research. The projects and thinking I have outlined are all essential for our research institution to remain dynamic. At the same time, we must make sure that our scientists are supported to the fullest extent possible and that the research remains of the highest possible quality, in the new academic style.

HIGHLIGHTS OF THE YEAR

Research Highlights

Cancer Genetics and Cell Division

In March, Cold Spring Harbor Laboratory (CSHL) scientists Michael Wigler and Clifford Yen with colleague Ramon Parsons, M.D., Ph.D., of the Herbert Irving Comprehensive Cancer Center and Columbia-Presbyterian Medical Center, announced the discovery of a tumor suppressor gene, which they named PTEN. The gene appears to be altered in a large percentage of brain, breast, and prostate cancers, and evidence suggests that loss of PTEN affects the way a benign tumor becomes malignant. Unlike mutations of genes such as *hMSH2* and *BRCA1*, which were found in people who have hereditary predispositions to cancer, PTEN was discovered by analyzing the more common sporadic cancers. More than 80% of all cases of cancer are sporadic, meaning that they have no obvious hereditary contribution.

M. Wigler

PTEN received its name because of its similarity to phosphatases and tensin. The similarity between PTEN and protein phosphatases, which remove phosphates from proteins, is significant because many oncogenes—genes that help to transform normal cells into cancer cells—encode tyrosine kinases, which add phosphates to proteins. Tensin is part of a complex of proteins that sits below the cell surface and controls cell shape. Thus, PTEN may also be involved in the spread of tumors, by localizing to the cell surface and removing phosphates from key signaling proteins. In a productive collaboration between the Wigler laboratory and Nicholas Tonks' laboratory at CSHL, the two groups quickly confirmed that PTEN is a phosphatase and have identified proteins with which it interacts. These studies should point to the pathway in which PTEN functions in normal cells and which is altered in tumor cells.

Representational difference analysis (RDA), an advanced genetic technology developed by Mike and Nikolai Lisitsyn, then at CSHL, played a key role in the identification of a PTEN tumor suppressor gene. RDA is a procedure used to analyze the differences between two genomes. (A genome is the entire DNA sequence of an organism.) By comparing DNA from diseased and normal cells from the same person, scientists can use RDA to identify DNA sequences that differ between the cancer cells and normal cells. In the case of PTEN, RDA was used to find unique DNA sequences present in normal tissue but missing in breast cancer. To date, the Wigler lab has located about a dozen genetic loci potentially involved in breast cancer. Each of these discoveries represents a vital step forward in the path to earlier diagnosis and improved treatment for breast cancer patients, and it illustrates the growing realization of the genetic complexity of cancer.

In 1994, to further utilize RDA in the search for cancer-related genes, the Laboratory and Mike formed Amplicon Corporation. In October 1997, the Laboratory announced the acquisition of Amplicon by biotech leader Tularik, Inc. Tularik is the largest privately held biotechnology company in the nation, and its scientists are enthusiastic about continuing

collaborations with CSHL scientists while using RDA in an extensive cancer research program. Although Tularik, Inc. is located in California, the oncology division of the company will continue to operate on Long Island for at least 5 years and will continue to collaborate with CSHL scientists.

There was good news and bad news from Carol Greider's lab in 1997: The good news was the report of a line of telomerase knock-out mice. The bad news was that Carol left Cold Spring Harbor after 9 years to accept a position as Associate Professor in the Department of Molecular Biology and Genetics at Johns Hopkins University School of medicine in Baltimore, Maryland, to follow her historian husband to his new faculty position at George Washington University.

In October, Carol's group published a report about mice that lack telomerase, an enzyme that she discovered in 1985 and has continued to study. Telomerase is necessary for maintaining chromosome integrity. Several studies have suggested that telomerase also plays a role in cancer and cell senescence. The ends of chromosomes, called telomeres, shorten each time a cell divides. It is thought that when telomeres reach a critically short length, the cell division cycle arrests and cells enter into a senescent state after which they never divide again. Telomerase appears to sustain telomeres against this shortening.

In collaboration with Ron DePinho's lab at Albert Einstein College of Medicine, Carol's group bred a line of mice that lacked the telomerase enzyme. The results showed that

erase is not essential for the development of cancer, it may play an important role in tumor formation.

Scott Lowe and David Beach made a surprising new discovery about the transformation of normal cells into cancer cells. Usually, most human cells undergo senescence, or permanent cell cycle arrest, after a restricted number of cell divisions. This, in effect, limits the cells' life span. Cancer occurs when cells continue dividing beyond the normal limit or fail to die when they should. In 1981, scientists, including Mike Wigler at CSHL, discovered that a gene called *ras* was involved in some human cancers. This was the first discovery of a human oncogene that was derived from a tumor. In 1983, Earl Ruley—then at CSHL, now at Vanderbilt University School of Medicine—showed that *ras* acts in concert with other oncogenes to cause cancer. It was determined that most of these cooperative oncogenes can independently extend the life span of—or even immortalize—cells. Recently, Scott and David reported the surprising observation that when the oncogenic form of *ras* is overexpressed in normal cells, it immediately induces the same sort of cell senescence that occurs during cell aging. Two other genes, p16 and p53, both extensively studied at CSHL and elsewhere, are necessary for this type of cell cycle arrest. When p53 or p16 are absent from the cell, *ras* now stimulates uncontrolled cell division, rather than cell division arrest. This research provides important information about the multistep nature of cancer and suggests that, in the right context, it may be possible to exploit oncogenes to reverse tumor cell most

in learning and memory in mice. In 1997, Alcino tied previous results together through an experiment with collaborator Howard Eichenbaum of Boston University in which he monitored the activity of specific cells in the hippocampus in the brains of living, functioning mice.

Alcino has been studying "place cells"—specific, identifiable brain cells that fire only when an animal is in a precise place in its environment, a place that the animal's brain recognizes. These place cells are representative of the "place circuits" that are stimulated as an animal becomes acquainted with a place or area. The establishment of such a series of circuits is called spatial orientation or learning; the mouse recognizes familiar things as it travels about. Alcino tested the function of place cells in two types of mutant mice, each representing a component in learning and memory that Alcino has been studying—the αCaMKII protein and a CREB protein. Alcino created genetically modified mice that carry a point mutation in a single amino acid of the αCaMKII protein. Instead of firing at specific times like wild-type cells, place cells in animals with this αCaMKII mutation fire randomly when they are exposed to familiar and unfamiliar places, which indicates a lack of learning. Mice containing decreased levels of CREB also display this reduced learning, albeit to a lesser degree. Behavioral studies corroborate this finding, as the same mutant mice demonstrate a marked lack of spatial orientation.

In a second set of experiments, Alcino's lab successfully reversed the learning deficit in mice with the NF1 mutation characteristic of neurofibromatosis type 1. These mice have proven to be a valuable model for the study of this disease. He has confirmed a mechanism that is defective in NF1 mice and has restored the ability of mice to learn by breeding in a second mutation that counteracts the effects of the NF1 mutation. These

Cell Death during Development and Cancer Progression

In the study of programmed cell death, or apoptosis, Michael Hengartner's lab has made significant progress in identifying the genes involved and their roles. Working with post-doctoral researcher Mona Spector, Michael has continued to gain new information about this process by studying the tiny worm *Caenorhabditis elegans*, an ideal model organism for genetics research. Previously, three genes were known to be essential for properly controlled programmed cell death to take place in *C. elegans*, and two of these genes were known to have counterparts, or homologs, in mammals. Michael and others had shown that CED-3 and CED-4 work in concert to kill unneeded cells, a necessary process cells during normal development, and that CED-9 suppresses this action. If the worm carries a mutation in either CED-3 or CED-4, then this necessary mechanism to rid the body of unwanted cells never takes place, resulting in excess cells in the adult worm. In contrast, if there is a mutation in CED-9, programmed cell death is not controlled and cells die at an abnormally high rate.

Recently, Michael and Mona identified a previously unknown physical interaction

In 1997, Tatsuya and his colleagues purified and characterized condensin. They

20 Years of Splicing

On August 23, during the *Eukaryotic mRNA Processing* meeting, the Laboratory held a special historic session and champagne toast to honor the 20th anniversary of the discovery of RNA splicing and split genes. In 1993, the Nobel Prize for Medicine or Physiology was awarded to Rich Roberts and Phil Sharp for their contributions to the discovery of split genes. The discovery—that some regions of a gene, the exons, are transcribed into messenger RNA (mRNA), whereas other regions, the introns, are spliced out—led to the creation of a new field of science, known as RNA splicing.

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Phil Sharp and his colleagues in the 6d5cove0((5Pri-wi9nn1ing ve0(workns, 4im((5Authe 4im((llmergetrp 4

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until 1992. On December 16, 1997, he traveled to Washington, DC, to accept the medal from President Clinton.

Banbury Conference Center

Executives' Seminar Weekend at Banbury Center

Our close relationship with J.P. Morgan and Co., Inc. continues and has led to their support of the annual Executives' Seminar meeting, Banbury Center's equivalent of the CSH Symposium. To be sure, the scales are different—the Banbury Center is about one-tenth the size of Grace Auditorium—but both meetings, in their different ways, are unique occasions for reviewing the most exciting and interesting biological research. This year, the topic of the Executives' Seminar was *Genetic Engineering*. The coverage was broad. Stanley Cohen (of the famous Cohen-Boyer recombinant DNA discovery) discussed the origins of his work, Jim Wells described the genetic engineering of molecules, Shirley Tilghman and Richard Michelmore discussed the genetic engineering of animals and plants, respectively, and Kay Davies led participants into the world of gene therapy. Of special note was Alan Colman's presentation on the cloning of Dolly the sheep, and on the hope of the biotechnology community for the use of cloning to produce genetically engineered proteins in animals.

Gene Therapy of Duchenne Muscular Dystrophy

An important function of Banbury Center meetings is to promote research by hosting discussions on important topics. A recent example was the meeting on *Up-regulation of Utrophin Gene Expre*[illegible]

a gene-reactivation strategy for treating the thalassemias. We will hold further meetings at Banbury so that the expertise and knowledge already gained in other systems can be brought to bear on this debilitating disorder.

The "Post-Genomics" World

In the past two years, a flood of complete genome sequences has been published, including those of the bacterial "workhorse," *E. coli*, and of the yeast *Saccharomyces cerevisiae*; the genome sequence of the nematode worm *C. elegans* will be completed in 1998. Knowledge of complete genome sequences will have a profound impact on the way biological research is carried out, and two Banbury Center meetings examined what is to be done in this so-called "post-genomics" world. One meeting—*Integrating Genetic, Biochemical, and Other Data*—discussed how best to make use of all the data on the functions of cells and organisms that have been acquired during the past 100 years, in light of the more recently obtained genome sequences. The goal of this meeting is to produce a "virtual cell" that can be used as a predictive tool.

Physiologists traditionally have used other techniques to study organisms on more of a systems level, and the American Physiological Society is keen to use the tools of genetics to further their research. The meeting *Genomics to Physiology and Beyond* was designed to introduce physiologists to some of the ways in which genomics and the analysis of complex genetic traits might be used to answer the kinds of questions that interest them.

Robertson Research Fund

The Robertson Research Fund has been a continuing source of support for the Laboratory since 1973. Robertson funds supported labs in each of the Laboratory's primary fields of research: cancer, neurobiology, and plant genetics. Cancer research recipients were Xiaodong Cheng, Ryuji Kobayashi, Yuri Lazebnik, Benjamin Lee, W.

At the close of the 1997 term (February 1998), John Cleary concluded his term as President of the CSHL Association and as Trustee. We are most grateful to John for his outstanding service to the Association and to the Laboratory in general and will continue to seek his valuable advice and guidance. We look forward to working with Vernon Merrill who has now assumed the position of CSHL Association President.

Wendy Russell has been named Honorary Trustee. Wendy began serving on the Board in 1984, has served four 3-year terms, and was Secretary in 1985–1987 and 1992–1997. She has served on the Development, Executive, Finance & Investment, Banbury, Building, and DNALC Committees, as well as the CSHL Association.

Wendy is a superstar in raising financial support for the Laboratory and was instrumental in starting the Corporate Advisory Board (CAB) for the DNA Learning Center. She was also a vital and wonderful part of the Laboratory's initiative to establish on-site child care. Her tireless efforts toward that end, as well as on behalf of the CSHL Association Annual Fund, are deeply appreciated.

The Laboratory's continuing success is due, in large part, to the outstanding leadership and support of the dedicated people who volunteer their time in support of an excellent cause. We offer heartfelt thanks to each of these individuals for their contributions and active participation and look forward to continuing our relationship in the future.

Our new scientific trustees, whose terms became effective in 1997, are Edward Harlow, Ph.D., of Harvard Medical School and Massachusetts General Hospital; John Kuriyan, Ph.D., a prominent X-ray crystallographer studying signal transduction and DNA replication among other things as a Howard Hughes Medical Institute Investigator

In November, we were deeply saddened by the death of a very special friend, Mary Jeanne Harris. Mary Jeanne and her husband Henry U. Harris, Jr., have been members

and employment.

The Association held its annual Major Donor Cocktail party on November 16 in the home of David and Jamie Deming. Association members and scientists shared a relaxed evening of wonderful food and good conversation in the Demings' warm and comfortable home.

DNA Learning Center

We were very pleased to learn that the DNALC has received a 3-year grant of $820,000 from the Josiah Macy, Jr. Foundation to create an extensive Internet site for public education about genetics. The DNALC's newly created multimedia communications group will first develop *DNA from the Beginning*, an animated "primer" to provide background

my lab. The Perkin Fund gave $50,000 to neurobiologist Alcino Silva in support of his work on learning and memory in mice.

We also received two very generous gifts of real estate. Jill Hershey of Laurel Hollow and Bob Garland of Oyster Bay have each gifted their homes to the Laboratory, with each retaining a life estate. Jill and Al Hershey have been a part of the Laboratory for many decades, and Al's death in 1997 was a loss that we shared with Jill. Bob Garland, a good friend to several of our trustees, has been a supporter of the Laboratory since 1990. We are most appreciative of these very generous planned gifts.

President's Council

The President's Council was formed four years ago in an effort to bring together a small group of individuals who have a keen interest in science and the work of CSHL. Through their annual commitment of $25,000, the members provide support for the Cold Spring Harbor Fellows program. The funding is critical in attracting top-notch young scientists fresh from their Ph.D. studies. It allows them to embark on an independent research career, rather than assisting in the laboratory of an established scientist.

A major feature of the President's Council is its annual meeting that brings together this select group of leaders from business, finance, and science to discuss the latest developments in genetics research and biotechnology. The Council's 1997 meeting, held May 16–17, commenced with lunch on Friday at Ballybung and was followed by thought-provoking lectures by Scott Lowe and Ueli Grossniklaus of CSHL. The keynote speaker, Matt Ridley, of the Evolution and Behavior Research Group, University of Newcastle, England, opened the evening session with his talk on Gender Warfare and Evolution. Saturday's highlights included lectures by Rudi Jaenisch, of the Whitehead Institute for Biomedical Research, Massachusetts Institute of Technology; Suzanne B. Cassidy, of the Center for Human Genetics, Case Western Reserve University; and David Haig, of the Museum of Comparative Zoology, Harvard University. The mix of leaders from the business field and the scientific community evoked interesting insights as well as provocative discussions. The meeting ended on Saturday with the guests gathering once again at Ballybung for a parting luncheon. The following are Members of the President's Council:

Abraham Appel, Appel Consultants
Peter Bloom, General Atlantic Partners
James Conneen, A.T. Hudson & Co.
Michel David-Weill, Lazard Freres & Co.
Stefan Englehorn
Leo A. Guthart, ADEMCO
Charles E. Harris, Harris & Harris Group, Inc.
Walter B. Kissenger, WBK Associates
Donald A. Pels, Pelsco, Inc.
George B. Rathmann, ICOS Corporation
Hubert J. P. Schoemaker, Centocor, Inc.
James H. Simons, Renaissance Technologies Corp.
Sigi Ziering, Diagnostic Products Corporation.

Gavin Borden Visiting Fellow

On May 17, Leland Hartwell, Ph.D., now President of Fred Hutchinson Cancer Research Center, delivered the annual Gavin Borden Lecture. Dr. Hartwell discussed the role of yeast genetics in cancer research as part of the Gavin Borden Visiting Fellowship, named for the late charismatic publisher of scientific textbooks. The annual event was initiated in 1995 in honor of Gavin, who died in 1991 of salivary gland cancer, and in an effort to carry on the mission that was so dear to him: the education of graduate students. With this goal in mind, the annual lecture by an inspiring scientist is directed toward that audience, although it is open to all Laboratory staff. During their a 2-day stay at the Laboratory, Gavin Borden Fellows spend time talking with the graduate students who are currently studying at the Laboratory. Discussions typically involve science, life in science

and careers in science.

Major Building Projects

Over the course of 1997, we saw the completion of two very important building projects. The Mary D. Lindsay Child Care Center, which involved extensive renovation of the old De Forest Stables, was readied for its young charges in the late spring. The dedication of the building, which represented the culmination of a decade of effort to secure on-site child care for our employees, was held on Saturday, June 21. Tributes and thanks to Mary Lindsay and the Child Care Capital Campaign Committee were offered by the Laboratory's Director of Public Affairs and Development Susan Cooper, Laboratory

Baltimore, a member of the first class, who went on to share the 1975 Nobel Prize in Physiology or Medicine. The URP program exposes students to hands-on experimental approaches to science and helps lead them to a greater understanding of the issues involved in biochemistry, genetics, and molecular and cellular biology. Participants live and work at the Laboratory for 10 weeks during the summer, so that they are exposed not only to science in the lab, but also to life as scientists.

A list of the students, their schools, mentors, and research projects may be found in

Malinow. The Cold Spring Harbor High School brought their Japanese exchange students

third Cold Spring Harbor Laboratory Lyme Disease Forum. Moderators of the discussion were Steven E. Schutzer, M.D., of the New Jersey Medical School Department of Medicine, and John Dunn, Ph.D., of Brookhaven National Laboratory's Department of Biology. The speakers, Patricia K. Coyle, M.D., of the University Hospital at Stony Brook Department of Neurology and Raymond Dattwyler, M.D., of the University Hospital at

brated their 25-year anniversaries. Over the years, Susan evolved from librarian, to marketing for the CSHL Press, to Director of the Library, then Director of Public Affairs, and finally took on Development as well. Her departure to become Director for Institutional Advancement at the Trudeau Institute in upstate New York (see Changes in Administrative Staff, below) left many holes to be filled at the Laboratory. Terri Grodzicker, who came to Cold Spring Harbor as a scientist in Joe Sambrook's James lab, went on to become a staff scientist and then Assistant Director of Academic Affairs and editor of *Genes & Development*.

Celebrating 15-year anniversaries were investigator David Beach, scientific secretary Patricia Bird, Director of Facilities Art Brings, typesetter Elaine Gaveglia, DNALC Director David Micklos, manager of equipment repair Clifford Sutkevich, and circulation manager Barbara Terry.

Watson. Her decision to accept the position of Director for Institutional Advancement at the Trudeau Institute came as a great surprise, although it is not difficult to see why Trudeau would have courted her. Susan worked double-time, with unparalleled dedication and true devotion. She arrived here in 1972 as head librarian in the Laboratory's Carnegie Library, and she grew up with the institution, later adding the roles of Director of Public Affairs and then Director of Development. Susan orchestrated and carried out the Lab's spectacular centennial celebration nearly a decade ago, as well as planning ceremonies and booklets for the Lab's many building dedications over the years. She had a remarkable rapport with our friends, neighbors, and supporters, and she helped foster the careers of many of our scientists. Susan's vitality and enthusiasm made the Laboratory an enjoyable and interesting place to work. That she has "left home" to make her mark elsewhere is saddening to many of us, but we wish her and her husband Bob the best and much success.

Changes in Scientific Staff

Departures

Carol Greider moved on to a position as Associate Professor with Johns Hopkins University School of Medicine, Department of Molecular Biology and Genetics, in Baltimore. Carol's work with telomeres and telomerase, the enzyme that regulates their length, earned her much scientific and popular acclaim during her years at Cold Spring Harbor. Carol came to the Laboratory in 1988 as a Cold Spring Harbor Laboratory Fellow after completing her Ph.D. with Elizabeth Blackburn at University of California Berkeley,

Arrivals

Neurobiologist Karel Svoboda joined our scientific staff in June. Karel studied physics at Cornell University and biophysics at Harvard, where he used a technique called laser-optical tweezers to measure the force generated by individual molecular motors. More recently, at Bell Laboratories in New Jersey, he used two-photon excitation laser scanning microscopy to obtain never-before seen images of neurons in living brains. Two-photon excitation laser scanning microscopy is an emerging imaging technology; it utilizes the tremendous concentrations of light achievable with pulsed-laser light sources to "excite" fluorophores by two-photon absorption. Karel is applying his knowledge of this technique to the establishment and further development of a state-of-the-art neural imaging facility at CSHL.

David Jackson arrived in September, after doing postdoctoral research in Sarah Hake's lab at the Plant Gene Expression Center in Berkeley, California. David is a maize geneticist; he has been using transposons—Barbara McClintock's jumping genes—to study such phenomena as development of flowering plants, including the formation of leaves from a small group of cells called the meristem. In addition, David is studying intercellular transport, the movement of proteins and other molecules from one plant cell into another.

Andy Neuwald joined us in November, from the National Institutes of Health, National Center for Biotechnology in Bethesda, Maryland. Andy is a computational biologist and is interested in the development and use of statistical and algorithmic methods to classify and model protein domains and is also working on the development of a comprehensive database in which to log the resulting data.

Promotions

Yi Zhong, a staff member with our neurobiology program since 1992, was promoted to Associate Investigator. Bill Tansey, a postdoctoral researcher in Winship Herr's lab since 1992, was appointed Assistant Investigator in 1997, and he is now combining two active areas of research, gene transcription and cell cycle control. Doug Conklin, a postdoctoral researcher in David Beach's lab since 1993, was promoted to the position of Senior Fellow. Postdoctoral researchers Neilay Dedhia from Dick McCombie's lab, Robert Lucito of Michael Wigler's lab, and Elly Nedivi of Hollis Cline's lab were each appointed Research Investigator. Graduate student John Connolly completed his Ph.D. from the Massachusetts Institute of Technology while working in Tim Tully's lab and is now doing postdoctoral research in the Tully lab.

In addition, two visiting scientists have joined our staff: Clifford Yen and Masaaka Hamaguchi, both of whom were visiting Michael Wigler's lab, have each been appointed Research Investigator.

Visiting Scientists

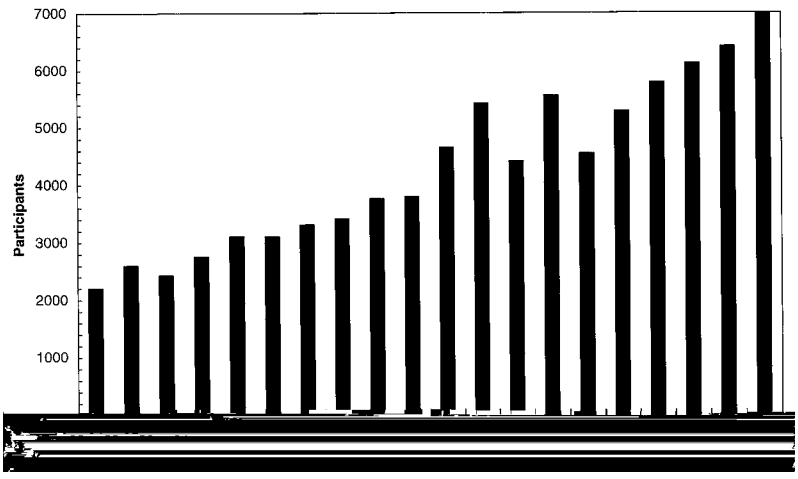
Nine visiting scientists wrapped up their sojourns to CSHL: Aiping Dong, visitor to Xiaodong Cheng's laboratory, has moved to a position as visiting scientist at Emory University in Atlanta, Georgia; Konstantin Galaktionov, who came from Leningrad, USSR in 1988, left David Beach's lab to accept an assistant professorship at Baylor College of

* Consists of Full time and Part-time Technical Support, Core Services, Publications, Meetings, Library, Public Affairs,

[redacted]

[redacted]

MEETINGS & COURSE PARTICIPANTS



Spring Harbor Laboratory remains a vital and exciting place to live and work. We have a very busy time ahead, but I am confident that we can efficiently incorporate these new programs into our existing infrastructure while maintaining a high standard of excellence and a leading role in biology and the biomedical sciences.

April 1998 **Bruce Stillman**