

HIGHLIGHTS OF THE YEAR

Research

Cancer

Scott Lowe has made an experimental breakthrough in “combination therapy” or the simultaneous use of two or more anticancer agents for treating the disease. Precancerous cells can be eliminated from the body by a self-destruct mechanism called programmed cell death or apoptosis. A hallmark of most cancers is a defect in apoptosis that enables precancerous cells to survive and proliferate. Because many traditional chemotherapy agents act in part by triggering apoptosis, such agents are frequently ineffective against tumors with defects in apoptosis.

Scott and his colleagues reasoned that using one drug to restore apoptosis (e.g., the mTOR inhibitor rapamycin) and another drug to trigger the process (e.g., doxorubicin) might be an effective way to treat cancer. They have shown that whereas rapamycin or doxorubicin treatment alone are ineffective against a mouse model of B-cell lymphoma, a rapamycin/doxorubicin combination therapy leads to remission of the disease. The study demonstrates that treatment decisions are best guided by knowledge of which gene products are functional or non-functional in a particular tumor, and it has produced a new paradigm for understanding and overcoming drug resistance in cancer patients.

Mike Wigler and Scott Lowe have collaborated with David Mu and Scott Powers of the Genomics Division of Tularik, Inc. to discover a previously unknown oncogene. The gene, called *KCNK9*, is expressed at abnormally high levels in half of the breast cancer specimens examined in the study and is similarly overexpressed in a large proportion of lung cancers. The experimental overproduction of *KCNK9* promotes tumor formation in mice, suggesting that elevated *KCNK9* levels may be sufficient to trigger the development of cancer. The discovery of *KCNK9* is significant because it reveals both a previously unrecognized mechanism for oncogene action (namely, potassium channels) and an attrac-

of virtually any gene (or genes) in cultured cells or in living animals. These findings enable them to use RNAi to carry out in-depth studies of tumor biology and treatment response, to design high-throughput screens to discover and validate new therapeutic targets, and to pioneer the use of RNAi itself as a potential therapy. As the first step toward opening that broad pipeline of cancer therapy discovery, Greg's lab has constructed a human genome-wide library of RNAi-based silencing vectors. In addition to using the library for his own work, Greg has made—and will continue to make—the library widely available for use by researchers throughout industry and academia.

Genomics and Bioinformatics

Lincoln Stein is pioneering the development of several powerful computer-based methods for analyzing a wide variety of biological data. For example, Lincoln's group has collaborat-

of productive effort, Nouria Hernandez and her colleagues recently achieved the first such reconstitution of human RNA polymerase III transcription.

RNA polymerase III uses the DNA of certain genes as a template from which it builds RNA transcripts, which in turn carry out a variety of essential cellular functions. Nouria's work has defined the entire molecular machinery required to carry out all steps of the transcription process (initiation, elongation, and termination) by human RNA polymerase III. Moreover, her studies have revealed an unexpected but intriguing role of another enzyme, called casein kinase II, in transcriptional regulation. Nouria's lab has shown that by phosphorylating different components of the transcription machinery, casein kinase II can either stimulate or inhibit transcription by RNA polymerase III. Cancer and many other diseases frequently stem from defects in transcriptional regulation. Nouria's results are therefore significant from both a basic research and a biomedical perspective.

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Most brain neurons are produced during embryonic development. However, several regions of the adult brain continue to spawn large numbers of neurons through the proliferation of neural stem cells. Moreover, it is becoming clear that these new neurons are integrated into existing brain circuitry. Grisha Enikolopov and his colleagues have discovered that a mole-

mechanisms that enable rodents to identify an odor in a single sniff may be similar to those that help humans take in an entire visual scene in a single glance. Part of Zach's work involves mapping the patterns of nerve cell activity in a rat's brain when the animal smells various odors. By discovering how the brain assigns identity and meaning to odors—and guides behavior based on such information—Zach and his colleagues are revealing new principles of neurobiology.

Linda Van Aelst studies the Ras and Rho family of proteins, which function—together with regulatory proteins called GAPs—as molecular switches that control a wide variety of important biological processes, including cell proliferation, cell morphogenesis, cell adhesion, and cell migration. Linda and her colleagues have recently explored the role in brain development of a particular RhoA GAP called oligophrenin-1. Loss of oligophrenin-1 function (e.g., as a result of a mutation in the corresponding gene) has been previously associated with X-linked mental retardation. In mouse RNA interference experiments, Linda has found that

plant viruses frequently spread through plasmodesmata, Dave's work may ultimately reveal new strategies for controlling such viral infections.

Marja Timmermans is investigating the role of stem cell patterning in the proper outgrowth of leaves and in generating the distinct top and bottom layers of leaves. She and her colleagues have isolated the *Rolled leaf1* gene and determined that the transcription factor it encodes specifies the top layers of leaves by conveying patterning signals from stem cells. Interestingly, Marja's lab has also shown that *Rolled leaf1* gene expression is spatially regulated—by RNA interference—through the inhibitory effect of a microRNA (miRNA166) that is complementary to a site in the *Rolled leaf1* messenger RNA. Marja's observations strongly support the emerging idea that microRNAs constitute a vital and widespread class of developmental signaling molecules in plants and animals.

Cold Spring Harbor Laboratory Board of Trustees

As is customary each November, Cold Spring Harbor Laboratory welcomed new members to the Board of Trustees. David Botstein, Ph.D., director of the Lewis-Sigler Institute at Princeton University, joined our Scientific Trustees. David was a trustee at Massachusetts Institute of Technology in the 1980s. Alan C. Stephenson, James M. Stone, Edward Travagianti, and Roy J. Zuckerman were welcomed as individual trustees.

Edward Harlow and Lorne Mendell concluded their terms and were honored for their outstanding service at the Board's November meeting. As noted in previous pages, we were saddened to learn of the death of our Vice Chairman, Edwin Marks, earlier in the year.

Laboratory Senior Management Restructured

After directing the Laboratory since 1994, I was named President of Cold Spring Harbor Laboratory by vote of the Board of Trustees on November 8. I will maintain my

Laboratory Employees

Long-term service

The following employees celebrated milestone anniversaries in 2003.

35 years	James Watson
30 years	Laura Hyman
25 years	Patricia Maroney, Christopher McEvoy, Charles Schneider, Beatrice Toliver, Jeanne Wiggins, Michael Wigler
20 years	Joan Ebert, Margaret Falkowski, Winship Herr, Daniel Jusino
15 years	Margot Bennett, Francis Bowdren, Nancy Dawkins-Pisani, Maryliz Dickerson, Grigori Enikolopov, Jeffrey Goldblum, Barbara Gordon, Jennifer Gordon, Kim Gronachan, Lynn Hardin, Salvador Henriquez, Louis Jagoda, Guy Keyes, Ronnie Packer, Jane Reader, Margaret Stellabotte, Arne Stenlund, Regina Whitaker

Recent staff

Adjunct Professor; Ken Chang to Research Investigator; Diane Esposito to Research Investigator; and Peter Sherwood to Director of Research Communications.

Departures

Shiv Grewal, Associate Professor; Douglas Conklin, Research Investigator; and Luca Cartegni, Senior Fellow, all departed the Laboratory in 2003.

Chief Financial Officer G. Morgan Browne retired from the Laboratory on December 31 after 19 years of service. Although he has agreed to stay active at the Laboratory, we will miss his day-to-day work on our finances. I wish to add my thanks to Morgan for his many years of dedicated and outstanding service.

Robertson Research Fund

The Robertson Research Fund has been the primary in-house support for our scientists for nearly three decades. During 2002, Robertson funds supported research in the labs of Carlos Brody, Dmitri Chklovskii, Josh Dubnau, Grisha Enikolopov, Josh Huang, Eli Hatchwell,

and the Hangzhou branch of the Beijing Genomics Institute. Several members of the Cold Spring Harbor Laboratory staff were in attendance, and Dr. Watson, who was unable to attend, delivered a videotaped speech.

DNA—The Future, a documentary directed by David Glover for Windfall Films in which Dr. Watson expresses his provocative views on DNA, science, and eugenics, was named the “Best Documentary on Science or the Natural World” by Grierson 2003. Grierson 2003 celebrates the best documentaries screened or broadcast in the U.K. between May 2002 and April 2003. The award was established in 1972, shortly

Harbor Laboratory's "recent advances in genomics," "its share of star genomics scientists" from James Watson to RNAi pioneer, Greg Hannon, *Arabidopsis* expert Rob Martienssen, and cancer genomics researcher Mike Wigler, and its broad research and educational mission. Cold Spring Harbor Laboratory Associate Professor Lincoln Stein was named "Most Innovative in Bioinformatics" in the same issue. *Genome Technology* readers—more than 20,000 scientists, researchers, technologists, and managers in advanced science research in drug discovery, molecular biology, genomics, proteomics, bioinformatics, and allied disciplines—are asked to submit nominations and votes for the "Institute of the Year" selection.

Building Projects

Several key scientific facilities were completed during the year. The Laboratory expanded its Bioinformatics center, creating much-needed new workspaces in the Williams building. The James Laboratory glassware kitchen was completely renovated and expanded to meet the growing needs of the building's scientific staff. Other scientific facilities, including a new Genome Center clean room for microarrays and a new confocal microscopy suite in Hershey, were constructed as well. Additionally, the Laboratory's new Flow Cytometry suite was completed in the Hershey building.

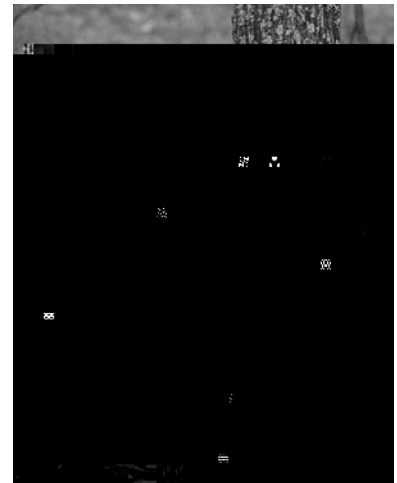
The Laboratory's program to improve housing for students and scientists has made considerable progress. The first phases of an ambitious project to provide housing for 32 students at Uplands Farm have been completed. A spacious, six-bedroom residence was completed at the Uplands Field Station, and the existing Caretaker's Cottage was completely renovated. Additionally, the foundations were laid for the construction of a new structure that will provide high-quality housing for half the total residents at the farm. We anticipate that this new structure will be completed by the end of 2004. In addition to the projects under way at Uplands Farm, the Laboratory has been systematically upgrading all of its existing housing. A tiny studio apartment in the Hershey building was gutted and expanded to a spacious two-bedroom apartment, and two apartments in Hershey were renovated and modernized.

Other facilities at the Laboratory received major improvements as well. Significant emergency power and air-conditioning upgrades were made to the Network Operations Center to help cope with the dramatic increase in demand for computing resources at the Laboratory. The Laboratory's Graphic Arts facility in the Hershey building was completely renovated and expanded to help facilitate its evolution into the new Media Arts and Visualization (MAV) department. Other projects included the resurfacing of Bungtown Road and a major renovation of the Russell Fitness Center in support of the Laboratory's recreation and employee wellness programs.

Education

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The high-quality production of the 27 courses and 19 meetings hosted at Cold Spring Harbor Laboratory throughout the year was impressive as usual. Most notable this year, however, was the entire Meetings and Courses, Facilities, and Food Services staffs' profes-



Rare red-tail hawk watching construction at Uplands Farm.

sional response to many unexpected and unusual challenges this year. With two very special meetings—*The Biology of DNA*, in celebration of the 50th anniversary of DNA, and *JDW: A Celebration*, in honor of Jim Watson's 35th anniversary at the Laboratory—on the agenda, the staff was prepared for a busy year without dealing with a disease epidemic, a blackout, and a major snowstorm as well.

For the first half of the year, the staff responsibly handled the dozens of questions, concerns, and fears regarding the SARS outbreak, which caused more than 8000 illnesses and more than 700 fatalities in two dozen countries, affecting the travel and safety of many of our international and national meetings and courses participants.

On August 14, most of the Northeast and Midwest were left in the dark when the United States suffered its largest blackout since 1977. For 22 hours we were wZZandwcdRa SWcdRblackallackout7i

friends from Lloyd Harbor. Harold Varmus, Nobel laureate, former Director of the National Institutes of Health and current President of Memorial Sloan-Kettering Cancer Center, was the guest of honor.

Throughout the rest of the year, there were 19 meetings at Banbury, with 654 participants. Of these, 81% came from the United States, drawn from 33 states. The participants from abroad came from 21 countries, once again showing the high esteem in which meetings at Banbury are held throughout the world. As usual, the Banbury Center program dealt with eclectic, interesting, and often controversial topics. *Taxonomy and DNA*; *Taxonomy, DNA, and the Bar Code of Life*; and *Integrating Progress in the Genetics and Neuropharmacology of Schizophrenia*, were of the most notable.

Education Center

In 2003, the long-awaited second edition to David Micklos and Greg Freyer's *DNA Science* was published. Now 100 pages longer, including two new lab projects and the first substantial treatment of eugenics available in a general biology text, this book is sure to continue to be largely responsible for bringing DNA experiments to advanced high school and beginning college students.

On a more global scale, *DNA Interactive (DNAi)*, the DNALC's newest addition to the World Wide Web, has already received more than 375,000 visitors and has contributed to a 23% rise in visitation to the DNALC's family of award-winning Web sites, which received 4.85 million visitors in 2003.

Clemson University (South Carolina) and the Roberson Museum of Arts and Sciences (Binghamton, New York) became the fourth and fifth licensees to use the DNALC teaching methods, Internet technology, and intellectual property, while DNALC *West*, the Singapore Ministry of Education, and the Science EpiCenter (New London, Connecticut) all fully developed their programs initiated in 2002.

In-house, the DNALC received four awards from the National Science Foundation to develop educational programs that closely parallel the work of CSHL scientists David Jackson, Dick McCombie, Marja Timmermans, and Lincoln Stein. These opportunities offer unique laboratory experiences to students and faculty alike.

Press

The CSHL Press enjoyed a very productive year. Eleven new book titles were published and a larger number of books—79,000 copies—were sold, in more countries around the world than in any previous year. Among the laboratory manuals published for working scientists, perhaps the most notable was *RNA Interference*, a guide to a new, powerful, and swiftly adopted way of silencing genes. CSHL scientist Gregory Hannon edited what became the first authoritative book on the biology and applications of this experimental approach. It has been an instant success.

Textbooks for undergraduates are a recent addition to the publishing program. James Watson's classic textbook *Molecular Biology of the Gene*—first published in 1965 and for 25 years the book of choice for advanced undergraduate teaching in genetics—was comprehensively revised and published to acclaim in December, in a fifth edition written by Richard Losick, Tania Baker, Steve Bell, Alex Gann, and Michael Levine that seems likely to restore the book to a central place in the curriculum.

In a year in which many scientific conferences, cultural events, and news reporting around the world were devoted to the 50th anniversary of Watson and Crick's proposal for the structure of DNA, the Press assembled a book to honor Jim Watson. With essays by more than 40 eminent people who have worked with Dr. Watson in all kinds of contexts, *Inspiring Science: Jim Watson and the Age of DNA*, edited by John Inglis, Joe Sambrook, and Jan Witkowski, succeeded handily in presenting a multidimensional view of its subject and his diverse and extraordinary accomplishments.

Journal publishing at the Laboratory, which began with one journal in 1987, is now a core competence of the Press. In its 16th year, the program grew to a list of five publications with the addition of the journal of The RNA Society, *RNA*. In its first year with Cold Spring Harbor Laboratory, the journal program's financial goals were achieved and its reputation enhanced by incisive peer-review and editorial decision-making and the continued publication of high-quality papers in molecular biology and genomics.

Watson School of Biological Sciences

James D. Watson raised the idea of a graduate school at Cold Spring Harbor Laboratory in the fall of 1995. Just seven and one-half years later, the Laboratory awarded its first Ph.D. degree. On May 13, 2003, Amy Caudy—of the entering class of 1999—became the first Watson School student to defend her doctoral dissertation. This fall, Ira Hall defended his thesis, after just over three years in the School.

When the Watson School established the goal of offering a four-year Ph.D. degree in the biological sciences, one concern raised was whether it would be possible for students to perform substantive research. Four years later, it has proven possible. Caudy was one of 16 international graduate students to receive the 2003 Harold M. Weintraub Graduate Student Award, sponsored by the Fred Hutchinson Cancer Research Center, based on the quality, originality, and significance of her work. During his studies, Ira Hall participated in two projects recognized in 2002 by the journal *Science* as the "Breakthrough of the Year." This year, the American Association for the Advancement of Science recognized these two studies with the 2003 Newcomb Cleveland Prize, which acknowledges an outstanding paper published in *Science*.

The 2003 student recruitment was also very successful. Of 13 offers made to applicants, 8 were accepted—more than a 60% acceptance rate. Students turned down offers from the University of California, Berkeley, Massachusetts Institute of Technology, Stanford, and others to join the School. With one deferral from 2002, there were nine entering students this year. On August 25, Hiroki Asari, Rebecca Bish, François Bolduc, Monica Dus, Angélique Girard, Christopher Harvey, Jeong-Gu Kang, Izabela Sujka, and Wei Wei began their adventure in becoming scholars in the biological sciences.

Collections and Resources

In 2003, the CSHL Library continued to provide information to its scientists, both traditionally and electronically. In addition to the many new databases that the library had acquired in 2002, they tested and added several new databases and e-books—including *Current Protocols* in nine subjects—to the collection this year. InterLibrary Loans are now mostly delivered in PDF format, and WebCat, the on-line catalog, now includes most of the titles in the Library's collection, including rare books. The library has continued to participate in the BioInformation Synthesis Collaborative (BISC), which the Harvard Libraries (Museum of Comparative Zoology and Biological Laboratories Library) joined in 2003. The Archives has

undergone tremendous growth and development as well. *The Oral History Project*, which aims to document Cold Spring Harbor Laboratory history through the eyes of the scientists who worked and visited here, grew to 40 interviews and will ultimately be made available through our Web page. In conjunction with *The Oral History Project*, a second archival project was initiated this year: the *Memory Board*. The *Memory Board* is an on-line forum that paints a picture of the lab through the eyes of anyone who contributes their written recollections to the Web site. These are typically casual contributions that attempt to capture a complete view of what makes Cold Spring Harbor Laboratory special.

50th Anniversary of the Double Helix

On the morning of Saturday, February 28, 1953, Jim Watson cleared his desk in the

Carrollis Laboratory, Cold Spring Harbor, New York. He had just received the first draft of the paper by James Watson and Francis Crick, with Maurice Wilkins, which would revolutionize biology. The paper, "Molecular Model of the Structure of the DNA Molecule," was published in the journal *Nature* on February 28, 1953.

- May 12 Barry Scheck, founder, *The Innocence Project at Cardozo Law School: Barry Scheck: The DNA Defender.*
- May 27 Eric Lander, one of the principal leaders of the Human Genome Project: *Eric Lander: Living in a Genomic World.*
- September 21 Tim Tully, Cold Spring Harbor Laboratory neuroscientist, and Suzanne Nalbantian, C.W. Post English professor:

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Matthew Schreiber, Cold Spring Harbor Laboratory's second artist-in-residence, returned on June 28 to display the holograms he created during and after his visit to the Laboratory the previous summer. The exhibit, which ran until July 16 and was open to the public, focused on the history of genetics in conjunction with the 50th anniversary of the double helix and the many important events that have taken place in Bush Lecture Hall.

After a hiatus in 2002, *FotoLab* returned to Bush Lecture Hall this year. Thirty-eight employees displayed their personal photography in *FotoLab II*. An opening reception took place on July 20, and the exhibit was open to the public until August 10.

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This summer, Cold Spring Harbor Laboratory teamed up with the Heckscher Museum of Art and the Cinema Arts Centre in Huntington for the first time to present *Spend a Day with DNA* on July 12, 26 and August 9, 23. Sponsored by Vytra Health Plans, the program was the

Kopec, Shraddha Pai, Charles Prizzi, Laurence Denis, Cara Brick, Ingrid Ehrlich, Susan Janicki, and Carla Margulies.

Institutional Advancement

Ca i a and ro ram Con ri ions

Private funding is critical to our research programs. Philanthropy enables the successful, innovative projects that are not yet eligible to receive public funding. For this reason, we especially appreciate our close supporters who make major gifts to our cancer and neuroscience programs. We gratefully acknowledge donors of \$100,000 or more to the cancer program—the Lustgarten Foundation for Pancreatic Cancer Research, the Miracle Foundation, the Louis Morin Charitable Trust, the Dana Foundation, Manyu Ogale, and the Seraph Foundation—and donors of \$100,000 or more to the neuroscience program—the Dart Foundation, Ira Hazan, the estate of William L. Matheson, the G. Harold and Leila Y. Mathers Charitable Foundation, the Simons Foundation, and the St. Giles Foundation.

so, a campaign was initiated this year to raise funds to add much-needed space and equipment to the existing structure, so that current and future generations of scientists and historians will be able to access, preserve, and study valuable archival and research materials. The new annex will include wheelchair accessibility; study space; storage, workshops, and reading areas; computer workstations; display space for the extensive archives and rare books collections; and the establishment of the Center for the History of Molecular Biology,

17-18. The theme was "The Mind of the Bird," and Council members were treated to lectures on Saturday. This year, the topics were "How Birds Will Save the World" (John W.

round, ongoing relationships between Cold Spring Harbor Laboratory and the thousands of scientists who have worked or attended a meeting or course at the Laboratory. In this inaugural year, it is a particular pleasure to acknowledge the gifts of alumni committed to sustaining Cold Spring Harbor Laboratory as a special place for science.

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In honor of the 50th anniversary of the double helix, our generous supporters made additional contributions, which enabled us to present a celebratory gala at the Waldorf-Astoria on February 28. The Dana Foundation provided a lead gift early-on and major support followed from foundations and corporations, such as Forest Laboratories, Genzyme Corporation, Pall Corporation, Pfizer, The Albert and Mary Lasker Foundation, and The Alfred P. Sloan Foundation. An historical exhibit which highlighted the contributions of New York area research to the discovery of the DNA double-helix was held at the New York Public Library's Science, Industry, and Business Library from February until August. "Seeking the Secret of Life: The DNA Story in New York" was generously funded by The Camille and Henry Dreyfus Foundation, The Ellison Medical Foundation, Morgan and Finnegan LLP, and The Rockefeller Foundation.

C ra ro rams

A group of Laboratory benefactors generously supported our efforts during the past year to purchase a Steinway "B" piano for our concert series. Ownership of a piano will enable the Laboratory to defray the high costs of renting a piano for individual concerts and will allow for additional programming in the years to come. We thank Lucy and Mark Ptashne and the Jefferson Foundation; Roger Hugh Samet; Victoria and Anthony Sbarro; Douchet and Stephen Fischer for their gifts.

Concluding Remarks

The combined research and education programs at Cold Spring Harbor Laboratory are unique and have become a model for how research can drive innovation in science education. Close collaboration between our research and education programs allows the DNA Learning Center and our advanced science courses to benefit from the latest advances in research. The growth of these activities has been significant, but it is moderated by the desire to remain the best at what we do and provide the highest quality of education. To maintain our leadership position, we must increasingly rely on philanthropic support. For this reason, I am most grateful to those who have helped us this year.

Bruce Stillman
President and CEO