobiology. The school, which brings together researchers and educators who are experts in a wide variety of disciplines, including medicine, biology, physics, and engineering, is based on the conviction that humans and animals are not merely a simple aggregate of genetic materials, molecules, and biological structures. Instead there is an ever-changing and complex system, the understanding of which necessitates a true interdisciplinary approach. The Graduate School of Frontier Biosciences consists of six main groups of laboratories and affiliated laboratories (Nanobiology, Biomolecular Networks, Integrated Biology, Organismal Biosystems, Neuroscience, Biophysical Dynamics, and Biomedical Engineering). Its goal is to nurture scientists who are well equipped to take biosciences to the next height in this top-level, active research environment, that is true to the pioneering spirit of Osaka at the center of western Japan.

Is Biology Education Locked in the Past?

By John D. Thompson, Editor

A recent report by the National Academies' National Research Council concludes that "biology education is still geared to the biology of the past."

The report, *Bio2010, Undergraduate Education to Prepare Biomedical Research Scientists,* says that a better understanding of DNA, new laboratory techniques, and greater computer power have revolutionized the field and changed the way biologists work, forcing them to develop know-how in other scientific disciplines. Math and computer models, it states, are crucial when trying to decipher the role played by a single gene among hundreds of thousands, and laser beams are being used by biologists to manipulate molecules.

To better prepare students for careers in biology, especially biomedical research, colleges and universities should re-evaluate their curricula and teaching approaches for biology majors.

"Undergraduate biology education, however, has not kept pace with these changes," according to the National Academies' report.

To better prepare students for careers in biology, especially biomedical research, colleges and universities should re-evaluate their curricula and teaching approaches for biology majors, says the *Bio2010* report. It recommends the inclusion of mathematics, physics, chemistry, computer science, and engineering in biology courses and lab experiments so that "interdisciplinary thinking and work become second nature" for biology students.

MCAT: A Constraint on Curriculum Change

Noting that many pre-med students major in biology, the report says medical school admissions requirements and the Medical College Admissions Test (MCAT) are hindering changes in undergraduate biology curriculum, in part because professors feel pressure to cover material on the test to the exclusion of other topics. Medical school admissions criteria and MCAT questions should be reconsidered in light of the reforms called for in the report.

A change in the MCAT, or in the way it is used for medical school admissions, would allow the biology curriculum to develop in a way that is beneficial to all students (including pre-med students) instead of allowing MCAT content to dictate what all students are taught.

Bio2010 recommends that laboratory courses and experiments be as interdisciplinary as possible so as to reflect the real world. Students could obtain real-world experience, as well as a deeper appreciation for how biology is applied to everyday problems, through independent research, which they should be encouraged to pursue early on in their education. Academic credit should be given for independent research done in collaboration with faculty or with off-campus researchers.

The report recommends the creation of new courses that will cover the most relevant math concepts in less time in the context of biological problems, and cites several examples of "Teaching That Works." Following are some examples of these programs.

Quantitative Life Sciences Education at the University of Tennessee

This two-semester course provides an introduction to a variety of mathematical topics of use in analyzing problems arising in the biological sciences. The goal of the course is to show how mathematical ideas such as linear algebra, statistics and modeling can provide answers to key biological problems and to provide experience using computer software to analyze data and investigate mathematical models. Students are encouraged to formulate hypotheses that test the investigation of real world biological problems through the use of data.

Each class session begins with students generating one or more hypotheses regarding a biological or mathematical topic germane to that day's material. For example, students go outdoors to collect leaf size data; they are then asked, Are leaf width and length related? Is the relationship the same for all tree species? What affects leaf size? Why do some trees have larger leaves than others? Each of these questions can generate many hypotheses, which students can evaluate after analyzing their data.

Teaching That Works On The Mechanics of Organisms

An upper-level course at the University of California, Berkeley, brings biology and engineering together. It teaches functional morphology (how things move) in terms of mechanical design principles. Organisms are intro-

duced as "Living Machines" and their abilities to fly, swim, parachute, glide, walk, run, buckle, twist and stretch are evaluated in the context of physics and engineering principles. Students learn about the different types of fluid flow, the fluid dynamic forces of drag and lift, and how organisms live on wave-swept shores. They consider how mechanical properties change during the life of an organism, and the physics of shape change in morphogenesis, among other topics.

The Flu Module at Carleton College

This organic chemistry course featured a "Flu Module" with a "capstone"—a burning question that informs and drives the curriculum. The capstone is "Why do we get the flu every year?" Because a lot is known about the viral system, this capstone provides a modern, familiar context in which

students can learn the basic chemistry of carbohydrates, proteins, molecular recognition and cell-cell interactions. The module was so successful, it is now used as a cohesive storyline throughout the entire two-semester course.

Although most second-term organic chemistry courses include the basics of carbohydrate and amino acid chemistry, most students would be hard pressed to recognize or appreciate the great importance that carbohydrates have in biochemical recognition. The flu module focuses on how the interaction of carbohydrates and amino acids allow viral invasion of cells and also how therapeutic agents can be developed. Students are able to relate complex organic molecules to biological questions and they develop the confidence to do so. The result has been a significant increase in student interest in organic chemistry.

First-Year Seminar on Plagues

The University of Oregon's first-year seminar, Plagues: The Past, Present, and Future of Infectious Diseases, helps communicate the excitement of science. It examines diseases such as malaria, bubonic plague, smallpox, polio, measles, and AIDS. In addition to the biology of the diseases, it also addresses their effects on populations and the course of history. Students investigate the conditions that influence the rate of spread of contagious diseases, and ways to prevent it. They discuss a number of ethical issues that arise in treating the sick, as well as development of policies intended to halt epidemics.

One segment of the course uses readings, discussions, computer modeling and lab activities to help students understand: (1) how the immune system works and why in some cases it doesn't; (2) why antibiotics work with some organisms but not others, and why many organisms are becoming resistant to antibiotics; (3) why so many new diseases seem to be suddenly appearing; (4) how vaccines work and why in some cases they don't; (5) how infectious diseases are transmitted; (6) why and how disease-causing organisms make humans sick; and (7) why most infectious diseases are usually not lethal.

Interdisciplinary Laboratory

All experiments in this Harvey Mudd College course include technique development, instrumental experience, question formation and hypothesis testing, data and error analysis, oral and written reporting and most importantly, the opportunity to explore in an open-ended way details of phenomena that are familiar and of interest to students. Students are paired with a different partner for each experiment, developing teamwork skills in the process.

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.

Michelle B. Arora
University of Illinois at Chicago

Lora Lee Burns
University of California, San Diego

Jerry E. Chipuk
Case Western Reserve University

Sumi Dinda
Oakland University

Matthew J. Flick
Purdue University

Sizhi Gao
University of Tennessee Health Science Center

Karen S. Gregson
University of Michigan

Felipe Jimenez, Jr.
Loma Linda University

Troy W. Joseph
City University of New York

Steve C. Lee
Loma Linda University

Herbert L. Ley III
University of Utah

Simonovic Miljan
University of Illinois at Chicago

Tamara C. Otto
University of Florida - Gainesville

Justin R. Savage
Brigham Young University

Mark L. Segall
University of Delaware

April E. Smith
University of Michigan

Colleen Tagliarino
Case Western Reserve University

H. Garrett R. Thompson
Loma Linda University

Lai Wang
University of Texas HSC at San Antonio

XinLe Wu
Case Western Reserve University

Haitao Zhang
Loma Linda University

Lab exercises include:

- Thermal properties of an ectothermic animal: Are lizards just cylinders with legs?
- Molecular weight of macromolecules: Is molecular weight always simple?
- Carbonate content of biological hard tissue: Of what are shells composed?
- An investigation of photosynthetic electron transport: How do biological systems convert physics into chemistry?

The Central Role of Faculty Development: A Proposed Summer Institute

It is often assumed that once a useful pedagogical approach is identified, it will be reproducible, easy to disseminate, and simple for another faculty member to implement in his/her home institution. The reality, according to the National Academies report, is that in teaching, as in research, faculty need to be trained to carry out new tasks and their efforts to do so need to be recognized.

The report proposes the creation of an annual summer institute dedicated to faculty development for biology professors and other science faculty to build on the ideas of *Bio2010* and foster continued innovation in biology education.

Potential topics include:

- The integration of quantitative examples into biology courses.
- Presenting examples of recent biological research that relies upon basic principles of chemistry or physics to undergraduate students.
- Ideas for exposing large numbers of students to research (how to think like a scientist) from laboratory courses to computer simulations to conceptual experiments.
- Developing teaching materials for the sharing of innovative approaches.

Incorporating emerging research on cognition and assessment (See the 1999 NRC report *How People Learn* and the 2001 NRC report *Knowing What Students Know*).

Bio2010: Undergraduate Education to Prepare Biomedical Research Scientists was sponsored by the National Institutes of Health and the Howard Hughes Medical Institute and is available for purchase from the National Academy Press by calling (202) 334-3313 or 1-800-624-6242.

by John D. Thompson, Editor

London Striving to Become Hub for Biotech Entrepreneurs

One spin-off a month, one patent a week—that is the biotech dream of three major London institutions: the University of London's Imperial College of Science, Technology and Medicine; King's College; and University College London. The big question, though, is whether London will be able to overcome one big advantage that its rivals, Oxford and Cambridge, have in abundance—space. According to a recent *Naturejobs* report, the University of London receives more investment from government and industry than either Oxford or Cambridge, but each still have a more developed biotech climate and fewer infrastructure problems.

Access to London's financial resources, business-development community, and legal expertise is a unique advantage for the city's colleges in their drive to become business incubators, as are easy access to air and rail transportation. However, the high cost of living in one of the world's most expensive cities, the difficulty of getting in and around London, and a lack of space for labs and offices are a damper on business development.

Some institutions, however, are overcoming these challenges. The University College of London (UCL), for example, has expanded its Institute of Ophthalmology, thanks to £8.8 million ($13.7 million U.S.) from the Wellcome Trust and the eye-research charity, Fight for Sight, together with £6.5 million from GlaxoSmithKline (GSK). The immunology chair set up by GSK lured AAI member Dr. Santa Ono to the institute from Harvard University. He told *Naturejobs* that the expanded institute represents "a pretty remarkable package," noting that UCL had enticed a dozen other scientists from outside the UK to the institute.

Rutgers Research Agreement Expected to Yield $4.3 Million

The Rutgers University spinoff company, Phytomedics Inc., has signed a new research agreement that will bring almost $4.3 million in grant funding from the company to the university during the next five years. Rutgers will use the funding to stimulate research on botanical therapeutics, which include botanical drugs, nutraceuticals and plant-produced novel proteins. The botanical therapeutics developed are expected to be natural, scientifically designed and optimized mixtures of plant-produced, health-promoting phytochemicals (natural chemicals in plants) that will supplement or substitute for conventional drugs. The results of the funded research are exclusively licensed to Phytomedics for commercial development and relicensing.

"For centuries people have used plants for healing," said Ilya Raskin, Phytomedics co-founder and Professor of Plant Science at Rutgers. "The 20th century gave us the 'pill option,' which diminished the historical connection between plants and disease treatment, but now, plants are poised for a comeback as sources of human health products."

Phytomedics is a Dayton, N.J.-based life sciences company that grew out of the laboratories and greenhouses at Rutgers. It focuses on human health care and plant biotechnology with the goal of discovering, developing and manufacturing new plant-based pharmaceuticals, botanical drugs and other related products. It is funded by private investors and the New Jersey Commission on Science and Technology. Phytomedics is currently taking a series of botanical drug candidates through clinical and preclinical development. It is also engaged in the manufacture of novel therapeutic proteins in plants. To date, Rutgers has received more than $2 million in grant funding from Phytomedics.

$40 Million Funds Search For Drug Synergies

Combinatorx, a biopharmaceutical company, has received $40 million in second-round funding from a variety of investors led by Flagship Ventures. The interest in the company is due to its approach to drug development that looks for synergistic effects when two or more drugs are used to fight a disease. The idea is that due to the complex nature of cellular signaling, a single drug might block one communication path that impacts a cell's behavior but there may be still be alternative paths that trigger a change in the cell. In contrast, a multi-drug approach might block alternative paths, perhaps offering a more robust way to fight a disease.

Animal and Plant Genomics Expand Job Market

Advances in plant and animal genomics hold the potential of thousands of new life science jobs in agriculture, once that industry overcomes regulatory and cultural obstacles. Fueled with billions of dollars in economic activity, the plant and animal genomics industry will have an increased need for life scientists and researchers skilled in bioinformatics and sequencing.

"Bioinformatics will be a major career area" for plant and animal genomics, said Caird Rexroad, Acting Associate Administrator of the Agricultural Research Service (ARS) of the U.S. Department of Agriculture (USDA), in a recent interview with the *Scientist*. "Folks in both public and private sectors are lining up to do some level of sequencing on most of the livestock genomes. So we'll continue to need people who understand data and how to mine it and how to put it into patterns that can match physiological and biochemical data."

According to Roger Wyse, Managing Director of Burrill & Co., a San Francisco-based venture capital firm that invests in agricultural biotech, "Job opportunities are in doing good, strong fundamental science in animal genomics. People coming into this category ought to think about doing fundamental genomics science, and their skill sets will have applications in a number of sectors." Desirable experience includes sequencing, gene mapping, gene regulation, and comparative genomics.

Biotech Drug Copycats Ready to Pounce

Generic producers are set to pounce on a goldmine of biotech medicines, with combined annual sales of around $15 billion, that are set to lose patent protection in the next few years. So far, drugs based on large biological molecules have been immune from copycat competition since most are still patent-protected and, critically, regulators in major markets have yet to set clear rules for approving generic versions.

Now, though, biogenerics are gaining a foothold in Asia, where patents on original versions have expired or patent protection does not exist, and generics firms are looking hungrily at Europe as their next major outlet. The richest prize, the U.S. market, is likely to be the hardest to crack, partly because many U.S. patents have longer life spans, but analysts say the warning lights are flashing there too.

Britain's Genemedix Plc, is one firm planning to stake an early claim in Europe.

This company, which currently sells only in China, recently completed construction of a second plant in Ireland and plans to enter the European market in about three years. Its CEO, Paul Edwards, has said that breaking into the market will not be easy, but pressure is building from healthcare providers for a system to permit generic versions of life-saving biotech drugs. He expects that biotech generics would reduce costs 40% to 50%.

Other companies reportedly evaluating the opportunities for marketing biogenerics in Europe include Novartis AG, Croatia's Pliva, BioGenerix in Germany and Swiss-based BioPartners. All expect that the new European Union guidelines on generic or "comparable" biotech drugs, which came into force in March this year, will allow the European Medicines Evaluation Agency to set a clear route to market.

University of Maryland Grants License for Vaccine Delivery

DNA Bactofection, a novel technology for introducing genes into cells using live, attenuated invasive bacterial vectors, has been licensed to Microscience Ltd. by the University System of Maryland (USM). The agreement gives the company exclusive rights to the delivery of DNA, using any strain or serovar of *Salmonella enterica*, in all fields except for delivery of HIV antigens.

Microscience, based in Berkshire, United Kingdom, will use its proprietary attenuated *Salmonella serovar Typhi* and *serovar Typhimurium* derivatives to deliver a range of DNA antigens for treatment of viral diseases and cancers and prevention of bacterial infections. The potential of Microscience's proprietary oral delivery system as vehicles for DNA vaccines was raised by a recent report of positive immune response and lack of adverse reactions in healthy volunteers after their oral immunization with Microscience's *Salmonella serovar Typhi* and *serovar Typhimurium* derivatives.

On Taking the King's Shilling

By Peter Farnham, ASBMB Public Affairs Officer

In the British army during the Napoleonic era, enlisting was referred to euphemistically as "taking the king's shilling," after the tradition of presenting a new recruit with a shiny new shilling once he had made his mark on his service papers. The recruit's acceptance of the shilling symbolized the subjugation of his personal wishes to that of the king, who he now served.

The term "taking the king's shilling" has evolved over the years into a reference to the unwritten requirement that political office-holders publicly adhere to administration positions even if they do not personally agree with those positions. An appointee's punishment for failure to keep this agreement may not involve being tied to a grate and flogged with the cat o' nine tails, but it is still severe, by Washington standards—almost always involving dismissal or eventual resignation.

With this as background, let us consider a letter sent to Senator Ron Wyden (D-OR) on September 17 concerning S.2817, the Senate version of the National Science Foundation reauthorization bill. This bill provides a 5-year authorization for the NSF, including generous funding for its research and education programs. Most of the science community supports it in principle (although it is not without serious flaws), as it authorizes the doubling of the agency—a policy goal ASBMB and a host of other scientific societies are supporting.

However, the letter in question states that "…we *oppose* S.2817 in its current form…." The letter then goes on for two more pages listing flaws in the bill, including the authorized funding levels—far more generous than those proposed by the administration in its own NSF authorization bill, sent to Congress in May.

Who signed this letter, one might ask? Office of Management and Budget Director Mitch Daniels? President Bush himself? Guess again. The person signing the letter was the agency Director herself, Dr. Rita Colwell.

We obtained a copy of this letter on September 19, and a story about it appeared in the Washington science press on October 1. The reaction was predictable. Some viewed the letter as a betrayal, and there were mutters that Dr. Colwell should have resigned rather than sign it.

But others took a more philosophical view. Dr. Sam Rankin, Chairman of the Coalition for National Science Funding—the largest coalition supporting NSF—characterized the resignation talk as "pretty tough. What was she supposed to do? She's an administration official and has to support administration policy, at least publicly. The Hill shouldn't be surprised to receive a letter such as this from the administration."

A longtime observer of these matters gave us a tutorial on how these letters get drafted. "OMB calls you up and tells you they want a letter," we were told. "We draft a pretty minimal letter and send it back to OMB, and they send it back to us with tougher language and more criticisms. It's a negotiation, but OMB holds all the cards. I can tell you, signing these letters is very painful, but an agency head shouldn't resign over it—you lose your platform if you do that. Every agency head has to support the administration position concerning their agency when they interact with Congress. It's just a fact of life. It isn't a big deal."

So was resignation the only alternative? Yes and no, we were told. Agency heads who do not publicly support administration policy "wouldn't be fired immediately, but they aren't viewed as team players. So, they lose any influence they had, and almost always end up leaving, sooner rather than later."

Congress has been paying a lot of attention to NSF this year—a sea change from previous years, when it languished near the bottom of most congressional priority lists. But, now that the doubling campaign for the National Institutes of Health is nearing fruition, many in the scientific community are looking to the next big challenge—increasing funding for the sciences that did not reap the benefits of congressional largesse enjoyed by biomedical research since 1999.

It is thus predictable that as NSF rises in importance in Congressional opinion, more attention gets focused on matters involving it that once were only of interest to the denizens of inside-the-beltway wonkery. And so a routine letter to a Senate committee chairman expressing the administration's views about an authorization bill that no one believes Dr. Colwell holds personally suddenly takes on a life of its own and becomes a much larger issue than it would have been in earlier years.

So, when one accepts the king's shilling, one implicitly agrees to play by the king's rules or suffer the consequences—resignation or dismissal having replaced flogging these days (but no less painful for that). To resign or not over a matter of principle is a decision each of us might someday have to weigh. Time will tell if Dr. Colwell made the right choice in this case.

However, for all the fuss, the incident is a positive sign for NSF. The agency is, at long last, becoming important enough to attract this kind of attention.

Career Opportunities

MOLECULAR BIOLOGIST:

Plan and conduct lab experiments in a high throughput commercial lab to conduct detection of genetically modified organisms. Perform genomic DNA isolation and purification, DNA sequence analysis, microarray (DNA biochip) exp., Taqman (real time PCR) assay and statistical analysis of data for quality control. Advance degree required plus two or more years experience in a molecular genetics laboratory. Resume to Genescan USA, 101 Woodland Hwy, Belle Chasse, LA 70037

NEW SALLIE ROSEN KAPLAN FELLOWSHIP for Women in Basic, Clinical, Population and Prevention Science National Cancer Institute

The Sallie Rosen Kaplan Fellowship is a new opportunity for women postdoctoral scientists in cancer research, made possible by a generous bequest to the Foundation for NIH (FNIH). Candidates for the Kaplan Fellowship must possess a doctoral degree, have less than 5 years postdoctoral research experience, and have U.S. citizenship or U.S. permanent residency (green card). Fellowship training at the NCI can serve as a first postdoctoral assignment, or offer more experienced postdoctoral scientists an opportunity to further their training. Program duration is normally 2 to 5 years.

NCI's Maryland campuses boast the best funded and equipped research facilities in the United States. Postdoctoral fellows have the opportunity to interact with internationally renowned scientists from a wide range of disciplines. Starting fellowship stipend is $35,000 to $45,000 commensurate with level of experience. Kaplan Fellows will receive first-year stipend augmentation of approximately $10,000. Health insurance is provided and optional family insurance coverage is available.

Applications and supporting letters must be received by February 1, 2003. Selected candidates will be notified May 1, 2003. Applicants are strongly encouraged to apply online. For important application criteria information and instructions to apply online or by mail for this special opportunity, please go to our training and employment website http://generalemployment.nci.nih.gov or contact: Mr. Lee McPhatter, phone: 301-496-4796, fax: (301) 451-6238, email: lm148g@nih.gov

NCI is an Equal Employment Opportunity and Affirmative Action Employer

CHAIR OF PHYSIOLOGY David Geffen School of Medicine at UCLA

The David Geffen School of Medicine at UCLA invites applications for Chair of the Department of Physiology. The successful candidate must have an exceptional record of research accomplishment in Physiology or a related discipline and a commitment to medical and graduate student education.

The Department is committed to integrating genetic and molecular approaches to physiological and biophysical problems with medical relevance. The Department has international stature with particular strengths in cardiovascular, neuro-, and gastrointestinal physiology and biophysics. The position provides a unique opportunity to define physiology in the 21st century.

Nominations or letters of interest and curriculum vitaes should be sent to: Physiology Chair Search Committee, c/o Jeanette Lim, David Geffen School of Medicine at UCLA, 10833 LeConte Avenue, 12-138 CHS, Los Angeles, CA 90095-1722. UCLA is an Equal Opportunity/Affirmative Action Employer.

EXECUTIVE DIRECTOR Federation of American Societies for Experimental Biology

Quick Leonard Kieffer is currently recruiting for a new Executive Director for the Federation of American Societies for Experimental Biology (FASEB).

Located in Bethesda, MD, FASEB is a coalition of 21 independent Member Societies representing the interests of biomedical and life scientists. The purposes of the Federation are to bring together investigators in biological and medical sciences represented by the Member Societies; to disseminate information on the results of biological research through publications and scientific meetings; and to serve in other capacities in which the Member Societies can function more efficiently as a group than as individual units.

The Executive Director reports directly to the President/Board and is the chief administrative officer of the corporation, responsible for implementing financial, publication, advisory, public relations, educational, and other programs and policies approved by the Board. He/she provides leadership and direction to approximately 110 professional, technical and clerical support staff and manages an annual operating budget of $14.9 million.

Qualified applicants should have executive/administrative experience with a record of achievement and leadership in academic, association or other nonprofit organizations. The ideal candidate will be a distinguished clinician/researcher with proven administrative and leadership capabilities, excellent interpersonal skills, knowledge and understanding of the legislative process, knowledge of current trends/issues facing the biological and life sciences, and a strong sense of diplomacy. An advanced degree (M.D., Ph.D.) is highly desirable.

For additional information, please contact:

Robert Kuramoto, M.D., or Zack Reynolds of Quick Leonard Kieffer by phone: 312-876-9800 or email: rkuramoto@qlksearch.com, zreynolds@qlksearch.com.

FASEB is an Equal Opportunity Employer

Calendar of Scientific Meetings

DECEMBER 2002

Biochemical Aspects of Health and Disease
Biochemical Society Christmas Meeting

December 16-18 • Imperial College, London
Abstract deadline: October 7
Early registration deadline: November 4
Contact: Meetings Office, Biochemical Society,
59 Portland Place, London W1B 1QW
Ph: +44 (0)20 7580 3481
Fx: +44 (0)20 7637 7626
Website: http://www.biochemistry.org/meetings/

13th International Conference on Genome Informatics

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

JANUARY 2003

18th Enzyme Mechanisms Conference

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

Apoptosis 2003: From Signaling Pathways to Therapeutic Tools

January 29-February 1 • European Parliament Conference Center, Luxembourg
Contact : Marc Diederich; Ph : + 352 46 66 44 434
Fx : + 352 46 66 44 438; Email :meeting@cu.lu

FEBRUARY 2003

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

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

MARCH 2003

Keystone Symposium, Proteomics: Technologies and Applications

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

APRIL 2003

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

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

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

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

MAY 2003

Proteomic Solutions in Cellular and Developmental Biology and Medicine

May 2–4, 2003 • Stowers Institute, Kansas City, Missouri
Contact: Kelly Gull; Tel: 301-634-7145; Fax: 301-634-7126
Email: kgull@asbmb.faseb.org; Website: http://www.asbmb.org

10th Undergraduate Microbiology Education Conference

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

JUNE 2003

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

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

ECM IV: Bone Tissue Engineering

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

JULY 2003

FEBS 2003 Meeting on Signal Transduction

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

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

July 18-20 • University of Toronto, Canada
Contact: Kelly Gull; Ph: 301-634-7126; Email: kgull@asbmb.faseb.org
Website: 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

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

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

16th International Mass Spectrometry Society Conference

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

SEPTEMBER 2004

Fourth International Conference on Relaxin and Related Peptides

September 5-10 • Jackson Hole, Wyoming
Email: relaxin-2004@ad.uiuc.edu
Website: http://www.life.uiuc.edu/relaxin2004/

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

Department Heads Take Note:

ASBMB Offers Free Membership to New Ph.D.s

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

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

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

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

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