

## HIGHLIGHTS OF THE YEAR

Each of the existing divisions of the Laboratory had a busy and successful year with exciting developments on many fronts, and expansion of our research and education efforts into new arenas. In addition to the formation of the new Watson School of Biological Sciences, new research initiatives in neurobiology were under way. We also began an expansion of our research facilities on our main campus and at a nearby technology center, and we worked with New York State to develop a nearby Biotechnology Park. Coupled with our existing activities, these initiatives will ensure that the Laboratory remains at the forefront of research and education as we enter the next millennium.

### Research Highlights

The research program at Cold Spring Harbor Laboratory continues to be strong and productive. Advances have occurred in cancer research; the neuroscience program has continued to grow; and plant biology has persisted as a powerful cornerstone of research. The bioinformatics initiative reported last year has proven to be an invaluable asset to the Laboratory and has been expanded, in terms of its scientific staff and the development of advanced courses on the use of computers to solve biological problems. There also continues to be important research on basic cell biology that advances our knowledge of the most fundamental aspects of life.

### *Cell Biology*

Last year, Tatsuya Hirano and his colleagues reported the discovery of condensins, protein complexes that work to physically compact chromosomes in preparation for cell division. This year, Hirano and his colleagues reported the identification of cohesins, other protein complexes that keep together the two parts of newly replicated DNA (sister chromatids) until they are split and transported into two daughter cells during mitosis. Condensins and cohesins both contain a subset of related components called the SMC (structural maintenance of chromosomes) proteins. The two SMC protein complexes help to ensure that the genetic information encoded in DNA that has been replicated segregates evenly during cell division. Not surprisingly, these proteins are conserved in bacteria and eukaryotes, which include human cells, and it is remarkable that such important proteins have, until recently, eluded cell biologists.

During the period between one cell division and the next, cells perform essential functions as part of tissue. One of the most important functions is the process of controlling which genes are expressed and which are silenced. This was the topic of this year's Symposium (described below). Nouria Hernandez studies how a particular class of genes within the genome is transcribed into small nuclear RNA molecules (snRNAs). The snRNAs play several roles in the cell, but their main job is to organize and participate in the complex machinery that processes the RNA that is transcribed from other genes to produce the messenger RNA (mRNA) that will then produce proteins. Like regulatory mechanisms for all genes, many pro-



N. Hernandez

teins bind to each snRNA gene promoter (the regulatory region of a gene), thereby controlling the expression of the snRNA genes.

In her studies on the mechanisms of gene control in human cells, Nouria and her collaborators have characterized SNAP<sub>c</sub>, a molecular complex made of five protein subunits that helps to direct transcription of genes that encode snRNAs. Recent results have demonstrated that SNAP<sub>c</sub> cannot bind to the promoter in the absence of an activator protein that binds to DNA adjacent to the SNAP<sub>c</sub> binding site. SNAP<sub>c</sub> and the activator cooperate to trigger gene transcription by direct protein-protein interactions. The activator is a protein called Oct-1, an activator of other genes—including those in the herpes simplex virus family—and the subject of research in Winship Herr's laboratory. The observation that SNAP<sub>c</sub> and the activator cooperate was striking because Nouria had shown previously that SNAP<sub>c</sub> also binds to another protein that binds to gene promoters, the TBP protein, and the two cooperate to activate gene transcription. The protein-protein interactions between Oct-1 and SNAP<sub>c</sub> and between SNAP<sub>c</sub> and TBP both involve the inactivation of regions of the proteins that prevent promoter DNA recognition. Thus, Nouria and her colleagues may have uncovered one of the mechanisms—if not the mechanism—of how activators of gene transcription cooperate to control the expression of genes in cells.

## **Cancer**

The breast cancer tumor suppressor gene *PTEN*, identified in 1997 by Michael Wigler's lab at CSHL in collaboration with Ramon Parsons of Columbia-Presbyterian Medical Center, has now been shown to be involved in many types of cancer. From the sequence of the protein, it was suspected that the gene product would prove to be involved in removal of phosphate groups from substrate proteins. A collaboration between Mike Wigler's lab and Nick Tonks' lab, then, was a natural.

Nick studies protein phosphorylation and its role in signal transduction, the process whereby extracellular signals are transmitted into the cell to control all manner of events. In fact, Nick helped pioneer studies of dephosphorylation, the removal of phosphate groups on tyrosine residues in proteins. A protein's condition (phosphorylated or dephosphorylated) helps to determine whether it is active or inactive. Phosphorylation and dephosphorylation regulate approximately one third of all proteins in a cell.

To pursue the function of the PTEN protein, Tonks and postdoctoral fellow Mike Myers collaborated with Javor Stolarov of the Wigler lab and Peter Downes of the University of Dundee to determine that the *PTEN* gene does encode a regulator of phosphorylation. But it turned out to be a poor enzyme that used proteins containing phosphates. After much investigation, its key target for tumor suppression was found not to be a phosphoprotein, but rather a membrane phospholipid called PIP<sub>3</sub>. PIP<sub>3</sub> functions in a variety of cellular responses related to cancer, including signaling from cell surface receptors to control whether a cell survives or undergoes cell death, or apoptosis. Apoptosis is the cellular equivalent of a suicide mechanism that, when triggered by serious DNA damage or external signals, causes a cell to self-destruct. Apoptosis is a natural self-defense mechanism against cancer; it rids the body of abnormal cells and prevents their replication.

The finding that the PTEN protein dephosphorylates PIP<sub>3</sub> is the first to indicate that mutations in a gene encoding a lipid phosphatase are directly linked to cancer. Mutations in *PTEN* occur in breast cancer, glioblastoma, prostate cancer, and endometrial cancer. In addition, mutations in *PTEN* are found in several disorders predisposing to cancer, including Cowden's

Syndrome, Lhermitte-Duclos disease, and Bannayan-Zonana syndrome, all of which are characterized by the formation of multiple benign tumors and an increased incidence of malignant tumors.

Several labs at Cold Spring Harbor continue to study apoptosis. Because apoptosis is a natural defense against cancer and causes the death of cells with serious genetic defects, it has become clear that the deregulation of apoptosis contributes to cancer. Yuri Lazebnik's lab is studying the molecular machinery that effects apoptosis and the signals that trigger it. His goal is to determine how this cell death mechanism—present in all cells—can be selectively reactivated to destroy cancer cells.

Yuri is following up on the observation that expression of certain oncogenes can either induce apoptosis or sensitize cells to the stimuli that cause apoptosis. It intrigues him that some of the cellular events that cause cancer may also be used to kill cancer cells.

All cells have the apoptotic machinery, but healthy cells lack the signals to trigger it. Oncogene expression naturally generates a signal that can activate apoptosis. When this signal is interrupted and fails to reach the apoptotic machinery, cancer cells can survive and become resistant to chemotherapeutic drugs. Yuri's plan is to develop a way to recouple the oncogenic signal and the apoptotic machinery in order to kill the otherwise apoptosis-resistant cells.

To understand the molecular mechanisms that link oncogene-induced signals and the apoptotic machinery, Yuri studies caspases. This family of cysteine proteases—enzymes that cleave, or cut, other proteins—comprise an essential component of the apoptotic machinery. Caspases are activated at the onset of apoptosis and they cause cell death by cleaving several proteins in a coordinated manner. Yuri's objective was to determine how oncogenic transformation triggers apoptosis, specifically to identify which caspases become activated.

Yuri's lab developed a cell-free system to study the apoptotic machinery and its activation by oncogenes. Through the use of this system, Yuri's lab has identified the caspase that is activated by oncogenes, caspase-9. What occurs in tumor cells, however, is that other mutations somehow prevent or bypass the activation of caspase-9.

Scott Lowe also studies apoptosis and has made significant contributions to the field with his work on the tumor-suppressor gene *p53* and its role in programmed cell death. Scott and CSHL adjunct investigator David Beach have identified another way in which tumor-suppressor genes, such as *p16* and *p53*, can prevent cancer. The *p53* protein has long been recognized as an important tumor suppressor, because it plays a vital role in programmed cell death. When cells lack active *p53*, programmed cell death (including oncogene-dependent apoptosis) does not occur and cells are robbed of an important defense mechanism against cancer. In their recent studies, Scott and David discovered that cells carrying the normal forms of the tumor suppressor genes *p16* and *p53*, as well as the oncogene *ras*, are prevented from becoming tumor cells by another mechanism. They found that the proteins *p16* and *p53* can also induce cell senescence—a state in which cells cease to divide but do not die.

Then in July, Scott, in collaboration with Charles “Chuck” Sherr, a Howard Hughes Medical Institute researcher at St. Jude's Children's Research Hospital in Memphis, Tennessee, reported that another gene, *p19 (arf)*, also functions like a tumor suppressor. *p19 (arf)* plays an important role in the pathways that lead to programmed cell death and senescence, the same pathways that are triggered by the normal *p53* gene. Together, Scott's recent studies indicate that two genes, *p16* and *p19* (which are physically overlapping in the genome of a cell), defend against cancer in different ways. *p16* works with *p53* (*arf*) to induce cell senescence, and *p19 (arf)* works with *p53* to induce programmed cell death as well as senescence. Both pathways can prevent tumor growth, and the loss of either pathway can promote tumor progression.

In recent studies, Scott and his colleagues have shown that APAF-1 and caspase-9 are downstream from the *p53* gene in the p53-dependent apoptosis pathway. Thus, loss of *p53*, which occurs in more than half of all cancers, or of *p19 (arf)*, which is mutated in many of the other cancers, eliminates a major signaling pathway to the cell death machinery in tumor cells. This may explain why these tumor cells eventually become resistant to chemotherapeutic drugs that are used to treat cancer by inducing cell death. Tumor cells lacking the proteins encoded by these genes cannot signal the cell death machinery to kill the cells; thus, the tumor continues to grow. It now seems clear that we now must find ways around this defect in tumor cells.

Greg Hannon's laboratory studies another aspect of oncogene-dependent cell death. He is looking for mutations that might inactivate this defense mechanism and allow the formation of a tumor and has developed a method for identifying such genes. A visiting scientist in Greg's lab, Roberta Maestro from the CRO in Aviano, Italy, identified a gene called *twist* using the screening method that Greg developed. The Twist protein may help to regulate diverse developmental processes; it was already known that mouse embryos lacking the *twist* gene die before birth. In 1998, Greg's lab found that Twist protects cells in culture from apoptosis. Because of these observations, Greg suspected that the *twist* gene might be a part of the *p53* pathway. Indeed, a variety of experiments confirmed that the Twist protein could interfere with activities of *p53* that are essential for tumor suppression.

The observation that the Twist protein might affect the p53 tumor suppressor pathway prompted Greg and his collaborators to search for mutations in the *twist* gene in human cancers. They found that *twist* is frequently expressed in rhabdomyosarcomas, a cancer of the bone, soft tissues, or connective tissue (e.g., tendon or cartilage) that is the most common soft-tissue cancer in children. It begins in the soft tissues of muscle and is thought to derive from skeletal muscle precursor cells that fail to complete terminal differentiation. The *twist* gene is not expressed in differentiated muscle cells, but in 50% of rhabdomyosarcomas, they found that *twist* expression is maintained.

In collaboration with Larry Kedes of UCLA, Greg and Roberta have demonstrated a likely role for Twist in this tragic childhood disease. The Twist protein interacts with a component of the p53 pathway, called p300, a gene transcription regulator. They also have provided the first evidence that Twist can disable cells' ability to commit programmed cell death, thus promoting the development of cancerous growth.



G. Hannon

### **DNA Microarray Technology**

One of the most powerful new techniques in modern biology, called DNA microarrays, or DNA chip arrays, emerged from recent studies on yeast at Stanford University. During the past year, we have been working to merge this method with techniques developed at the Laboratory that were designed to identify mutations in human cancers. Mike Wigler has entered into a collaboration with Larry Norton, M.D., of Memorial Sloan-Kettering Cancer Center in New York City, to use DNA chip technology to look for genes that are mutated in breast cancer.

To use chip technology, researchers place fragments of different DNA samples on a glass microscope slide in a grid of very high density. They expose the slide to labeled DNA, or a complementary DNA (cDNA) copy of mRNA, which hybridizes with the DNA on the glass slide, and then analyze the amount of hybridization in each spot on the slide. The results are color-coded,

so that the most active genes (with the greatest degree of hybridization) are colored red, and genes that are repressed (hybridized the least) are colored green. Alternatively, the experiment can be set up so that genes that are overrepresented in cancer cells are labeled red and genes that are missing in the tumor cells are labeled green. Mike and his associates are using the method to compare the genes in healthy versus cancerous breast tissue and at various stages of breast cancer progression.

This year, thanks to a \$300,000 grant from the Lillian Goldman Charitable Trust through The Breast Cancer Research Foundation in New York City, Mike installed state-of-the-art microarray equipment in his Demerec Laboratory. His lab will now be able to analyze tremendous numbers of DNA samples from breast cancer tissue. The emerging DNA chip technology should make possible the development of better methods for the diagnosis and treatment of breast cancer, because it will allow researchers to design treatment aimed at the specific mutations present in each patient.

Just as Mike uses the microarray technology to study gene activity at various points in disease progression, Bruce Futcher is using it to locate and characterize genes whose activity is determined by the stages of the cell division cycle in yeast.

Bruce is collaborating with David Botstein and Patrick Brown of the Stanford University School of Medicine. In 1998, they used DNA microarray technology to find, characterize, and analyze yeast genes whose activity is regulated by the cell division cycle. In just four months, the two labs located and characterized about 800 yeast cell-cycle-regulated genes. During the past 15 years, many scientists had identified and characterized only 103 cell cycle-regulated genes in yeast, revealing the power of the new technology.

Microarray technology has yielded an unprecedented increase in the rate of accumulation of data. The microarrays used in Bruce's cell cycle experiments contained 6000 discrete DNA fragments, each of which represents one of the approximately 6000 genes in yeast. Michael Zhang, one of our bioinformatics experts, is using the power of computational analysis to sift through the enormous amounts of data.

Knowing the set of 800 yeast genes that are regulated by the cell cycle has provided a wealth of information that is contributing to a more complete understanding of cell division. For example, researchers now have an overview of the different kinds of biochemical processes that change with cell division. They can study the clusters of dozens or hundreds of coregulated genes that cooperate in these processes and probe the molecular mechanisms that allow the different clusters of genes to be turned on one after another in an orderly way. Researchers can begin to identify the functions of uncharacterized genes by analyzing the known functions of genes in the same coregulated cluster. The combination of biochemical studies and microarray analysis is destined to lead to an ever-greater understanding of the vital cell process of cell division in yeast—and in higher organisms.

Through the acquisition of a small campus in nearby Woodbury—a building of 60,000 square feet located on 12 acres—the Laboratory has positioned itself to further exploit and develop microarray technology. The property was previously owned by the American Institute of Physics and will provide the Laboratory with much-needed space for expansion of high-technology research, such as genome sequencing and microarray research.

In structural biology, Leemor Joshua-Tor is continuing her studies of the three-dimensional structure and activity of the enzyme bleomycin hydrolase (BH), which is similar in humans and yeast. (Researchers discovered human bleomycin hydrolase [hBH] in the 1970s when they realized that it detoxifies the anticancer drug bleomycin and causes resistance to the drug.) Leemor has found that yeast BH interacts with its substrate (the bleomycin molecule) in an unusual way.

Six molecules of BH come together to form a barrel-shaped structure with a channel in the center. One end of each molecule of the enzyme projects toward the central channel and into the active site region of the enzyme. This spatial configuration allows the enzyme to interact specifically with bleomycin.

Leemor, in collaboration with Stephen Johnston of the University of Texas-Southwestern Medical Center, recently solved the three-dimensional structure of hBH, in its wild type and a mutant form. Knowing the three-dimensional structure of a molecule often provides important clues about its function. Although the structure of hBH was predictably similar to that of yeast BH, Leemor's lab found a striking difference in the human molecule's electrostatic charge: The inner channel of the yeast BH has a strong positive charge, but the same region of the human enzyme has a slight negative charge.

Like the enzymes that Yuri studies, bleomycin hydrolase is a protease—an enzyme that cleaves other proteins. BH deactivates bleomycin, the anticancer drug, by cutting each bleomycin molecule at a particular place. Although most proteases determine the cleavage site on their targets (usually proteins) by finding a specific point in the target molecule's amino acid sequence, Leemor found that the point at which BH cleaves its target is determined not by an amino acid sequence, but by the relative positions of the negative and positively charged ends of the substrate. The protease acts like PacMan, eating the substrate protein away from its end.

### **Neuroscience**

Surprisingly, in 1998, several labs reported a possible link between bleomycin hydrolase and Alzheimer's disease. A group led by Robert Ferrell and John Lazo at the University of Pittsburgh found that individuals with two copies of a particular allele (type) of the BH gene were four times more likely than the average person to develop sporadic Alzheimer's disease. Then, Carmela Abraham of Boston University and her collaborators purified BH from the brains of individuals with Alzheimer's disease while looking for amyloid precursor protein (APP), a protein that is processed to yield  $\beta$ -amyloid, a component of the plaques that occur in the brains of Alzheimer's patients.

Leemor's lab is currently studying the connection between BH and APP processing, specifically the relevance of a BH polymorphism suspected of playing a role in this process. In addition, her lab is continuing its studies of the protease's effect on the anticancer drug bleomycin and ways to ameliorate the resulting drug resistance in order to preserve the drug's anticancer activity.

Roberto Malinow, a senior neurobiologist who was recently appointed by the Board of Trustees to the Harrison Chair of Neuroscience, has also discovered a possible link between his research and Alzheimer's disease.

Scientists at other institutions have shown that mutations in the presenilin 1 gene (*PS1*) are associated with the most common cause of familial Alzheimer's disease. Roberto's lab is studying mice that carry a mutant form of the *PS1* gene—the same mutation that some human Alzheimer's patients carry. These mice provide an experimental model for studying certain molecular aspects of Alzheimer's disease. (Although the mice do not display the behavioral changes characteristic of Alzheimer's patients, this is not unexpected, as the same mutation in humans is present at birth, yet 30 or more years typically pass before the onset of the behavioral manifestations of the disease.)

Roberto's lab studies long-term and short-term potentiation (LTP and STP)—a strengthening of synaptic communication between neurons that occurs when neurons are repeatedly



stimulated at high frequency. Roberto's lab found that LTP and STP are notably—and unexpectedly—elevated in brain cells of the *PS1* mutant mice. Surprisingly, synaptic inhibition, which suppresses LTP and STP as well as the firing of electrical impulses, was also enhanced in the mutant mice. This increased synaptic inhibition may represent a compensatory homeostatic response to the increased ability to produce LTP and STP. Roberto's lab then further inhibited synaptic activity in these *PS1* mutant brain cells by applying the drug benzodiazapine, which returned synaptic potentiation (LTP and STP) to normal levels.

Coincidentally, clinicians in Sweden recently reported that the regular use of the benzodiazapines Xanax and Valium correlated with a markedly reduced incidence of Alzheimer's disease in the patients studied. Although the mechanism of the drugs' action is known as it relates to their traditionally prescribed use as anti-anxiety agents, it was not clear how these drugs affected the likelihood of developing Alzheimer's disease. Roberto's studies of the relationship between the molecular biology of the *PS1* gene and the activity of the benzodiazepines may reveal a greater understanding of ways to prevent or treat Alzheimer's disease.

Roberto's lab is also continuing to study factors involved in neuronal plasticity, i.e., the ways in which neurons change their activity or shape during development or as a result of learning, trauma, or other events. The researchers have developed improved tools for studying the activity of brain cells and the connections between them, called synapses. One new method developed by the Malinow lab involves the introduction, using a viral vector, of recombinant proteins whose movement in cells and at synapses can be monitored by electrophysiology and imaging techniques. By attaching these proteins to specific molecules important for learning and the formation of memories, Roberto can track the movement and activity of important nerve cell factors. The studies also utilize the sophisticated two-photon laser-scanning imaging system that Karel Svoboda brought to CSHL in 1997, as well as high-resolution electron microscopy, to track the movement of other important proteins in the brain during learning.

Karel, in collaboration with Roberto and postdoctoral fellow Mirjana Maletic-Savatic, used the new imaging system to observe and document the effect of synaptic stimulation on the shape of brain neurons. Karel custom-built a two-photon laser-scanning microscope to study living nerve cells in brain slices from rat hippocampus, a region of the brain that is important for the formation of memories. The researchers stimulated axons from one group of nerve cells that form synapses on a small dendritic branch of a neighboring cell—a strong but highly localized stimulus. They found that the stimulus triggers the growth of new dendritic protrusions called filopodia. Growth of filopodia begins within 20 minutes after the stimulation and continues for at least 40 minutes more. The new filopodia may ultimately form new synapses, an important phenomenon during development and learning and memory. By comparing stimulated and unstimulated dendritic regions, the researchers found that growth of filopodia evoked by strong electrical stimulation was limited to regions of the dendritic tree close to stimulated synapses.

Mirjana, Roberto, and Karel also found that the growth of dendritic filopodia requires activation of *N*-methyl-D-aspartate (NMDA) neurotransmitter receptors at the synapses under study. Other studies had shown that activation of these receptors is required for the formation of memories and for normal brain development. In the recent experiments, the blockade of NMDA receptors prevented stimulation-induced growth. Thus, synaptic transmission, and activation of NMDA receptors in particular, is required to produce this kind of dendritic growth.

In the cells affected by the synaptic stimulation, the growth of filopodia subsided about 45 minutes after the stimulus ended, but the filopodia remained, and some formed bulb-like tips which suggests that they may become functional synapses. Karel and Roberto will continue to study the structure of the outgrowths, as well as their signal transduction properties.

Meanwhile, Jerry Yin and postdoctoral fellow Marcia Belvin at the University of California at Berkeley have made a fascinating observation that suggests how and when memories are formed. Neuroscientists have long suspected that important brain functions take place while people are sleeping. Jerry and Marcia found that the activity of CREB, a protein that Tim Tully and Jerry Yin previously showed is important in memory formation, displays circadian, or 24-hour cyclical, patterns of activity. The Yin lab is trying to determine the functional connection between the nighttime peak in CREB activity and memory formation. Given what is known about memory formation in mammals, it is likely that some aspect of memory consolidation occurs at night, probably during sleep.

### ***Advanced Neuroscience Imaging***

In an exciting expansion of the Laboratory's neuroscience program, close on the heels of the establishment of the Beckman Neuroscience Center in 1992, an advanced neuroscience imaging facility is being constructed on the main campus just west of James Laboratory. The new building, named the Nancy and Edwin Marks Building, will house advanced imaging facilities for use in studies of the living brain—a great advance for neurobiology research. Karel Svoboda will use and further develop state-of-the-art laser-scanning microscopy to extend his ongoing studies of neuronal activity and synaptic plasticity in individual neurons in functioning brains of live animals. In addition, scientists from around the world will take courses in the Marks Building to learn how to use this sophisticated new technology. The imaging facility is scheduled to open in August 1999.

In another expansion of existing neuroscience facilities, the Laboratory is replacing the old visitors' cabins just north of the Beckman Neuroscience Center with a small building dedicated to computational neuroscience. The new facility, made possible by Laboratory Trustee William Murray, will be known as the Samuel Freeman Building. There scientists will use the latest computerized tools to model how the brain works.

### ***Plant Biology and Plant Genetics***

In April, Ueli Grossniklaus and his colleagues reported that *MEDEA*, a gene in the widely studied model plant *Arabidopsis*, is important for the maternal control of plant embryo development. If a plant embryo (in a seed) has inherited one mutant copy of the *MEDEA* gene from the mother plant, cells in the embryo grow excessively and the embryo dies. But if the embryo inherits one mutant *MEDEA* gene from the father plant, it lives and functions normally. Because of this difference, researchers call *MEDEA* a "maternal-effect gene," meaning that it dictates certain behavior (in this case, cell division and embryo development) only if the gene comes from the female parent. Ueli found that the function of the *MEDEA* gene product in plants resembles the *Polycomb* group of genes in animals, which are important for controlling cell proliferation and for mediating the expression of traits inherited from one parent.

Also in plant genetics, the Laboratory's role in the global *Arabidopsis* Genome Sequencing Project continues to go well. Dick McCombie's sequencing expertise and Rob Martienssen's work with the gene traps he developed with Sundaresan Venkatesan have proved to be an invaluable contribution not only to the sequencing effort, but also to the determination of gene function in this small, flowering plant. Rob continues to do research on other aspects of plant genetics as well, and he recently made an important discovery about the movement of intracellular proteins across cell membranes.



The May 1998 Genome meeting occurred in the wake of Craig Venter's surprising announcement of plans to complete the sequence of the human genome on an accelerated schedule. (Venter now heads the Celera Corporation in Rockville, Maryland.) Most of the leaders in human genome research were in attendance, which resulted in lively discussions about—and considerable media interest in—Craig's plan. The Laboratory's goal in these efforts is to produce a timely, accurate body of data that is made available to all researchers.

The Laboratory also plans to expand its genomics research program. A significant portion of the recently acquired building in high technology center in nearby Woodbury will be dedicated to genome sequencing projects. This expansion of the existing program will enable CSHL to more quickly play a role in other sequencing projects.

### **Broadhollow Bioscience Park**

The long quest to establish a suitable biotechnology park within close proximity to the Laboratory has finally been fulfilled. The new facility will allow start-up biotech companies based on CSHL research as well as research from other academic centers and companies to locate nearby and to maintain easy scientific interactions and collaboration. John Cleary, who has been a member and president of the CSHL Association and a member of the Laboratory's Board of Trustees, was instrumental in securing substantial backing for the park from Governor George Pataki and New York State, as well as the support of many local business and political leaders.

The park is located on 20 acres of land adjacent to the State University of New York (SUNY) Farmingdale campus on nearby Route 110 in Farmingdale. The Broadhollow Bioscience Park will be supervised by a separate not-for-profit organization that will be controlled by Cold Spring Harbor Laboratory and SUNY Farmingdale. Completion of the facility will enhance the transfer of innovations and discoveries in basic research to the private and public business sectors, and thereby enhance the utility of our research efforts.

### **Watson School of Biological Sciences**

As described above, another long-standing initiative came to fruition in 1998 when the New York State Board of Regents voted in November to approve accreditation of Cold Spring Harbor Laboratory as a Ph.D.-granting institution. The Laboratory is now in the process of raising funds to endow the school.

In the initial application for accreditation, the school was named the Cold Spring Harbor Laboratory School of Biological Sciences. In January, the state approved the new name for the graduate school at Cold Spring Harbor: The Watson School of Biological Sciences, named for the Laboratory's long-time Director and now President James D. Watson.

To supplement housing for Watson School students, the Laboratory recently purchased a grand old house on land adjacent to Laboratory property on Route 25A, facing the inner harbor. The house was constructed in the 1700s, and it once served as the general store and post office for Cold Spring Harbor. The house was also home to many generations of the illustrious Long Island Jones family, including Jones descendant and former CSHL Trustee Townsend Knight. The building, located at 222 Main Street in Cold Spring Harbor, was recently named the



Knight House

Knight House in honor of Townie and will serve as housing for graduate students attending the Watson School of Biological Sciences. But due to its considerably run-down condition, the house will first undergo considerable restoration.

### **Symposium LXIII**

Transcription, the copying of one strand of DNA into a complementary RNA sequence, was the topic of the 63rd CSHL Symposium, Mechanisms of Transcription. For five days, from June 3 to June 8, Grace Auditorium was filled with talk of promoters, transcription factors, and chromosome structure. In attendance were the best-known scientists in the field, as well as many younger ones.

On Sunday evening, as is customary, the Laboratory welcomed neighbors and friends for the annual public Dorcas Cummings Lecture. Ronald M. Evans, a Howard Hughes Medical Institute investigator at the Salk Institute, discussed "The Molecular Biology of Fat: Weighing the Risks," a subject of broad interest to a general audience.

Dr. Evans described the role of hormones, the signaling molecules secreted by glands and other tissues. Hormones coordinate the activities of organs and tissues by regulating gene activity. His group discovered a hormone called 15-deoxy- $\Delta$ 12,14-prostaglandin J<sub>2</sub>, which directs muscle and fibroblast cells to become fat cells. This hormone is now being used to treat type II diabetes. Evans advocated a diet with fewer saturated fats, such as a Mediterranean-style diet which is rich in legumes and grains.

Jim and Liz Watson invited Australian artist Lewis Miller to attend the annual Symposium as artist-in-residence. Miller sketched visiting scientists at meeting sessions, breaks, and at the Symposium picnic. A collection of his marvelous framed sketches now appears along the staircase in Blackford Hall.



Sketch by Lewis Miller in Grace Auditorium during the Symposium

### **Jim Watson's CSHL Anniversaries**

In addition to a milestone birthday, 1998 marked two special anniversaries for Jim Watson. It has been 50 years since his first visit to Cold Spring Harbor Laboratory as a graduate student doing summertime research, and 30 years since he became director of the Laboratory. To commemorate these events, the Laboratory held a special late-winter conference called *Pathways to Cancer*. CSHL alumnus and Trustee Ed Harlow, of Massachusetts General Hospital and Harvard University, Jan Witkowski, and I, were coorganizers.

The meeting included sessions entitled “Cancer Genetic Pathways,” “Cancer Cell Growth Controls,” and “Cancer Pathways”—a discussion of research from the cell to the clinic. But the highlight of the meeting came on Thursday evening when the BBC film *Life Story* was shown in Grace Auditorium. What an extraordinary experience it was to see Jim Watson stand before us offering his thoughtful comments on the movie that was based upon his 1968 best-selling book *The Double Helix*. The showing of the movie in the context of a modern meeting on biology highlighted how far we have come since those exciting days in 1953.

### **Banbury Center**

#### ***From Molecules to Brains—The J.P. Morgan Meeting***

The unusually broad topic of the 1998 annual Executives' Seminar weekend, sponsored by J.P. Morgan, was *Imaging: From Molecules to Brains*. Carlos Bustamante described his work using the atomic force microscope with which he images single molecules and tries to “see” how a DNA molecule is synthesized. Paul Sigler described his X-ray crystallography studies of the



Banbury meeting participants watch cells in three dimensions.

structures of large protein assemblies, and Mark Ellisman showed some remarkable three-dimensional pictures of cells taken with a powerful electron microscope. Bruce Rosen and John Gabrieli discussed their studies of the brain. We are indebted to Sandy Warner and David Deming for their continuing support of this unique occasion.

### ***Horse Genetics and the Performance of Thoroughbreds***

The 1998 Banbury Center meeting on horse genetics was stimulated by CSHL Trustee and race horse owner Charles Harris. It was his belief that the performance of racing thoroughbreds has fallen and that this decline might be related to inbreeding. Horse geneticists, scientists who study horses and humans, and thoroughbred owners and breeders considered this question and offered an in-depth analysis of the current state of the genetic map of the horse as well as ways to promote genetics research on the horse. Such policy issues have been raised at previous Banbury meetings and have been influential in stimulating funding of research in this area.

### ***Finding Individual Differences in Human Disease Genes***

One of the most important advances in human genetics came in 1980 with the development of a new method for identifying individual differences in human genes that are linked to specific diseases. The new strategy, based on small but common variations called single nucleotide polymorphisms (SNPs), has generated a great deal of excitement. Many unresolved issues remain, however, and the Banbury meeting, *Large-scale Discovery & Genetic Applications of SNPs*, tackled some of them: how to find these variations, how many will be needed for effective mapping, and how to use them. The group also discussed interesting and controversial questions of intellectual property.

## **Robertson Research Fund**

Since 1973, the Robertson Research Fund has supported Cold Spring Harbor Laboratory's scientific program. Its balance is now almost \$80 million, up from approximately \$8 million in 1973. Once again this year, Robertson funds supported labs in each of our primary fields of research—cancer, neurobiology, and plant genetics.

In 1998, Robertson funds supported cancer research by providing start-up support for new bioinformatics investigators Andy Neuwald, Andy Reiner, and Lincoln Stein and research program support for established scientists David Helfman, Michael Hengartner, Nouria Hernandez, Tatsuya Hirano, Scott Lowe, Ryuji Kobayashi, Adrian Krainer, Jacek Skowronski, David Spector, Nick Tonks, and Rui Ming Xu. In neurobiology, the fund supported research in the labs of Karel Svoboda, Holly Cline, Grisha Enikolopov, Alcino Silva, Jerry Yin, and Yi Zhong, and furthered plant research by Erich Grotewold, Hong Ma, Rob Martienssen, and David Jackson.

The Robertson Research Fund also helps to support many postdoctoral researchers, graduate students, and scientific seminars.

In addition, the Marie H. Robertson Memorial Fund, dedicated to neuroscience, gave support to Grisha Enikolopov and Yi Zhong.

## **Board of Trustees**

David L. Luke III completed a more than 12-year tenure with the Board of Trustees, and the Laboratory remains deeply indebted to him for his outstanding leadership during a time of significant growth and improvement. Very few people have devoted as much time and effort to the Laboratory as has David. His guidance has ensured that we remain a dynamic and growing institution, and the generosity of David and his wife, Fanny, has reflected their love of the Laboratory. I am most pleased that David has agreed to continue to serve the Laboratory as chair of the campaign to endow the Watson School. In November 1998, David retired as Chairman of the Board and was elected Honorary Trustee. In April 1999, he was feted at a dinner in his honor.

It is our great fortune that William Miller has stepped into David's shoes as our new Chairman of the Board. Bill, retired Vice Chair of Bristol Myers Squibb and Co., served as David's deputy and has already made major contributions to the Laboratory.

The following members of the Board of Trustees also completed their terms in 1998: John R. Reese, Arnold J. Levine, J. Anthony Movshon, and Joan A. Steitz. David H. Koch completed his term on the Board as well, and to him we are indebted for a Watson School of Biological Sciences fellowship that will endow one student per year. Thomas A. Saunders III stepped down from the Board due to other commitments, and John Cleary completed his term on the Board as he completed his term as President of the CSHL Association. During John's tenure as Association President, the organization expanded considerably and increased its support of the Laboratory's programs. John was also very helpful in the creation of the Graduate School and Broadhollow Bioscience Park and is still making major contributions as Broadhollow's chairman. The Laboratory is grateful for the guidance and input of every Trustee.

We are pleased to welcome the following individuals, who joined the Board in 1998: Charles E. Harris, chairman and CEO of the public venture capital firm Harris & Harris Group, Inc.; Leslie C. Quick, cofounder of one of the first and largest discount stock brokerage firms, Quick and Reilly, Inc.; Howard Solomon, president and CEO of the pharmaceutical company Forest



Laboratories; Susan Hockfield, professor of neurobiology at Yale University School of Medicine and dean of the Yale University Graduate School of Arts and Sciences; Rudolf Jaenisch, M.D., member of the Whitehead Institute for Biomedical Research and professor of Biology at Massachusetts Institute of Technology; Charles J. Sherr, M.D., Ph.D., Howard Hughes Medical Institute investigator and professor at St. Jude's Children's Research Hospital; and James Spingarn, senior vice president of investments at Gruntal & Co. located in Great Neck, New York, and president of the CSHL Association.

At the November 7 meeting of the Board of Trustees, the playground of the Mary D. Lindsay Child Care Center was dedicated to Honorary Trustee Wendy Vander Poel Russell. Mrs. Russell has a long and rich history with CSHL; in fact, as a small child she participated in the Lab's Nature Study program. More recently she was instrumental in securing on-site child care for CSHL.

A champion fund-raiser at the Laboratory, Wendy has been tireless in her devotion to various projects over the years, including those for Grace Auditorium, the Beckman Neuroscience building, and the Mary D. Lindsay Child Care Center. She was instrumental in establishing the Corporate Advisory Board as a supporting body for the DNA Learning Center and has been a consistent and ardent supporter of the CSHL Association Annual Fund. She began serving on the Board of Trustees in 1984 and has since served four 3-year terms including those as Secretary in 1985–1987 and 1992–1997. She has served on the Board's Development, Executive, Finance & Investment, Banbury, Building, and DNA Learning Center committees and has been a long-time member of the CSHL Association.

It was our honor to name the playground for her. What more cheerful recognition could we have offered to such an upbeat and dynamic lady?

Sadly, one of the newer members of the Board—and a long-time member of the CSHL Association—passed away in July. Mrs. Vernon L. Merrill, who assumed the position of president of the CSHL Association in February, had been an active and generous supporter of the Laboratory since 1985. She, too, was an ardent proponent of the Laboratory's initiative to establish on-site child care, and served on the Building, Development, and Executive committees for the Board of Trustees. Mrs. Merrill lost her long and valiant battle with breast cancer on July 13. Her enthusiastic involvement will be deeply missed, and the Laboratory extends deepest condolences to her husband, Robert, and their family.



V.L. Merrill

## **CSHL Association**

Following the death of Mrs. Merrill, CSHL Association member James Spingarn assumed the role of acting president of the Association. He has since been elected President. Jim has been a most enthusiastic supporter of the Laboratory's research programs and public education efforts.

On February 1, the CSHL Association held its Annual Meeting and hosted Judah Folkman as its keynote speaker. Dr. Folkman is a senior associate in surgery and the director of the Surgical Research Laboratory at Boston's Children's Hospital and Harvard Medical School. His research on anti-angiogenic factors has attracted much attention during the past year. His work is directed at stopping the development of new blood vessels (angiogenesis) in tumors as a way to shrink and eradicate them. His proposed therapy, using compounds such as endostatin and





Dr. Folkman

angiostatin, has proven successful in controlling tumors in mice. Dr. Folkman's talk was entitled "Anti-angiogenic Therapy."

On April 18, the Association hosted the Blue Hill Troupe musical group for a most successful fund-raiser. The group performed a variety of Gilbert and Sullivan operettas and joined concertgoers for a spectacular dinner in Blackford Hall following the performance.

Association members Jim and Carol Large hosted an enjoyable cocktail party at their home in Locust Valley in October in honor of the Association's major donors. Thanks to the warm evening weather and a beautiful backyard patio, much of the mingling and conversation between scientists and Laboratory supporters took place outdoors.

Everyone at the Laboratory was saddened to learn of the death of a cherished Association member and friend of the Laboratory, Mrs. Edna Davenport. Edna became involved with Cold Spring Harbor Laboratory in early 1970 when she and her husband, retired Pfizer Pharmaceutical executive John Davenport, donated generously to the Laboratory with the intention of helping initiate the tumor virus research program in James Laboratory. Their initial gift enabled the Laboratory to execute a much-needed expansion of James Lab, and after John passed away in 1988, Edna's continued generosity became a cornerstone of support for the Laboratory's young scientists through the CSHL Association. While we sense a terrible loss in Edna's passing, we are even more sympathetic to her son Peter and daughter Linda Spire and their families for their loss.



The Blue Hill Troupe musical group

## **DNA Learning Center**

The DNA Learning Center experienced record growth in 1998, with income increasing by 59%, to \$1,393,100. The greatest single source of growth in 1998 was funding from the Josiah Macy, Jr., Foundation to create "DNA from the Beginning," an online, animated primer on genetics. Targeted at the level of a bright teenager, the site uses a number of multimedia elements and tools—animation, video clips of scientists and historians, archival photographs, audio glossary, interactive quizzes, and powerful navigation tools—to let users master genetics at their own pace and according to their own learning style. The first installment of DNA from the Beginning was a resounding success, with more than 10,000 log-ins during its first eight weeks on the World Wide Web. Four additional releases are planned in 1999–2000.

## **Cold Spring Harbor Laboratory Press**

In 1997, the productivity of CSHL Press was improved through management restructuring and investment in technology. These gains were consolidated in 1998 and resulted in improved financial performance.

The journals, *Genes & Development (G&D)*, *Genome Research*, and *Learning & Memory*, all improved in several ways. Scientists submitted more and better manuscripts for publication and each journal published more pages than ever before. *G&D* led the way with a 30% increase in the number of submitted manuscripts. *G&D* continues to rank in the top ten of all journals in the life sciences, in terms of the number of citations reported by the Institute for Scientific Information. All three CSHL journals are published online as well as in print, and online users now have access to several improved services, including E-mail alerting services. The three journals either maintained or improved their subscription base, a significant achievement in a period of continued change in library purchasing habits and increased electronic distribution of information.

The CSHL Press published 14 new books in 1998. The most widely anticipated was *Using Antibodies*, a techniques manual by Laboratory alumni Ed Harlow (currently a Trustee) and David Lane. A complete update of their 1988 *Antibodies: A Laboratory Manual*, the new book, with its innovative design and improved binding, seems likely to attain the classic status of its predecessor. Two other former Laboratory staff also revised a highly successful book: Ray Gesteland and John Atkins, in collaboration with Nobel prize winner Tom Cech, edited a second edition of the influential monograph *The RNA World*. A collection of essays by Max Perutz, entitled *I Wish I'd Made You Angry Earlier*, attracted glowing reviews and brisk sales and is now being translated into several languages. Other strong titles included *At The Bench*, a quirky introduction to life in the laboratory by Kathy Barker, and the 1997 Symposium volume *Pattern Formation during Development*, which brought together excellent science from widely differing areas of investigation. These lead titles, and a high-quality backlist, increased book sales by 25% over the previous year.

The Laboratory's well-established publishing activities for professional scientists expanded in 1998 to incorporate an ambitious new program for creating undergraduate textbooks. Opportunities to reshape university teaching in a variety of fields have been identified, and, led by newly appointed Senior Editor Alex Gann, teams of talented, innovative authors have begun work on these projects. The acquisition of the Meier House in Lloyd Harbor, and its conversion for use as a writing center by textbook authors, has provided an extraordinary asset in building

this program, which has potentially far-reaching consequences for the future growth of the Press.

For several years, that growth has been hampered by space limitations and by the distribution of the staff at three sites: Urey Cottage and the Library on the main campus, and a warehouse in Plainview. The pending renovation of the Woodbury property should allow the Press to consolidate many of its activities while retaining a base of editorial activities at the Laboratory's main campus.

## **Major Gifts**

Private support has been a cornerstone of the Laboratory's research program for many years, but it is particularly important for special projects like building construction and renovations or the creation of graduate school. Government grants for such initiatives, regardless of their worthiness, are scarce.

The initial campaign to endow the Watson School of Biological Sciences was quite successful. Contributions received in 1998 included \$5,068,568 from a donor who wishes to remain anonymous, \$885,000 from Mr. and Mrs. Leslie C. Quick, Jr., and \$548,748 from Mr. and Mrs. David L. Luke III. The William Stamps Farish Foundation gave \$350,000 and the Seraph Foundation gave \$50,000. Additional gifts came in after the new year, and the public phase of the capital campaign will begin in April 1999.

The Nancy and Edwin Marks Building will house our new brain imaging program and allow for expansion of the Laboratory's strong neuroscience program, including creating space for more teaching labs. This project has also received substantial support. The Marks Family Foundation gave \$1,261,531; the Booth Ferris Foundation gave \$100,000; The Weezie Foundation donated \$100,000; the Estate of Sophie Rubenfield gave \$57,731; the Fairchild Martindale Foundation gave \$50,000; and Mary D. Lindsay made a gift of \$50,000. We have added previous gifts from Thomas Saunders and David Koch to this project.

In support of neuroscience research, the Lita Annenberg Hazen Foundation gave \$200,000 to the Lita Annenberg Hazen Fund for Neurobiology, and Mr. and Mrs. William L. Matheson gave an additional \$50,220 in support of their previous gifts that established the Matheson Fund for Neuroscience. The Seraph Foundation gave \$27,000 for neuroscience research in Grisha Enikolopov's lab, as well as \$23,000 for cancer research in Yuri Lazebnik's lab.

Support from breast cancer advocacy groups has continued to be quite helpful to our cancer research program. In 1998, Mike Wigler's lab received a \$300,000 grant from The Lillian Goldman Charitable Trust through the Breast Cancer Research Foundation and our long-time supporter, 1 in 9: the Long Island Breast Cancer Action Coalition, donated \$100,000 to the Michael Scott Barish Human Cancer Fund. Both donations, along with \$25,000 from the Huntington Breast Cancer Action Coalition and \$4,600 from the Long Island Foundation for the Elimination of Breast Cancer, will be applied to the development of the DNA microarray facility.

The renovation of the old Power House and Carpentry Shed, to make room for the Laboratory's growing Public Affairs, Development, and Human Resources departments, was subsidized in part by a \$200,000 gift from the William and Maude Pritchard Charitable Trust and a \$200,000 gift from the Estate of Vernon L. Merrill. The Development conference room will be named for Mrs. Merrill, and the building will be named in honor of former Chairman of the Board of Trustees, and now Honorary Trustee, David L. Luke III and his wife Fanny.

The Stone Foundation gave \$60,000 in support of the Mary D. Lindsay Child Care Center; the Gladys Brooks Foundation donated \$57,000 for the purchase of microfilm equipment for

the Library; and the Joseph G. Goldring Foundation continued support to Bruce Stillman's laboratory through a gift of \$50,000 for two postdoctoral fellows. In addition, Alan and Edith Seligson once again gave \$35,000 in support of one postdoctoral researcher, as they have since 1990. The Goldring support went to Kate Simpson and Bill Henry and the Seligson fellowship supported Howard Fearnhead in his final year as a postdoc.

## **President's Council**

The President's Council was formed five years ago in an effort to bring together a small group of leaders from business, research, and biotechnology who are interested in science and in the work at Cold Spring Harbor Laboratory. Members of the President's Council contribute \$25,000 or more to support research and educational programs at the Laboratory. The funding helps the Laboratory attract top young scientists fresh from their Ph.D. or M.D. studies. The fellowships allow promising young researchers to pursue their own high-level, independent research, rather than assisting in the laboratory of an established scientist.

The 1998 meeting of the President's Council, held May 15–16, focused on the topic of human evolution and began with lunch on Friday at the President's House. The luncheon was followed by an afternoon lecture by CSHL scientist Karel Svoboda on imaging neuronal function in the intact brain. The keynote speaker, Dr. Roger Lewin, a member of the science and engineering technology development company AEA Technology in Oxfordshire, U.K., and a collaborator of renowned Kenyan anthropologist and conservationist, Richard Leakey, described what archaeology is able to tell us about evolution. The speakers on Saturday were Dr. Sean Carroll of the University of Wisconsin, Dr. Mark Stoneking of Pennsylvania State University and Dr. Michael Hammer from the University of Arizona.

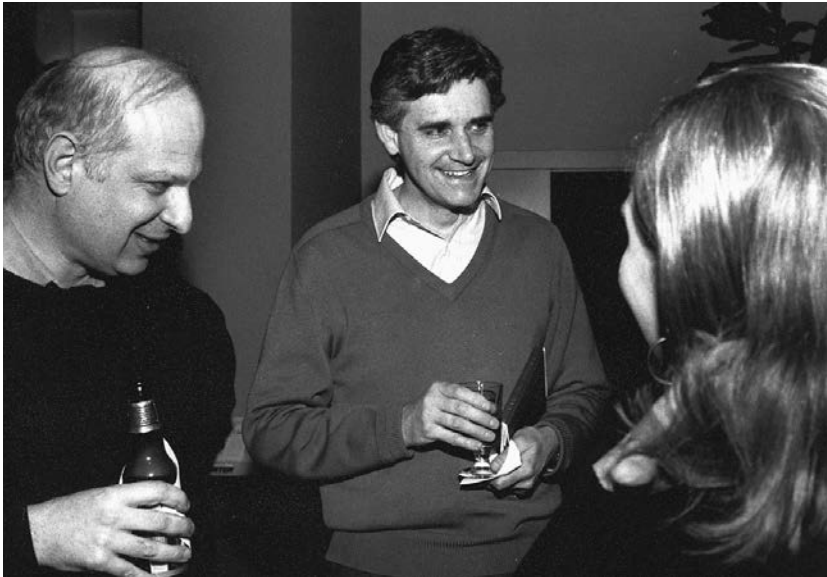
The following are members of the 1998 President's Council:

Abraham Appel, Appel Consultants, Inc.  
Peter Bloom, General Atlantic Partners, LLC  
James Conneen, A. T. Hudson & Co.  
Theodore N. Danforth, Oxford Bioscience  
Michel David-Weill, Lazard Freres & Co.  
Stefan Englehorn M.D.  
Leo A. Guthart, ADEMCO  
Charles E. Harris, Harris & Harris Group, Inc.  
Walter B. Kissinger, WBK Associates  
Thomas J. McGrath, Simpson Thacher & Bartlett  
Donald A. Pels, Pelsco, Inc.  
George B. Rathmann, ICOS Corporation  
Hubert J. P. Schoemaker, Centocor, Inc.  
James H. Simons, Renaissance Technologies Corporation  
Sigi Ziering, Diagnostic Products Corporation

## **Gavin Borden Visiting Fellow Lecture**

This annual event was initiated in 1995 to honor scientific textbook publisher Gavin Borden, who died in 1991 of salivary gland cancer, in an effort to carry on the mission that was so dear to him—the education of graduate students. Each year, the visiting Gavin Borden Fellow gives





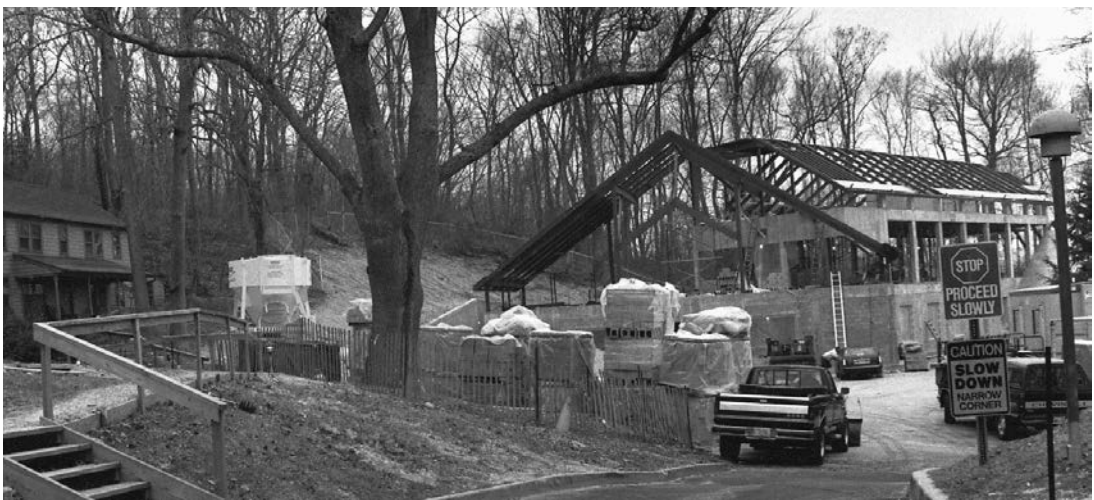
M.W. Kirschner, B. Stillman

a lecture to students and spends time dining and talking with them about science and careers in science.

The Gavin Borden Fellow in 1998 was Marc W. Kirschner, chair of the Department of Cell Biology at Harvard Medical School and a prominent contributor to science policy issues. His talk on March 23 was entitled “Proteolysis Control of the Mitotic Cycle.”

### **Building Projects**

Construction of the Nancy and Edwin Marks Building, on the hill to the north of James Laboratory, began in early 1998. It will contain a state-of-the-art brain imaging and research facility, together with a new teaching laboratory. The building is scheduled to be in operation by the fall of 1999.



Nancy and Edwin Marks Building site



Power House renovations

Renovation of the Laboratory's old Power House, built on the waterfront in 1913, and the adjacent former Carpentry Shed began in 1998. By the spring of 1999, the buildings were converted into office space for the Departments of Public Affairs, Development, and Human Resources. The new complex is called the David and Fanny Luke Building in honor of long-time Laboratory supporter and retired Chairman of the Board, David L. Luke III and his wife.

In November, members of the facilities staff removed the old guest cabins north of the Beckman Neuroscience Center to make room for the construction of the new Samuel Freeman Building. The new building will house facilities for computational neuroscience, an important component in the further expansion of neuroscience program. We were saddened to see the historic (albeit utilitarian) cabins come down, but it was not possible to preserve them for relocation due to their extensive deterioration.



Historic Guest Cabins



## **Undergraduate Research Program (URPs)**

The 1998 summer Undergraduate Research Program, through which students live and work at the Laboratory for 10 weeks during the summer, consisted of 23 students (12 men and 11 women) from nine countries. They were chosen from among 459 applicants from 39 countries. The students receive room and board on Laboratory grounds as well as a stipend.

The objectives of the program are to provide students with a greater understanding of the principles of biology, to instill in them an awareness of major topics of investigation, to help them develop intellectual tools necessary in modern research, to expose them to the process of research, and to allow them to meet people involved in that research.

The URP program received support this year from the C. Bliss Memorial Fund, the Burroughs Wellcome Fund, the Jephson Educational Trust, the National Science Foundation, the Dorcas Cummings Fund, and the URP endowment (which includes proceeds from the Emanuel Ax Fund, the Garfield Fund, the Glass Fund, the Libby Fund, the Olney Fellowship, the Shakespeare Fellowship, and the Von Stade Fellowship).

## **Partners for the Future (PFF)**

Each year, the Laboratory selects several outstanding high school seniors to work on original research projects in a laboratory under the supervision of a scientist-mentor. The students are expected to spend a minimum of ten hours per week at the Lab, beginning in October, and to present scientific summaries to an audience of scientists, teachers, parents, and Laboratory administrators at the conclusion of the program in March. They gain valuable research experience and are paid a small stipend for their efforts.

The participants for the 1998–1999 school year were Francis Browne of Cold Spring Harbor, Cold Spring Harbor High School (mentor: Michael Hengartner); Mariza Daras of Manhasset Hills, Herricks High School (mentor: Michael Weinreich); Peter Hallock of Holtsville, Sachem High School North (mentor: Jean-Philippe Vielle Calzada); Rachael Neumann of Woodbury, Syosset High School (mentor: Grigori Enikolopov); Allison Scheff of Islip, Islip High School (mentor: Robert Filipkowski); Diane St. Fleur of Brentwood, Brentwood High School (mentor: Guy Birkenmeier).

## **Outreach**

Outreach initiatives through the Department of Development include the Next Generation Initiative (NGI), a series of talks and tours designed to inspire an interest in basic research among individuals in their 30s and 40s. The Young President's Organization provides similar experiences for young leaders of industry and companies, and the Harbor Society is a small group of Laboratory supporters who have contributed to the Laboratory's planned giving program.

## **The Harbor Society**

The Harbor Society gained six new members (or member couples) in 1998: Jim and Jan Eisenman, Lois Learned, Ed and Betty Palmer, Sam and Ann Parkinson, John and Joyce Phelan, John and Hope Reese, and one who wishes to remain anonymous. The Harbor Society

is a group of distinguished individuals, now numbering 44 (see report in the Financial Section) who have included the Laboratory in their estate planning. We are most grateful to these individuals and families for their generosity.

## **Public Education**

The Laboratory continues to participate in Project WISE, a program to promote the entry of women into science and engineering. The program is run by SUNY Stony Brook and is designed to benefit high school students.

Once again, for the fourth year, the Laboratory hosted a group of Japanese exchange students and their teachers who were visiting Cold Spring Harbor High School in July. The Laboratory also continues to host the West Side School Science Nights, which are now open to all local elementary schools. Lectures this year included of Leemor Joshua-Tor talking about “Proteins in 3-D” in January; Michael Hengartner discussing “A Matter of Life and Death: How Cells Die, and Why That’s A Good Thing” in March; and Jean Philippe Vielle-Calzada on “Fertilization Tales: Doing It With or Without Tails” in May.

The “Great Moments in DNA Science” lecture series is still a big hit with high school audiences. In April, Linda Van Aelst talked about “The Role of Cell Signaling in Cancer.” In May, Jan Witkowski spoke on “Ian Had a Little Lamb: The Cloning of Dolly,” and Karel Svoboda presented “Imaging Neurons in Action.”

## **Breast Cancer Support**

Our long-time supporter 1 in 9: The Long Island Breast Cancer Action Coalition donated \$100,000 to the Laboratory for breast cancer research at its annual gala in October. The money was applied toward the new DNA microarray facility being developed by Michael Wigler. Also at the gala, 1 in 9 presented the Laboratory with an Olympus BX-40 microscope, which was donated by Dan Biandi, a vice president at Olympus America, through a breast cancer research fund-raiser held by Chameleon Hair Design in Port Jefferson.

The Laboratory also gained the support in 1998 of three other breast cancer activist groups: the Huntington Breast Cancer Action Coalition, the Breast Cancer Research Foundation, and the Long Island Foundation for the Elimination of Breast Cancer.

Huntington Breast Cancer Action Coalition founder and president Karen Joy Miller and vice president Marcy Usdan-Hyman made a \$25,000 donation to Mike Wigler’s lab at the Coalition’s annual gala in October for use in the development of the DNA microarray technology. This was the group’s first major research grant award and we are quite honored to have been the recipient.

Mike Wigler’s breast cancer research program also received a \$300,000 grant from The Lillian Goldman Charitable Trust through the Breast Cancer Research Foundation, a New York City-based organization led by president Evelyn H. Lauder. This major grant enabled the Wigler lab to purchase the expensive equipment necessary for the development of the DNA microarray technology. This technology is being used to search for new genes that are mutated in breast cancer.

The Long Island Foundation for the Elimination of Breast Cancer became a CSHL supporter in 1998 with gifts totaling \$4,600. The Laboratory is pleased to have the support of this local grass-roots organization and looks forward to cultivating this and other new relationships with local activists who are so vital to raising funds and awareness for this important issue.

## Special Events

Grace Auditorium was put to good use in 1998 not only for scientific conferences, but also for a host of cultural events. In March, Cablevision held the New York premier of the award-winning HBO mini-series "From the Earth to the Moon." Participants included astronaut Buzz Aldrin; actor Bryan Cranston, who played Aldrin in the HBO production (and is now famous for his role in "Saving Private Ryan"); Andrew Chaikin, author of the book on which the HBO production was based; Cablevision executives; and retired Grumman Aerospace engineers who designed and built the Apollo aircraft.

Also in March, Patrick Cunningham, Professor of Animal Genetics at Trinity College in Dublin, Ireland, gave a public lecture on horse genetics and the history of horse breeding. All of today's thoroughbred horses descend from a handful of stallions imported to England from North Africa and the Middle East back in the 1600s. In fact, about one third of the genes in current thoroughbreds can be traced to three top stallions of that century, and a full half of the genes in today's thoroughbred horses can be traced to ten seventeenth-century stallions. Dr. Cunningham, who was attending a Banbury Conference, has been studying genetics and animal breeding for more than 20 years. He initiated studies of thoroughbred breeding in the 1970s.

In May, Laboratory staff and visitors enjoyed a poetry reading entitled "the single secret," a phrase borrowed from an e.e. cummings poem. Performers Jane Lapotaire and Paul Jesson of England's Royal Shakespeare Company were in New York City for a series of performances of Shakespeare's "Henry VIII" at the Brooklyn Academy of Music. Their show for the Laboratory included an entertaining assortment of poetry by British and American writers including William Shakespeare, John Donne, Dorothy Parker, and e.e. cummings.

In October, during the meeting on Gametogenesis, several visiting scientists participated in a public forum about cloning. Moderator Dr. Anne McLaren, principal research fellow of the Institute of Cancer and Developmental Biology at the Wellcome CRC Institute, in Cambridge, England, led panel members Dr. Brigid Hogan, investigator at Howard Hughes Medical Institute and professor of Cell Biology at Vanderbilt University Medical School in Nashville, Tennessee;



News 12's Doug Geed interviewing astronaut Buzz Aldrin



Paul Jesson and Jane Lapotaire, in the Single Secret

Dr. Ryuzo Yanagimachi, professor in the Department of Anatomy and Reproductive Biology at the University of Hawaii Medical School (who had recently reported the production of 50 cloned mice); and Dr. Anthony Mahowald, professor and chairman of the Department of Molecular Genetics and Cell Biology and chairman of the Committee on Developmental Biology at the University of Chicago in Illinois.

Then, in November, Alan Kay, fellow and vice president of Research and Development at Walt Disney Company, discussed “Origins of the Personal Computer—and Beyond.” Dr. Kay’s “Dynabook” is considered to be the forerunner of the personal computer. He also invented the forerunner of today’s Macintosh and Windows interfaces, and led one of several groups that together developed modern workstations, the Smalltalk programming language, and the EtherNet—the technology used today by the Internet. He was a member of the University of Utah Advanced Research Project Agency (ARPA), a federal Department of Defense research team that developed three-dimensional graphics, and he participated in the development of ARPANet, which became the Internet in the 1970s. Before joining the Walt Disney Company, Dr. Kay also worked for Xerox Palo Alto Research Center, Atari, and Apple.

Concerts in Grace this year included the following: May 9, Mary Phillips, mezzo soprano and Ted Taylor, pianist; May 23, Alex Velinzon, violinist and Inessa Zaretsky, pianist; May 30, Dmitri Berlinsky, violinist, and Elena Baksht, pianist; June 8, Irina Muresanu and Mark Ptashne, violinists; August 22, David



Mark Ptashne and Irina Muresanu

Korevaar, pianist; August 29, the Harold Betters Jazz Quartet; September 5, Jennifer Fratuschi, violinist, and Benjamin Loeb, pianist; September 12, Anton Barachovsky, violinist, and Sonya Ovrutsky, pianist; and September 26, Bion Tsang, cellist, and Benjamin Loeb, pianist.

The Banbury Center also served as a forum for public events. In February, Lloyd Harbor resident Dick Opsahl talked to community members about “Running on Everest: A Personal Account of a Marathon Starting at Everest Base Camp,” and in November the Laboratory offered a Tax & Estate Planning Seminar at Banbury.

### Long-term Service

On July 9, several employees celebrated long-term anniversaries with the Laboratory at a pool-side dinner at Robertson House on the grounds of the Banbury Center. Jim and Liz Watson celebrated the 30 years that have passed since Jim became the Laboratory’s director in 1968. I presented Jim with a beautiful, abstract lead crystal sculpture engraved with the image of Ballybung and “With Deep Appreciation, 30 Years of Dedicated Service, 1998.” In addition, he received a three-tiered, custom-made base for the sculpture created by Long Island sculptor John Roper. Liz was presented with a framed print of the collage of dedication booklet covers that appeared in the tribute to Jack Richards that Liz edited in 1997. The calligraphy inscription read “30 Years of Dedication, Our Sincerest Gratitude, 1998.” Liz’s advice about the adaptive re-use and historic preservation of Laboratory buildings, and her 1991 book, *Houses for Science*, are enduring and most valuable contributions to Cold Spring Harbor Laboratory.



(Back row) W. Herr, C. Schneider, B. Stillman  
(2nd row) M. Simkins, J. Wiggins, J. Watson, M. Wigler, P. Wendel  
(3rd row) D. Jusino, M. Falkowski, J. Ebert, C. McEvoy, M. McBride  
(Front row) P. Maroney, B. Toliver, L. Hyman



Laura Hyman joined the Library 25 years ago as a part-time library assistant when the Library staff consisted only of Susan Cooper and her volunteers. Since that time, Laura has become business manager for three departments—Development, Public Affairs, and the Library—as well as the Laboratory’s art curator. Laura has selected, obtained, framed, arranged and supervised the hanging of most artwork in the Laboratory’s many buildings.

Senior scientist and cancer researcher Michael Wigler celebrated his 20-year anniversary with the Laboratory. Mike came to Cold Spring Harbor in 1978, and three years later he codiscovered the first human oncogene, *ras*, now the object of much study at CSHL and elsewhere. Laboratory technician Jeanne Wiggins, Banbury administrative assistant Beatrice Toliver, Banbury grounds foreman Christopher McEvoy, Facilities’ draftsman/estimator Charles Schneider, and payroll administrator Patricia Maroney also celebrated 20-year anniversaries.

Assistant Director and Dean of the Watson School of Biological Sciences Winship Herr celebrated his 15-year anniversary with the Laboratory. Winship came to Cold Spring Harbor Laboratory in 1983 as a postdoc in Joe Sambrook’s lab. The following people also celebrated 15-year anniversaries: CSHL Press project coordinator Joan Ebert, laboratory technician Margaret Falkowski, shipping and receiving foreman Daniel Jusino, meetings registrar Michaela McBride, personnel manager Marilyn Simkins, and laboratory technician Patricia Wendel. Connie Hallaran, who has been running the Laboratory’s bookstore since its inception, also celebrated a 15-year anniversary. She now works under the auspices of Barnes & Noble.

### **Administrative Staff Changes**

In April, W. Dillaway Ayres joined the Laboratory as associate administrative director. Dill earned a B.A. from Princeton University, where he majored in English literature, and an M.B.A. in finance from Columbia University Graduate School of Business Administration. He gained extensive experience in corporate planning and finance at several companies, including Capital Cities/ABC Inc. and American Express Company, and was an investment banker at Veronis, Suhler & Associates Inc., which specializes in television and radio broadcasting. Most recently, he was cofounder, executive vice president, and chief financial officer of Business and Trade Network (BATNET), which provides Internet services to national and international associations.

In July, after working for several months as a consultant, Deborah Barnes became director of Public Affairs. Deborah earned a Ph.D. in biology from Georgetown University and did postdoctoral research at the Children’s Hospital at Harvard Medical School. She taught high school biology for five years, was a news writer for the journal *Science*, taught science writing for the Johns Hopkins University Graduate Program, and for seven years was editor of *The Journal of NIH Research*. Deborah has initiated a public lecture series about cancer and the production of a video about CSHL tentatively entitled “A Year in the Life of the Lab.”

Late in 1998, soon after the Watson School of Biological Sciences became a formal entity, Lilian Gann was recruited as Assistant Dean. Lilian received her Ph.D. from the University of St. Andrews in Scotland for her research on adenovirus transcriptional regulation. After postdoctoral studies at Memorial Sloan Kettering Cancer Center, Harvard Medical School, and the Imperial Cancer Research Fund (ICRF) in London, she became administration manager at the ICRF and earned an M.B.A. In her role as administration manager, she helped direct the graduate student and postdoctoral programs. Most recently, Lilian was director of cancer support services at CancerBACUP, a U.K. charity that helps people with cancer. Lilian, too, worked as a consultant before assuming her full-time position in early March 1999.



## **Changes in Scientific Staff**

### ***Departures***

Hong Ma left to become an associate professor at Pennsylvania State University in College Park. Akila Mayeda accepted an appointment as assistant professor at the University of Miami School of Medicine, in the Department of Biochemistry and Molecular Biology. Elly Nedivi left our neuroscience program to accept a position as assistant professor in Brain and Cognitive Sciences at the Massachusetts Institute of Technology, in Cambridge. Alcino Silva is now an associate professor in the Department of Neurobiology, Psychiatry, and Psychology at University of California, Los Angeles, and Erich Grotewold went on to become an assistant professor in the Department of Plant Biology at Ohio State University.

### ***New Arrivals***

Shivinder “Shiv” Grewal, who studies chromosome dynamics and epigenetic control of gene expression, was recruited to CSHL as an assistant investigator. Shiv comes from the National Cancer Institute’s Frederick Cancer Research and Development Center. Lincoln Stein was recruited as an assistant investigator in bioinformatics. Lincoln specializes in database integration and management as it applies to biological data accessible via the Internet. He was formerly the director of bioinformatics at the Whitehead Institute for Biomedical Research/MIT Center for Genome Research.

We also have two new research scholars this year. Both were students at Eton College in Windsor, U.K., and are now living at Ballybung with the Watson family while they get experience working in the laboratory. Robin Holden is studying transcription in Winship Herr’s lab, and Indraneil “Neil” Mahapatra is working in the lab of Holly Cline. Neil is cloning a family of genes encoding proteins that are involved in axon pathfinding in the developing brain.

### ***CSHL Fellow***

Marja Timmermans joined the Laboratory in June as a CSHL Fellow. The CSHL Fellow program provides an outstanding opportunity for talented scientists who have recently received their Ph.D. or M.D. degrees to establish strong independent research programs. Each CSHL Fellow has a lab and technician, as well as access to all of the resources of Cold Spring Harbor Laboratory.

Marja earned her Ph.D. in the lab of Jo Messing, at the Waksman Institute at Rutgers University in Piscataway, New Jersey. Marja is a maize geneticist who has focused on discovering and understanding the genes involved in maize leaf development. She has studied two such genes, *leafbladeless 1* and *rough sheath 2*, which are required for leaves to grow into their proper shapes.

### ***Promotions***

Hollis Cline was promoted to investigator. Holly came to the Laboratory in 1994 as part of our developing neuroscience initiative, and since that time, her work in neuronal development has been outstanding. Investigator is the highest research position at the Laboratory, comparable to

full professor status at an academic institution. Rather than tenure, though, the investigator appointment provides “Rolling 5” status—the contract is renewed each year for five years.

Michael Hengartner, Tatsuya Hirano, Yuri Lazebnik, Scott Lowe, and Linda Van Aelst were each promoted to associate investigator.

Masaaki Hamaguchi, of Mike Wigler’s lab, was promoted to assistant investigator. Masaaki, who was formerly a gastrointestinal surgeon in Japan, came to do postdoctoral research in the Wigler lab after deciding to make the change from clinical medicine to basic research.

### ***Visiting Scientists***

Seven visiting scientists joined us this year: Yoshitaka Azumi of Nagoya University in Japan spent time in Hong Ma’s lab; Simona Ceccarelli of the University of Milan was working in Peter Nestler’s lab; Jyoti Raychaudhura of Lincoln Hospital in the Bronx and Winthrop University Hospital in Mineola, New York, joined Yuri Lazebnik’s lab; Shern Chew of the University of Cambridge worked in Adrian Krainer’s lab; Jyotsna Dhawan of Boston University spent time in David Helfman’s lab; Costaicis Frangou of the University of Portsmouth in the United Kingdom worked in Greg Hannon’s lab; and Benjamin Horwitz of the Technion Israel Institute of Technology spent three weeks in Hong Ma’s lab as part of an ongoing collaboration.

Several other visiting scientists also wrapped up their stays at the Laboratory. Paula Enrietto, who was working with Tom Marr, returned to a staff scientist position with Tom’s company, Genomica, in Boulder, Colorado. Eli Hatchwell completed his studies in Mike Wigler’s lab and returned to his clinical work at Southampton University in the United Kingdom; and Mirjana Maletic-Savatic left Roberto Malinow’s lab to finish her residency at SUNY Stony Brook School of Medicine’s Department of Neurology.

### ***Postdoctoral Departures***

The Laboratory has long been a springboard from which many scientists launch their research and academic careers. In 1998, the tradition continued with the following postdoctoral researchers moving on to other positions.

Concurrent with Alcino Silva’s move to UCLA, many of his lab members accepted new positions as well. Nikolai Fedorov is now an assistant researcher with Alcino in the Department of Neurobiology at UCLA; Masuo Ohno is a visiting assistant professor there. Three of Alcino’s CSHL postdocs have relocated to parallel positions at UCLA as well: Ype Elgersma, Paul Frankland, and Jeffrey Kogan. Karl Peter Giese, of Alcino’s lab, accepted a position as lecturer at University College in London.

Three postdoctoral researchers from Hong Ma’s lab moved with Hong to the Pennsylvania State University Biotech Institute. Hiroyasu Onaka, Yixing Wang, and Ming Yang will all continue their postdoctoral research there.

From Nick Tonks’ lab, Anton Bennett accepted a position as assistant professor at Yale University School of Medicine; Michael Gutch became a manager at Electronic Publishing Company in New York City; and Andrew Garton is now a senior scientist at OSI Pharmaceuticals in Uniondale, New York.

From the Stillman lab, Chun Liang accepted a position as assistant professor at the Hong Kong University of Science and Technology, and Alain Verreault went on to become a lab head at the Imperial Cancer Research Fund Clare Hall Laboratories in Potters Bar, United Kingdom.

Jianzhong Ding and Yu Liu both moved on from Rui Ming Xu's lab—Jianzhong to become an engineer with Aeroflex Laboratory Inc., in Setauket, New York, and Yu as a postdoctoral researcher at the Hong Kong University of Science and Technology.

Andrea Doseff from Yuri Lazebnik's lab accepted a position as research scientist at Ohio State University in Columbus; Jeffrey Dickinson from Tim Tully's lab went on to become a programmer at Zeneca Pharmaceuticals in Wilmington, Delaware; Cameron Gray of Karel Svoboda's lab went to Philadelphia to pursue other interests; and Fei Guo from Erich Grotewold's lab is continuing his postdoctoral research in Erich's new lab at Ohio State University's Department of Plant Biology.

Ruiping Liu moved from Peter Nestler's lab to a position as research scientist with 3-D Pharmaceuticals, Inc., in Exton, Pennsylvania; Yi Liu went from Winship Herr's lab to the position of Research assistant professor at the University of Southern California School of Medicine; Martin Lock moved from Jacek Skowronski's lab to continue his postdoctoral studies at the University of Pennsylvania, Bensalem; and Tom Misteli moved from David Spector's lab to the National Cancer Institute to become a principal investigator there.

Indrani Rajan from Holly Cline's lab is continuing her postdoctoral research in the Department of Pathology at the University of Washington in Seattle; Brandt Schneider moved from Bruce Futcher's lab to become an assistant professor at Texas Tech Medical School in Lubbock; Yung-Chih (Judy) Wang went from David Helfman's lab to the Ferring Research Institute, Inc., in California as a research scientist; Bill Henry finished up in Nouria Hernandez's lab and moved on to a position as assistant professor at Michigan State University; and Mark Curtis completed his Ph.D. in Rob Martienssen's lab, and, after a brief period as a postdoctoral fellow at CSHL, moved to the United Kingdom to pursue research in private industry.

### **Graduate Students**

Eleven graduate students completed their Ph.D. degrees at the Laboratory this year. From Alcino Silva's lab, Ofelia Carvalho is now a staff research scientist with Alcino at UCLA Department of Neurobiology, and Pin (Adele) Chen is continuing her graduate studies in the Silva lab at UCLA (although she is expected to receive her degree from SUNY Stony Brook).

From Nouria Hernandez's lab, Ethan Ford went on to do postdoctoral research in the Department of Biochemistry and Molecular Biology at Oregon Health Sciences University in Lagunitas, California, and Debra Morrison went on to do postdoctoral research at Mount Sinai Rutenberg Cancer Center in New York City. Craig Hinkley completed his studies and went to embark on postdoctoral studies in Bill Henry's lab at Michigan State.

Degui (Charlie) Chen from David Helfman's lab went on to do postdoctoral research at UCLA; Richard Freiman went from Winship Herr's lab to do postdoctoral research with former staff scientist Bob Tjian of the University of California at Berkeley; Anthony (John) lafrate completed his Ph.D. in Jacek Skowronski's lab and went on to complete clinical training for his M.D. at SUNY Stony Brook; and Kenneth LaMontagne went from Nick Tonks' lab to do postdoctoral research with Judah Folkman at the Children's Hospital in Boston.

Peter Rubinelli finished up in Hong Ma's lab and went on to do postdoctoral research at Ohio State University in the Department of Biochemistry and Plant Biology; Hua Tu went from Mike Wigler's lab to a postdoctoral research position at Tularik, Inc., in San Francisco; and Qiang Wu of Adrian Krainer's lab left to do postdoctoral research at Harvard University's Department of Molecular and Cell Biology.

## **Twenty Years at CSHL**

At the time of writing, it has been 20 years since I came to Cold Spring Harbor Laboratory from Australia, initially as a postdoctoral fellow for two years. Much has changed during those years, yet the Laboratory remains a vibrant and exciting place to work. I am pleased to have been welcomed into this marvelous community with such warmth.

This year happens to be one of the busiest on record, and all the staff at the Laboratory must be congratulated for their efficiency and dedication. Because of the combined effort of all our staff, CSHL remains one of the most exciting addresses in science, making my life interesting every day.

On a personal note, I was most happy to learn at the end of the year that in the 1999 Australia Day honors list (January 26th), I was named as having received the Order of Australia (AO). This high national honor from my homeland is particularly pleasing as it recognizes the contributions to science and humanity at large by an Australian scientist who happens to be working in the United States, emphasizing the international nature of modern biomedical research.

*May 1999*

**Bruce Stillman**