HIGHLIGHTS OF THE YEAR

Research Highlights

Our research programs in cancer biology, plant genetics, neurobiology, computational biology, and structural biology all saw significant progress this year. In cancer research, some of the most exciting work came from David Beach's laboratory. In 1993, David's group discovered the first members of a new family of cancer-related genes. Called cyclin-dependent kinase inhibitors, the proteins made by these genes inhibit a major class of proteins, the cyclin-dependent kinases, which are the key regulators of the cell division cycle. The first two of these proteins called $p16^{INK}$ and p21 were the founders of two different families of growth regulators that have grown during the last year. The $p16^{INK}$ gene is altered in a wide variety of human tumors, suggesting that it acts as a tumor suppressor, and a new member of this family has been demonstrated to be induced by an extracellular growth inhibitor called tumor growth factor ß· In other work, the Beach laboratory has linked signal transduction through the RAS pathway to control of the cell cycle by cyclin-dependent kinases, via a known regulatory protein called cdc25. In collaboration with the Beach laboratory, Bruce Stillman's group has shown that the p21 cell proliferation inhibitor has a dual role in cell cycle regulation. The p21 protein inhibits DNA replication via its interaction with proliferating cell nuclear antigen (PCNA), an essential protein required for DNA replication and DNA repair, but interestingly, it still allows DNA repair. The gene encoding the p21 protein is activated by the well-known tumor suppressor protein p53. Damage to a cell's DNA, by radiation or other mutagen, will induce p53, which in turn induces p21 and begins a molecular cascade that inhibits progression through the cell cycle. This allows the cell to respond to genetic damage by pausing its progression through the cell cycle while it repairs its DNA, thus helping to prevent the propagation of potentially dangerous mutations.

The ras gene was among the first human oncogenes to be discovered, back in 1981 by Mike Wigler's group, and last year Mike reported that the RAS protein signals to another oncogene product, the RAF protein kinase, thereby controlling cell growth and proliferation. This year, Wigler's group obtained evidence that RAS and RAF are near the beginning of a signal transduction cascade of protein kinases that passes extracellular signals to the nucleus. Staff Investigator Linda Van Aelst and Wigler also isolated several additional RAS-binding proteins. Among these was AF6, a protein that has been implicated in acute lymphoblastic leukemias. In collaboration with Senior Staff Investigator Nikolai Lisitsyn, Mike Wigler has been developing a powerful technique called representational difference analysis (ADA). This technique, which allows researchers to identify subtle differences between two DNA sequences, can detect both additions to a chromosome, such as the insertion of viral DNA, and deletions caused by mutation. Recently, the technique was used by researchers at Columbia University who found that Kaposi's sarcoma, a common complication of AIDS, may be caused by a virus that is related to the herpes simplex viruses.

In other work, Nouria Hernandez has dissected a complex of transcription factors that regulates transcription of small nuclear RNAs (snRNAs), short RNA molecules that do not code for proteins. Surprisingly, one of the components of the transcription factor for snRNAs turned out to be the same as a major messenger RNA transcription factor, the TAT A-box-binding protein (TBP). TBP has now been shown to have an essential role

in the transcription of all genes in the nucleus of cells. Transcription is activated by other gene-specific DNA-binding proteins, and in the last year, Winship Herr's group collaborated with scientists at MIT to elucidate the crystal structure of the POU domain, an unusual bipartite DNA-binding domain common to a number of transcriptional regulatory proteins.

A major breakthrough in studies on the replication of DNA came from Carol Greider and her group's work on telomerase, a ribonucleoprotein that adds telomeric DNA sequences onto the ends of chromosomes. Telomerase has been attracting a great deal of interest because of its potential target for anti-cancer therapy. Most normal human cells have little or no telomerase because they do not need to extend the length of their chromosomes' ends, but in many kinds of cancer cells, telomerase is activated. Several years ago, Carol and her colleagues suggested that telomerase may be required for the growth of immortal cancer cells. This year, Carol's group, in collaboration with scientists at Geron Corp. in Palo Alto, California, succeeded in cloning the RNA component of the human telomerase. Using this information, they also cloned the mouse telomerase RNA and found that it is regulated during mouse development. The cloned RNAs will enable her group to pursue experiments to determine the role of telomerase in normal and cancerous cell growth. Finally, Kathy Collins and Greider, in collaboration with Senior Staff Investigator Ryuji Kobayashi, succeeded this year in cloning genes encoding two protein components of telomerase. These proteins do not have striking similarity to other polymerases, except for a distant relatedness to RNA-dependent RNA polymerases, indicating that telomerase represents an entirely new class of polymerase enzyme.

Since 1990, the Plant Group has been developing potentially powerful genetic methods for the detection and mapping of new plant genes. Called the gene trap/enhancer trap system, the technique was first developed in bacteria and has been used with impressive results in *Drosophila*. The group has succeeded in adapting this approach to the small mustard-family plant *Arabidopsis*. Their approach employs the *Ac/Ds* transposable elements discovered at Cold Spring Harbor more than 50 years ago by Barbara McClintock. These transposable elements come in two versions that have been transferred into the *Arabidopsis* genome. In one plant, the *Ds* transposable element has a genetic marker associated with it and is stable in the absence of an enzyme called transposase. In the other plant, the modified *Ac* element encodes the enzyme transposase. When these two plants are crossed, the transposase in the hybrid plants of the first generation cause the *Ds* transposon to "jump" around the genome, randomly inserting into the plant's genes. Self-fertilization produces a new generation of thousands of plants that all differ by the insertion of a single *Ds* element. If the *Ds* element is inserted into a gene, the genetic marker it carries is often expressed, telling where in the plant the gene is functional. Phenotypic alterations in the plant give clues to the function of the disrupted gene. This work is a collaboration among Venkatesan Sundaresan, Rob Martienssen, Hong Ma, and our new Cold Spring Harbor Fellow, Ueli Grossniklaus, who comes to us following graduate studies in Walter Gehring's laboratory in Switzerland. This exciting work promises to yield much new information about plant development.

Our neurobiology program has had success in teasing out the genetic basis of learning and memory. For many years, a central question in learning and memory research has been to define a difference between long-term and short-term memory. Is long-term memory simply short-term memory that lasts a long time or is it a physiologically distinct process? An important breakthrough came when Senior Staff Investigator Tim Tully and his group were able to establish long-term memory in *Drosophila* and show that formation of memory can be divided into genetically separable components.

These different forms of memory, called short-term, anesthesia-resistant, and long-term, combine to produce specific memory patterns in the brain of flies. A collaborative effort among Tim Tully, Jerry Yin, and Alcina Silva has shown that a DNA sequence-specific transcription factor in the nucleus of cells, the CREB protein, has a key role in long-term memory in both fruit flies and mice. The complementary approaches of "knockout" mice and transgenic mutant flies with inducible genes have yielded insight into what appears to be a highly conserved mechanism for producing lasting memories. In subsequent research, Yin and Tully have demonstrated that it is possible to enhance long-term memory formation in transgenic flies by inducing the expression of an activating form of CREB. Flies normally require ten (spaced) training sessions to form a permanent long-term memory. Remarkably, transgenic flies carrying the CREB activator do it after only one training session, which is functionally equivalent to a "photographic" memory.

In structural biology, Xiaodong Cheng, who has collaborated with Rich Roberts to produce a high-resolution crystal structure of the DNA methyl transferase Hha-1, has produced a structure for the important cellular enzyme casein kinase 1. Our computational biology group, headed by Senior Scientist Tom Marr, has been undertaking one of the most difficult tasks of molecular biology—identifying the genetic components of complex, multigene diseases. This effort is centered on the Laboratory's effort within the Dana Consortium for Manic Depressive Illness (MDI), a cooperative alliance with research groups at both the Johns Hopkins University and Stanford University Schools of Medicine. Tom's group has been working with Staff Investigator Harriet Feilotter to identify the genes involved in MDI by screening families with a history of MDI, documenting their genotypes, and analyzing the pedigrees statistically. An ultimate goal is to use powerful modern genetic analyses to identify the genes involved and eventually bring some relief to this all too common disease.

Finally, the Laboratory has expanded its cancer research effort into an area known as programmed cell death, or apoptosis. Two new scientists, Michael Hengartner and Yuri Lazebnik, have moved into the first-floor labs of Demerec Laboratory to pursue investigations of genetically programmed cell death, which is an essential feature of normal development but is often abnormal in human cancer. They were joined early in 1995 by Scott Lowe, our new Cold Spring Harbor Fellow, who as a graduate student at MIT studies apoptosis in cancer progression and remission.

Symposium LIX: Molecular Genetics of Cancer

More than 450 scientists gathered this year at the annual Symposium to share their insights and data on the genetic origins of cancer and how it can best be controlled. Research has progressed rapidly, and it is now possible with some cancers to define the genetic changes that occur as the disease progresses from a barely detectable growth to a vigorous metastatic tumor. This was emphasized by Harold Varmus, Director of the National Institutes of Health, in this year's annual Dorcas Cummings Lecture entitled, Why Is It Important to Understand the Genetic Basis of Cancer? Varmus, along with Michael Bishop, was awarded the 1989 Nobel Prize in Physiology or Medicine for his role in demonstrating that cellular genes can cause cancer. His lecture drove the point home: Cancer is fundamentally a genetic disease. "This does not mean that all cancers are inherited," he pointed out, "rather it means cancer results from defects, inherited or acquired, in genes." Other

Harold Varmus

discussions covered basic research into how cancer cells develop, function, and proliferate. Former Cold Spring Harbor scientist Ed Harlow delivered a thoughtful summary that harbored cautious optimism that understanding the genes and their products will lead to new therapies.

An Exciting Roster of Meetings at the Banbury Center

Of all the meeting places where molecular biologists congregate, none enjoys a greater reputation than the Laboratory's Banbury Center. We strive to select topics that have reached that stage of development when critical review is necessary to prepare for further advances. There were some outstanding examples of such meetings this year. "Secretory Pathways: The Molecular Basis for Their Specificity" was a remarkable synthesis of studies across organisms and cell systems, focusing on the newly emerging molecular understanding of the transport of proteins. It was especially fitting that Nobel laureate George Palade, one of the founders of the field, attended the meeting and made the closing remarks. Another meeting that achieved the same degree of synthesis was that on "Telomeres." These structures found at the ends of chromosomes and telomerase, the enzyme complex that keeps them the correct length, are fascinating in their own right, but it now seems that they have a role in aging and cancer. Banbury Center is also noted as a neutral ground for meetings in which matters of science policy loom as large as matters of science. A meeting in the spring of 1994 on "The Genome of *Arabidopsis*" was devoted to research on the genome of this small plant whose enthusiasts see as the laboratory mouse of the plant world. The meeting reviewed progress in mapping and sequencing the *Arabidopsis* genome and, through the participation of representatives of the National Science Foundation and the United States Department of Agriculture, was able to make significant progress in setting new research priorities.

Sabin Meeting

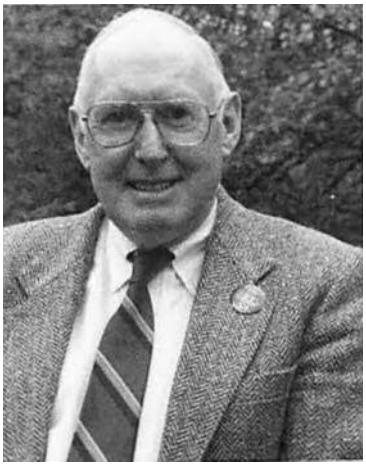
In October, the Laboratory hosted the 1994 Albert B. Sabin Vaccine Foundation Colloquium. The Sabin Foundation, named for the inventor of the oral polio vaccine, promotes the control and eradication of infectious diseases by sponsoring research and scientific meetings and by increasing public awareness of the need for vaccination. Participants at the Colloquium represented all disciplines of vaccine development, manufacture, and distribution. Among them were scientists, pharmaceutical and biotech representatives, congressional staffers, and physicians. The goal of the Colloquium was to improve the development and distribution of vaccines to American children. A highlight of the Colloquium was the presentation in Bush Auditorium of the 1994 Albert B. Sabin Gold Medal Award, to D.A. Henderson, Deputy Assistant Secretary for Health at the Health and Human Services Agency in Washington. Henderson then gave a moving lecture on arguably the world's most successful public health effort—the eradication of smallpox. The Sabin Foundation also sponsored this year's October meeting on "Molecular Approaches to the Control of Infectious Diseases."

E.O. Wilson and J.D. Watson

J.P. Morgan Executive Meeting

The Laboratory has a long and fruitful relationship with the J.P. Morgan Bank, stretching back to J.P. Morgan himself who, in 1924, was a founding patron of the Long Island Biological Association, continuing with the enormous contributions of our long-time Trustee and Morgan CEO, Walter Page, through to the present day with Sandy Warner, the current CEO of J.P. Morgan, also one of our Trustees. So it was with great pleasure, and not a little trepidation, that we learned that J.P. Morgan Bank was going to take over sponsorship of our annual Executives' Conference. The trepidation came from fear that we would not be able to reproduce the quality of the remarkable series of meetings of the past eight years. Our fears proved groundless, for the meeting's topic—The Biology of Human Behavior—could hardly have been better timed with the extraordinary current interest in human behavior and genetics. The speakers were outstanding, and it was particularly pleasing that E.O. Wilson, the celebrated Harvard zoologist, gave the keynote talk. Dean Hamer later discussed his controversial findings on a genetic basis for male homosexuality. Helen Fisher, author of Anatomy of Love, also gave a stimulating discussion of the evolution of human behavior and later followed with a public lecture with the provocative title of "The Evolution of Marriage" to members of the Cold Spring Harbor Laboratory Association.

Laurie J. Landeau



M.Maxwell Cowan

A Vital Board of Trustees

At our annual Board meeting in November, we bid farewell to two Trustees, who have been members of our Board since 1988—Laurie J. Landeau, distinguished veterinarian and Assistant Director of the Program in Aquatic Veterinary Medicine at Woods Hole, Massachusetts, and W. Maxwell Cowan, Vice President and Chief Scientific Officer of the Howard Hughes Medical In-

J.D. Watson, Henry Wendt, and David Luke III at the Wendt Cabin Dedication

stitute. Mr. Cowan has been a major force in the development of the Laboratory's Neuroscience Program since the early 1970s. Happily, they are replaced by new members also of high caliber—Bruce Stillman and Henry Wendt. Bruce joins the Board as he steps into the role of Laboratory Director. Henry Wendt has just stepped down as chairman of SmithKline Beecham. By becoming a Trustee, he strengthens his already solid relationship with the Laboratory, which involved a major role in the Laboratory's Infrastructure Program. We also welcome to the Board our neighbor John P. Cleary, Esq., who is a distinguished local attorney associated with the firm Farrell, Fritz, Caemmerer, Cleary, Barnosky & Armentano. Mr. Cleary is a long-time member and is now Chairman of the CSHL Association.

Wendt Cabin Dedicated

On November 4, we dedicated the last of our current cabins for visiting scientists to new trustee Henry Wendt, who now divides his time between Philadelphia and his Northern California winery, Quivira Vineyards. In 1986, as the Chairman of the Board of SmithKline, Inc., Mr. Wendt participated in our first "hands-on" Banbury Conference designed to expose leading executives in the pharmaceutical and biotechnology industries to the latest ideas, results, and techniques of molecular biology. The cabin dedication was in recognition of Mr. Wendt's establishment of the Wendt Fellows program, which provides postdoctoral fellowships in neuroscience. The first two Wendt Fellows are Jim DeZazzo, in Tim Tully's group, and Zhong Wang, who works with Alcino Silva. Following the dedication, Tim Tully and Alcino Silva gave a special lecture on their exciting recent findings on the genetics of learning and memory in fruit flies and mice.

Robertson Research Fund

The Robertson Research Fund is an essential financial resource that gives the Laboratory a measure of independence essential to a small private research institution. It allows us to support scientists who are early in their careers or who are beginning untried research projects for which it is difficult to obtain federal grants—the kind of cutting-edge research that is a bit risky but has a high payoff. The Fund was established in 1973 by the generosity of Lloyd Harbor neighbor Charles Robertson and his family. After Charles Robertson died in 1981, his son Bill Robertson and daughter Anne Meier continued the family tradition of association with the Laboratory. Through conservative management, the original endowment of $8 million has grown to nearly $48 million. This year, the Fund distributed $1.6 million in research support to Cold Spring Harbor scientists. The Robertson Research Fund supported 12 staff scientists this year, as well as our Cold Spring Harbor Laboratory Fellow, Ueli Grossniklaus. In addition, the Fund supported postdoctoral fellows, graduate students, and scientific communications via the meetings and courses programs. The Robertson family, through the Banbury Foundation, supports the Marie Robertson Memorial Fund for neuroscience research at Cold Spring Harbor, long a special interest of Charles Robertson. This year, Marie Robertson funds supported an April meeting on the Genetics of Learning and Memory at the Banbury Center as well as memory and learning research in Beckman Laboratory by Alcina Silva and Tim Tully.

Major Gifts

We gratefully acknowledge the support we received last year from individuals, foundations, and corporations. The Cancer Research Fund was brought to near completion, thanks to gifts of $300,000 from the Ira DeCamp Foundation; $75,000 from the William and Maude Pritchard Charitable Trust; $25,000 each from the Louis Berkowitz Family Foundation, the David Koch Foundation, and the Edward S. Moore Foundation; $10,000 each from Arrow Electronic, Inc., and the Daphne Seyboldt Culpepper Foundation; and $5,000 from the Dextra Baldwin McGonagle Foundation, and a bequest of $5,000 from H. Turner Slocum. Dr. David Pall donated $21,750, and the Marks Family Foundation made a gift of $10,000 in honor of Dr. Pall's 80th birthday. These contributions came to us as unrestricted funds, which allows the Laboratory to apply the funds where they are most needed. A grant of $45,000 made to the Carnegie Library by the Gladys Brooks Foundation will help address the cramped situation in our library by providing funds for microfilm.

Fellowships were funded in 1994 by the Goldring Family Foundation ($30,000) and the Seligson Foundation ($75,000). The Robert Leet and Clara Guthrie Patterson Trust awarded $50,000 to support of the research of CSHL scientist Hollis Cline. The Laboratory found a new and wonderful friend in 1-in-9: The Long Island Breast Cancer Action Coalition. 1-in-9 donated $20,000 to support cancer research in the lab of Michael Wigler and pledged their ongoing support.

In June, we launched a new planned giving program, the “Next 100 Years.” Planned giving utilizes creative financial planning, enabling donors to see real lifetime benefits as a result of their charitable donations. The program is designed to help build our endowment, a step that is vital to the maintenance of the Laboratory. We currently have 30 donors in the planned giving program, with gifts in the neighborhood of $6.5 million.

In addition to their generous personal support of the capital projects of the DNA Learning Center, our long-time friends Henry and Mary Jeanne Harris have gifted $20,000 through the Edwin S. Webster Foundation for unrestricted support of Learning Center programs.

DNA Learning Center

In July, the DNALC received a five-year grant of $400,000 from the Howard Hughes Medical Institute's Pre-college Science Education Initiative for Biomedical Research Institutions. The DNALC grant was the second largest of the 42 awards given. The Hughes program will support ongoing work with local school districts to vertically integrate genetics instruction at the elementary, middle, and high school levels. Significant resources will also be used to provide intensive enrichment for minority students at several New York City schools and to link these resource-poor schools to North Shore schools that have well-developed genetics education programs. The grant provides large-scale support for the Learning Center's *BioMedia* Computer Laboratory to model uses of high-level computing in biology education, including the *Student Allele Database*, which allows students to submit electronically their own DNA fingerprints and compare them with those of other students from around the world. This grant, plus annual support from the Corporate Advisory Board, allowed the Learning Center to recruit computational scientist Robert Muratore. Robert has training in engineering and biophysics, with work experience in the aerospace industry, medical research, and academia. Robert is responsible for operating the *BioMedia* Laboratory and administering the Learning Center's local area network of 25 UNIX, Macintosh, and Pentium computers. He is also developing an Internet node, through which students and teachers will access the *Student Allele Database*. His thesis work on three-dimensional imaging of brain activity will be important in an upcoming project to develop a computer-generated tour of a human cell to play in the *Multitorium* theater.

Scientific Awards

Several of our scientists were honored with prestigious awards this year. On November 11, David Beach was elected a Fellow in the American Academy of Microbiology, the highest honor awarded in this national organization. Earlier in the year, Nouria Hernandez was appointed Associate Investigator by the Howard Hughes Medical Institute. At year-end, James Watson was honored by the Charles A. Dana Foundation with a Distinguished Achievement Award in Health. The award was in recognition of Watson's work with the Human Genome Project and his participation in the founding of the Dana Alliance for Brain Initiatives.

CSHL Press

In 1994, CSHL Press published 12 new books and 3 new videotapes, launched a new journal, doubled the frequency of both existing journals, and prepared a new publication, *The Lab Manual Source Book*. Among the notable new books was the second edition of *Manipulating The Mouse Embryo* by Brigid Hogan, Rosa Beddington, Frank Costantini, and Elizabeth Lacy. The first edition published in 1986 illustrated the techniques needed for the new molecular approaches to the study of development. The new and entirely revised edition brings those techniques completely up to date and has already joined those perennial best-sellers *Molecular Cloning* and *Antibodies* as the most sought-after lab manuals from Cold Spring Harbor.

The popularity of these manuals prompted the development of a complementary publication—an annually updated source book for the users of the techniques the manuals describe. *The Lab Manual Source Book* organizes and indexes the materials needed

for work with genes, cells, and proteins and connects users with commercial suppliers of these materials. The 1995 edition has data on 15.000 products and 1400 companies and will be distributed free to manual purchasers early in 1995.

The development of publications with a popular, educational purpose continued with the release of a videotape and teachers guide. *Stories from the Scientists*, and a beautifully illustrated book/audiotape package, *The Double Talking Helix Blues*. The scientific "talking blues," sung by twins Ira and Joel Herskowitz. was featured on both network and cable television programs. Joel is a physician and Ira is a noted molecular biologist whose association with the Laboratory goes back to the late 1960s.

In journals, both *Genes & Development* and *PCR Methods and Applications* made strong progress editorially and in subscription levels. Both fared well in the annual release of citation analysis data, a measure of the extent to which papers published in journals are subsequently referenced in the scientific literature, and confirmed their respective importance in the areas of science they serve. We increased publication of *G&D* to twice monthly and of *PCR* to bi-monthly. In both cases, the transition was managed smoothly and has resulted in more rapid publication for the papers submitted. In June, we launched a new journal entitled *Learning & Memory*. Its appearance as a forum for the new molecular and cellular analysis of higher brain functions is an indicator of the optimism within this young, growing, and immensely exciting field. The journal has started well, and its distinguished editors are dedicated to publishing only papers of a high standard. Making this publication a financial as well as an editorial success will be a challenge in this underfunded field, but everyone concerned is agreed that the task is important and also optimistic that the goals will be reached as the extraordinary science in this area continues to advance.

A Strong Year for the CSHL Association

Since the Long Island Biological Association was formed in 1924 to assume control of the Biological Laboratory at Cold Spring Harbor from the Brooklyn Institute of Arts and Sciences, loyal supporters from the local community have been an important source of strength. The Cold Spring Harbor Laboratory Association, descendant of LIBA, continues to support science with its Annual Fund, which provides unrestricted money for research. This year. the Association raised nearly $600,000 to support Cold Spring Harbor science. Special mention should be made of a $100,000 gift from Edna Davenport, widow of John Davenport, our first "angel" in the late 1960s. Mrs. Davenport continues to be an angel to the Laboratory. Under the able direction of Association President Mary Lindsay, membership in the Association reached 741. Mary's strong leadership of the Association this last year has been a boon. Although we are sad to report that she has stepped down from the presidency, we are pleased that she retains a vital presence as Vice Chairman of the Laboratory's Board of Trustees. Long-time Lab oratory friend and supporter John Cleary is now the new president of the Association. We look forward to a productive term under John's able hand.

Mary Lindsay

CSHL Cruises onto the World Wide Web

This year, the Laboratory merged onto the Infobahn. A joint effort among the Press, Meetings, and Public Affairs Departments and with programming by Corp Reed from Tom Marr's group has resulted in CLIO—CSHL Information Online. CLIO is a server on the World Wide Web, the multimedia branch of the Internet. Via CLIO, anyone with Internet access can obtain information about CSHL Press books, upcoming meetings, or general information about the Laboratory. Users can even order books or register for meetings right from their desktop. Having a "Web server" provides us with an opportunity to increase our on-line offerings and continue to serve the academic community. The URL, or Internet address, for CLIO is http://www.cshl.org/.

A Broad Spectrum of Fund-raising Events

In our perpetual search for novel ways to combine the arts or recreation with fund-raising for science, we hosted a variety of events this year. On May 1, piano virtuoso Peter Orth returned to the Laboratory for a fund-raising concert. Mr. Orth's concert raised $7400 for the Undergraduate Research Program. On June 7, we held the first CSHL Golf Tournament at the nearby Piping Rock Club. This event attracted 125 participants who helped to raise more than $48,000 for science education at the DNA Learning Center. Special thanks are due to the tournament's organizers, led by Rick Clark (who replaced Douglas Fox this year as chairman of the Corporate Advisory Board): Morgan Browne, Douglas Fox, Arthur Herman, Michael Vittorio, and William Keen. We also thank the Badge Agency and ITI Hartford for co-sponsoring a $30,000 hole-in-one opportunity on the 17th hole. In July, the CSHL Association put on "Hot Jazz at Cold Spring Harbor," a dinner and concert featuring the Big Band sounds of Jerry Jerome and his All-Stars. This concert netted over $7500 to support Laboratory scientists.

Undergraduate Research Program

Each summer the Laboratory welcomes a new group of promising college students to take part in the Laboratory's Undergraduate Research Program. In 1994, 21 students were selected from a field of 180 applicants to spend 10 weeks living and working here at the Laboratory. The program not only taught the students about molecular biology, but also acquainted them with scientific life and modern research tools and methods. As ever, the 1994 participants worked on a wide range of projects, including crystallization of biologically important proteins, the biochemistry of nerve cells, biochemical pathways involved in cancer, and plant genetics. This year, the URP projects represented a particularly good cross-section of the science at the Laboratory, with nearly every major research group represented. Funding for the Undergraduate Research Program came from BioRad Laboratories, Burroughs-Wellcome Fund, C. Bliss Memorial Fund, The Garfield Internship, Hanson Industries, Libby Internship, National Science Foundation, Phillips Petroleum Foundation, Inc., Powers Foundation, William Shakespeare Internship, and Frederica von Stade Internship.

Partners for the Future

Autumn of 1994 ushered in a new group of Partners for the Future—five high school seniors who worked 10 or more hours per week in our labs after school from October

Front row: Maureen Berejka, J.D. Watson, Herb Parsons
Middle row: Susan Schultz, Judy Cuddihy
Back row: Jim Hope, Mike Ockler, Bruce Stillman, John Meyer

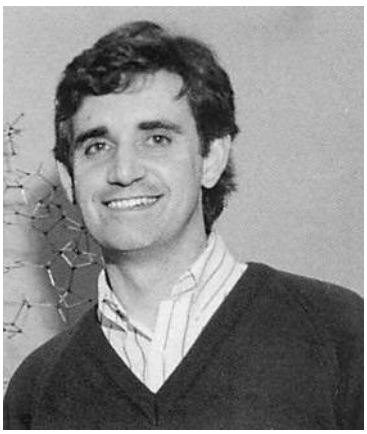
through March. This was the fifth such group to have the opportunity to work in high-level molecular biology labs of noted scientists and to be paid a stipend for doing so. The students, their respective high schools, and their mentors were as follows: Michael Burstein (Syosset High School) carried out cancer research in the Lab of Dr. Michael Wigler: Jay Bikoff (Huntington High School) studied plant genetics with Dr. Venkatesan Sundaresan: Vinay Gupta (Half Hollow Hills High School) studied neuroscience with Dr. Jerry Yin; Sharon Hoffmann (Oyster Bay High School) worked with Dr. James DeZazzo on *Drosophila* learning and memory; and Brian Fox (Cold Spring Harbor High School) worked with Dr. Michael Regulski and also studied learning and memory in *Drosophila*.

Long-term Service

Three of our employees celebrated 20-year anniversaries with us in 1994. Annette Kirk, Print Buyer and Production Manager; Michael Mathews, Senior Staff Scientist; and Lane Smith, Lead Plumber, were each congratulated on two decades of service. Celebrating their 15-year anniversaries this year were Maureen Berejka, Administrative Assistant to the President; Judith Cuddihy, Editor of *PCR Methods and Applications*; James Hope, Director of Food Service; Carlos Mendez, Cash Management Bookkeeper; John Meyer, Painter; Michael Ockler, Art/Photo Supervisor; James Herb Parsons, Audiovisual Manager; James Sabin, Materials Supervisor; Susan Schultz, Grants Manager; and Bruce Stillman, Director.

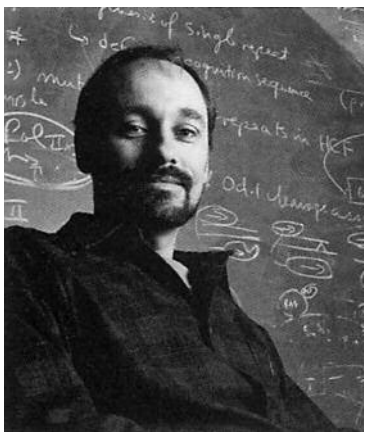
Changes in Scientific Staff

Cold Spring Harbor is traditionally a place with a high turnover of scientists. Most of our scientists are young and spend several highly productive years here before moving on to tenured positions at universities. Adding to this situation is the change in scientific funding, which in recent years has made jobs in industry increasingly appealing. This year, an unprecedented number of staff scientists took positions in industry. Michael Gilman, Senior Staff Scientist and a member of the Lab since 1986, accepted a position as Vice President and Science Director of Ariad Pharmaceuticals in Cambridge, Massachusetts. Robert Franza, who had been with us since 1982, moved to Delmar, California, to start a new company. Dan Marshak moved to Baltimore to become Senior Vice President of Research and Development for Osiris Therapeutics , Inc. Several members of our structural biology group moved on as well. Senior Staff Investigator James Pflugrath, with us since 1986, has taken a position with Molecular Structure Corp., in The Woodlands, Texas. Senior Staff Investigator Jeff Kuret went to Molecular Geriatrics in Lake Bluff, Illinois, and Senior Staff Investigator and crystallographer John Anderson moved on to Jacksonville, Florida. We also said goodbye to the excellent crystallographer and CSHL Fellow David Barford, who is now a University Lecturer at Oxford University in the U.K. David has maintained a collaboration with Senior Staff Scientist Nick Tonks. Senior Staff Investigator Dafna Bar-Sagi has taken a tenured faculty position at SUNY Stony Brook.



Bruce Stillman

Several visiting scientists have wrapped up their stays here. Saulius Klimasauskas from Rich Roberts' and Xiaodong Cheng's laboratory has gone to the Institute of Biotech Fermentas in Lithuania as a Senior Staff Scientist; Alexandre Melnikov is now a visiting scientist at the University of Georgia; Brian Cox from Bruce Fulcher's lab has returned to the U.K.; and Gavin Screaton, who spent a sabbatical in Adrian Krainer's lab, returned to Oxford University. John Scott, a visiting scientist in the Stillman lab, has returned to Hawaii. Tokio Tani, visiting David Spector's lab, returned to Kyushu University in Japan. Visiting computer scientist Stephen Lincoln spent the year in Tom Marr's group and left for Molecular Tool, Inc., and Roussoundan Bourtchouladze from Alcino Silva's lab accepted a staff position at the Psychiatric Institute at Columbia University.



Winship Herr

New Staff Members

With the arrival of Michael Hengartner and Yuri Lazebnik in the tall, the Laboratory begins a new research program in apoptosis. Hengartner comes to us straight from graduate school at MIT for a Staff Investigator position, and Lazebnik comes from postdoctoral work at Johns Hopkins as a Senior Staff Investigator. The Laboratory welcomed two new neuroscientists this year: Robert Malinow and Hollis Cline, a husband-and-wife team who come to us from the University of Iowa in Iowa City to become Senior Staff Investigators. Visiting scientists coming this year include Young-Seuk Bae from Kyungpook University in Korea, working with Dan Marshak; Boris Kuzin from the Russian Academy of Science, working with Grigori Enikolopov; and Ron Pruzan from Geron Corporation in Menlo Park, California, working in Carol Greider's lab.

Promotions

With the creation of the position of President of the Laboratory tor James Watson, on January 1 Bruce Stillman assumed the directorship, while still running a large, vigorous research lab—a feat no CSHL director has managed since Milislav Demerec retired in 1960, when the Laboratory had about one-fifth the staff it does today. To aid in some of the administrative duties of running a research lab, Stillman has appointed Senior Staff Scientist Winship Herr as Assistant Director. Winship received his Ph.D. from Harvard in 1982, after which he worked with DNA sequencing pioneer Fred Sanger at the MRC in Cambridge. He came to Cold Spring Harbor as a postdoc in 1983 to work with tumor virologist Joe Sambrook. Winship was promoted to the scientific staff in 1984 and became a Senior Staff Investigator in 1985 and Senior Staff Scientist in 1988.

Senior Staff Investigators Adrian Krainer, Carol Greider, Nick Tonks, and Tom Marr were promoted to Senior Staff Scientist. Although Cold Spring Harbor does not have a formal tenured position, Senior Staff Scientists have an appointment called 'rolling five,' which is renewed each day for five years. Adrian received his Ph.D. from Harvard in 1986. He came to Cold Spring Harbor that year as our first Cold Spring Harbor Laboratory Fellow and worked with Rich Roberts on RNA splicing. The Cold Spring Harbor Fellows program was modeled after Harvard's Junior Fellows program, which allows young investigators to pursue independent research. Adrian was awarded the fellowship in 1987, was promoted to the scientific staff in 1989, and then to Senior Staff Investigator in 1990. Carol Greider has followed a similar trajectory. After finishing up her Ph.D. at the University of California at Berkeley, where under Liz Blackburn she discovered the enzyme telomerase, Carol came to Cold Spring Harbor as a CSHL Fellow in 1988. She was appointed to the scientific staff the next year and to Senior Staff Investigator in 1992. Nick Tonks came to Cold Spring Harbor from the University of Washington in Seattle as a Senior Staff Investigator in 1990. Carol, Adrian, and Nick have in common the fact that they are all Pew Scholars. This prestigious program of support for young lab heads selects candidates from a small, elite group of nominating institutions. The Laboratory joined the ranks of Pew nominating institutions in 1990, and in the first three years, first Carol, then Adrian, and then Nick were elected to the Pew Scholars program. Tom Marr received his Ph.D. in 1981 from New Mexico State University. He then went on to research positions at the University of Arizona, E.G. & G., and Los Alamos National Laboratory, before coming to Cold Spring Harbor as Senior Staff Investigator in 1989. He is a leading expert on computational informatics, the science of using computers to uncover and analyze information in biological sequences. He has also become an integral part of the Dana Foundation Consortium on the genetics of manic depressive disease.

Crystallographer Xiaodong Cheng and protein chemist Ryuji Kobayashi were promoted to Senior Staff Investigator. Linda Van Aelst from Mike Wigler's lab was promoted to Staff Investigator. Rui-Ming Xu was promoted to Staff Associate II, and William Chang from Tom Marr's group was promoted to Staff Associate I.

Nick Tonks

Tom Marr

Adrian Krainer

Carole Greider

Postdoctoral Fellows

From Bruce Stillman's lab, Stephen Bell has accepted an Assistant Professorship at MIT and Thomas Melendy is now an Assistant Professor of Microbiology at SUNY Buffalo School of Medicine. Jeffrey Kazzaz finished up in David Helfman's lab and took a position at Winthrop University Hospital Cardiopulmonary Research Institute as a Research Scientist and Assistant Professor, while Mark Pittenger has gone on to work with Dan Marshak as a Senior Research Scientist at Osiris Therapeutics, Inc., in Baltimore. Timothy Connolly from David Beach's lab has also gone to Osiris as a Senior Scientist, and Tomohiro Matsumoto, also from Beach's group, has moved to Albert Einstein College of Medicine as an Assistant Professor. From Michael Mathews' group, Ben-Hao Dong returned to China as a postdoc and Claude Labrie has gone on to Lavel University Medical Center in Quebec. From Dafna Bar-Sagi's lab, Judy Cupp-Burris moved to West Palm Beach, Florida, and Michael Boyer has taken a position at Children's Hospital in Pittsburgh, Pennsylvania. Scott Henderson, from David Spector's lab, accepted a position with Mount Sinai School of Medicine as Director of Microscopy/Research Assistant Professor. Gokul Das left Winship Herr's lab for a position at the Texas Medical Center-Baylor College of Medicine, Cancer Therapy Research Center in San Antonio as an Assistant Professor. Three of Robert Franza's staff departed: Manfred Neumann and Annette Wilisch went to Tübingen, Germany, and Judith Scheppler went to SUNY Stony Brook. From Tom Marr's lab, Wentian Li left for Columbia University Department of Psychiatry. From Mike Wigler's lab, Anthony Polverino and Stevan Marcus have moved on, Polverino as a visiting scientist to Amgen, Inc. in Thousand Oaks, California, and Marcus to the University of Texas M.D. Anderson Cancer Center as an Assistant Professor. Lin Mantell, from Carol Greider's lab, is now a research associate at Winthrop University Hospital.

Graduate Students

From Bruce Stillman's lab, Karen Fein and York Marahrens went on to postdoc positions, Karen at Columbia University and York at the Whitehead Institute at MIT. From Dafna Bar-Sagi's group, Kurt Degenhardt, Tom Joneson, and ShaoSong Yang have moved with her to Stony Brook; Nicholas Gale went to Regeneron Pharmaceuticals in Tarrytown, New York; and Linda Graziadei went to MIT in Cambridge, Massachusetts. From David Helfman's lab, George Mulligan has gone on to a postdoc position at the MIT Center for Cancer Research, while Stefan Stamm has gone on to the Max-Planck Institute for Psychiatrie in Munich, Germany. Raymond O'Keefe, from David Spector's lab, went on to postdoc work at the Medical Resource Council Laboratory of Molecular Biology in Cambridge, England. From Robert Malinow's group, Neal Hessler took a postdoc position at the University of California at San Francisco, Yuchi Li left the group to join Oncogene Science in Uniondale, New York, and Diana Pettit has gone to Duke University in North Carolina. Zhong Wang, from Alcina Silva's lab, departed for Cornell Medical College in New York City as a research assistant and Celeste Casciato went from the lab of Xiadong Cheng to a position in Philadelphia. Sridaran Natesan went with Mike Gilman to Ariad Pharmaceuticals in Cambridge, Massachusetts, and Gary Lee left Gilman's lab to become a Research Assistant at Tularik, Inc., in San Francisco. Gilles Carmel went from the lab of Jeff Kuret to Molecular Geriatrics in Lake Bluff, Illinois. Dusan Kostic left Hong Ma's lab to accept a position with the Roswell Park Cancer Institute/Grace Cancer Drug Center in Buffalo. Roberto Mariani left Jacek Skowronski's group for a position at the Aaron Diamond AIDS Research Center. From Bruce Fulcher's group, Wolfgang Seufert

went to University of Munich in Germany as a Heisenberg Fellow. William Thomann has left Winship Herr's group to attend NYU Law School.

Residential Transitions for the President and Director

Late this spring of 1995, both of our families completed moves to our new homes, Ballybung and Airslie. The new position of President, with its major fund-raising activities, necessitated an on-campus President's House, and construction of Ballybung commenced in June 1992. It is located on virtually the same site where the Henry de Forest house Nethermuir had stood for almost 100 years before it mysteriously burned to the ground at the end of World War II. By then, it had been vacated by the elderly Mrs. de Forest following her husband's death and the breakup of its adjoining estate lands into two-acre parcels. In its place was built an unimaginative split-level ranch-style house, inappropriate for its magnificent site looking down Cold Spring Harbor and across to the Connecticut shore. No sighs were heard when it disappeared in less than two May days, since it was soon to be replaced by a much more appropriate dwelling of classical, somewhat Regency style. Preparing its plans were the talented architects, William Grover and Mahdad Saniee of Centerbrook, the widely respected Essex, Connecticut, architectural firm. During the past 20 years, Centerbrook has designed many important buildings for the Laboratory, including the Grace Auditorium and the Neuroscience Center.

The shape of the land parcel on which Ballybung was to be built dictated its almost square shape, with its key design feature being a skylight-topped two and one-half storied central hall which uses mirrors to magnify the light sent below, particularly into the eight internal windows that open into second-floor rooms and corridors. This architectural trick was employed near the end of the eighteenth century by the English architect John Soane, who was celebrated for the plans of many fine country homes as well as his London town home in Lincoln's Inn Fields and the monumental Bank of England located in the City.

Its unusual design made the construction not simple, and we were served well by the builder, William Baldwin, who previously played key roles in our Blackford Hall and McClintock Laboratory renovation-expansion projects. Equally important was the supervision by our own talented builder and Director of Buildings and Grounds, Jack Richards, who saw that the final costs closely approximated the budgeted target forecasts. Until its completion, we (Jim and Liz) remained uncertain as to what we should call it, but finally its name reverted to our first choice, Ballybung, the Gaelic name for Bungtown. From the start, we were tempted to give its exterior stucco-like "drivit" finish a strong color, finally settling on a creamy pumpkin orange hue frequently used in Italy. Helping us make the decision was our friend the English landscape architect, Elizabeth Banks, who while touring Lloyd Harbor noted the effective use of this color on a house on Middle Hollow Road. Later, Liz stood firmly behind the color choice when most of us were more faint-hearted.

The basement level of Ballybung contains windows with marvelous views of the Harbor, and adjacent to them there exists living space for visiting scientists. Currently, it is occupied by two English students, Jonathan Montagu and Greg Jefferis, who are here for a year doing research in their "gap year" between Eton College and their later university years in Oxford and Cambridge, respectively. Also within the basement is a specially designed archival space for the storage and study of the scientific and personal papers of what we anticipate will be a long line of accomplished Laboratory presidents.

Airslie was constructed in 1806 on the grounds of Nethermuir for cavalry officer and agricultural enthusiast Major William Jones, a member of the distinguished Long Island Jones family. The house and surrounding land changed hands several times over the following century—its name was found on a map dated 1855 detailing the estate of G.L. Willard, Esq.—and by the early 1900s was a part of the Henry de Forest estate. In 1942, four years after Henry de Forest's death, his widow donated the de Forest stables, built in 1914, and a parcel of land to the Laboratory, and the following year the Laboratory purchased Airslie and the surrounding seven acres.

Built in traditional Federal style, with a wide front porch and stately columns, the two and one-half story house has served as director's residence since that time. When then-director Milislav Demerec took up residence in Airslie, the century-old building underwent little change. Renovations on the house did not take place until 197 4 after former Laboratory director John Cairns departed for England. Prior to the Watsons moving into Airslie, the house was updated through structural renovations, the upgrading of mechanical services, and reconfiguration of the interior space to accommodate a young twentieth-century family. The renovations included the creation of a central staircase in the front of the house to the third floor. As they extended the twisting stairs upward, the architects opened the area in an inverted V-shape, to reveal the upper-most window of the house, a round, arched window in a sunburst design, created some 100 years before. Masterminded by architect Charles Moore and associates, this renovation was the beginning of an ongoing professional relationship between the Laboratory and Moore and his collaborators in the creative re-use of old buildings.

Despite 20 years of family living since the 1974 renovation, the stately house needed little renovation prior to the arrival of the Stillman family earlier this year. The exterior was repainted, the body of the house in its original cream color, and the trim changed from a greenish-gray to a rich, dark red. Set in the natural beauty of the harbor region, Airslie is shaded on the north side by an Amun Cork and a Kobus Magnolia, rare trees imported from the Orient, and an American Horse Chestnut, all planted for Miss Julia De Forest circa 1909 by Olmstead Brothers Landscape Artists (noted for their landscaping of Central Park and other major sites). Now mature trees, they are all among the largest of their kind on Long Island. Symposium picnics, Easter egg hunts, and other outdoor functions have been held on Airslie lawn since its acquisition in 1943, making it an integral part of our Laboratory home.

Inside Airslie, Grace has restored a cozy nineteenth century decor. With dark wood and traditional country furniture, the house is welcoming and warm. Flooded with sunlight—Airslie has large bay windows at both ends of the house and large windows all around—the house is spacious and airy. Soft mauves and greens are comfortable and soothing, making Airslie a wonderful home in which to raise a boy and a girl as well as a suitable place for the social affairs that are so vital to the Lab's function.

As we settle into our new dwellings, our residential relocations complete, we both look forward to many more productive and satisfying years at Cold Spring Harbor Laboratory.

July 19, 1995

James D. Watson, *President*
Bruce Stillman, *Director*