

## 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.



Scott Lowe

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 attractive target for the development of novel cancer therapies.

*KCNK9* was discovered by using a method that compares two sets of DNA (e.g., normal vs. cancer cell DNA) and reveals segments of DNA that are either deleted or amplified. The method, called *representational difference analysis* (RDA), was previously developed by Mike Wigler and Nikolai Lisitsyn. Recently, Mike, Rob Lucito, and their colleagues have devised a new RDA-based technology that is one of the most powerful methods that now exists for profiling the genetic basis of cancer. The method is called *representational oligonucleotide microarray analysis* or ROMA. Mike and Rob have already used ROMA to uncover a striking collection of chromosomal deletions and amplifications associated with breast cancer through a collaborative study with Larry Norton of Memorial Sloan-Kettering Cancer Center and Scott Powers. Mike and Rob intend to use ROMA to survey a large number of breast, ovarian, and pancreatic tumors and cell lines, as well as leukemias and lymphomas.

Greg Hannon continues to make great strides toward developing RNA interference (RNAi) as a tool for manipulating gene expression in mammalian cells. Greg and his colleagues have demonstrated that they can use RNAi to efficiently and permanently silence the expression



Greg Hannon

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 collaborated with the USDA and Cornell University scientists to create a database called Gramene\* ([www.gramene.org](http://www.gramene.org)). Rice, wheat, corn, barley, and rye provide humanity with some 90% of its calories worldwide. All of these crop species are relatively closely related grasses with similar genome structures bearing many blocks of "colinear" genes. Gramene enables researchers to efficiently compare genome sequence data from these grasses and to identify genes of interest that may be used to develop new crop varieties with improved agricultural characteristics. (\*The name Gramene is based on the Latin "gramen" meaning "grass" and on the Grameen Bank, which makes loans to the rural poor in emerging economies.)

Lincoln is also a principal participant in the International HapMap Project ([www.hapmap.org](http://www.hapmap.org)) which released its first results in 2003. The project involves mapping the



Lincoln Stein

locations of variations in the human DNA sequence, many of which may ultimately be found to underlie specific diseases or differential response to therapeutic intervention. The goal of the project is to help researchers discover genes associated with cancer, heart disease, diabetes, neurological disorders, and other ailments, as well as genes associated with treatment response.

By applying a "methylation filtration" method they recently developed that captures gene-rich regions and excludes the vast majority of repetitive, gene-poor DNA, Dick McCombie and Rob Martienssen have achieved a dramatic shortcut to sequencing the genes of corn. The approach should provide a similar boost to the sequencing and comparative analysis of other genomes in a wide variety of biological, biomedical, and biotechnological settings.

### ***Biochemistry***

A Holy Grail of biochemistry is to reconstitute the activity of complex cellular machinery in the test tube from highly purified components. Only when such purity is achieved can researchers be sure that they have identified everything that is required—and nothing that isn't—for cells to carry out all the steps of a particular biological process. After several years

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.



Nouria Hernandez

### **Neuroscience**

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 molecule called nitric oxide (NO) is a pivotal, natural regulator of the birth of new neurons in the adult brain. Grisha, Mike Packer, and Yuri Stasiv have shown that blocking NO production stimulates neural stem cell proliferation and hence dramatically increases the number of neurons that are generated in the brains of adult rats.

Importantly, the new neurons that arise as a consequence of blocking NO production display properties of normal neurons, and they appear to contribute directly to the architecture of the adult brain. Grisha's work suggests that modulating NO levels might be an effective strategy for replacing neurons that are lost from the brain due to stroke or neurodegenerative disorders such as Alzheimer's, Parkinson's, and Huntington's disease.

Thousands of odors that smell the same to us, or that we cannot perceive at all, are quickly recognizable as distinct and potentially meaningful odors to rodents and other animals. By studying how rodents can rapidly and accurately discriminate one odor from another, Zach Mainen is uncovering fundamental principles of brain function that apply in many settings, including how our own brains work. Zach and his colleagues use olfaction as a model system for exploring how groups of neurons participate in perception, motivation, decision-making, and ultimately consciousness.

Recently, Zach and Naoshige Uchida found that rats get a complete sense of an odor with each sniff, and they speculated that rodents probably use a rapid series of such olfactory snapshots to solve complex problems like tracking the source of an odor. Humans are far more attuned to the visual world. However, according to Zach, the neural



Zach Mainen

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 oligophrenin-1 is required for nerve cell structures called dendritic spines to form normally in

a region of the brain required for learning and memory called the hippocampus. Moreover, Linda and her colleagues showed that the effect of decreased oligophrenin-1 on brain development can be mitigated by a drug that inhibits RhoA signaling. The latter finding may ultimately lead to treatments for X-linked mental retardation.

Humans obviously differ from the fruit fly *Drosophila* in many ways. Nevertheless, because we have much in common with it (e.g., thousands of very similar genes, a nervous system, and an ability to learn and remember), studies with fruit flies have revealed a great deal of information about human biology. Yi Zhong is now using the power of *Drosophila* research to explore the causes of Alzheimer's disease and to drive therapeutic discovery.

Versions of proteins implicated in Alzheimer's disease (e.g., amyloid precursor protein) are present in the *Drosophila* brain, suggesting that the functions disrupted in Alzheimer's are conserved in the fly. Yi and scientists at Novartis have taken advantage of this fact and have shown that expressing a pathogenic fragment of amyloid precursor protein (human A $\beta$ 42) in the *Drosophila* brain causes nerve cell death, plaque formation, and memory deficit reminiscent of Alzheimer's disease. Research using mouse models of Alzheimer's are still essential. However, Yi's work establishes a powerful alternative for testing new theories about how the disease develops and progresses, for identifying new gene or protein targets for treating Alzheimer's disease, and for rapidly screening large numbers of drugs for their therapeutic potential.



Yi Zhong

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

Stem cells generate new organs and tissues throughout the lives of plants—sometimes for centuries. The size, shape, location, and many other properties of such organs and tissues are determined by a complex process called stem cell patterning. One aspect of stem cell patterning involves the movement of regulatory proteins from cell to cell through channels, unique to plants, called plasmodesmata. To begin to reveal the components, architecture, and functions of plasmodesmata, Dave Jackson and his colleagues have isolated a number of mutations that affect the transport of a test protein through plasmodesmata. Consistent with the notion that transport through plasmodesmata is important for stem cell patterning, some of the mutations display developmental phenotypes. In addition, because devastating



Marja Timmermans

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. Zuckerberg 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.



Ed Harlow



Lorne Mendell

### 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 positions as the Chief Executive Officer and as Director of the CSHL Cancer Center. Through a simultaneous vote, Jim Watson was named Chancellor, after serving as Cold Spring Harbor Laboratory's President since 1994. This new position reflects his continuing role in supporting the Laboratory's educational mission through its programs for high school, undergraduate, and graduate students, especially through its Watson School of Biological Sciences, named after him at its inception in 1998.

Following these new appointments, Dr. Hollis Cline accepted the position of Director of Research. Holly is the Charles Robertson Professor at Cold Spring Harbor Laboratory and has made major contributions to the understanding of brain development and function. Holly has been serving as the Laboratory's Associate Director of Research since August 1, 2002. She will continue to serve in similar capacities, with increased involvement in the future research directions of the Laboratory.



Edwin Marks



## **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

### ***New Staff***

Alexei Koulakov joined Cold Spring Harbor Laboratory as an Assistant Professor in May. Alex came to us from the University of Utah where he was an Assistant Professor in the physics department. He received his graduate degree in physics from the University of Minnesota and was a fellow at the Sloan Center for Theoretical Neurobiology at the Salk Institute for Biological Studies.

Partha Mitra was appointed to the position of Professor in August and will strengthen our neuroscience program. Partha came from Bell Laboratories where he worked as a researcher in the theoretical physics department. He received his graduate degree in physics from Harvard University. Partha is also an adjunct associate professor at Cornell University Medical School, an adjunct faculty member at both Princeton University and the New York University Medical School, and a visiting associate at Caltech.

In December, Wolfgang Lukowitz was appointed to the position of Assistant Professor in the plant genetics department. Wolfgang came from the Carnegie Institute's Plant Biology Department at Stanford University. He received his graduate degree in genetics from the University of Tübingen in Munich, Germany.

Cordula Schulz arrived at the Laboratory as a Research Investigator in December. Cordula came from the Stanford University School of Medicine. She received her graduate degree in biology from the Maximilian-Ludwig University in Munich, Germany. We were also pleased to welcome Visiting Professors Matthew Ridley and William Benjamin this year.

Michael Townsend joined the Laboratory as Director of Information Technology in March. Mike was previously with Lehman Brothers in New York where he managed numerous functions and special projects including equity securities infrastructure, Y2K Disaster Recovery, and Fixed Income E-Commerce Projects.

### ***Promotions***

A number of our staff were promoted in 2003, including Tatsuya Hirano to Professor; Yuri Lazebnik to Professor; Josh Dubnau to Assistant Professor; Rusiko Bourtchouladze to

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, Winship Herr, Yuri Lazebnik, Alea Mills, Vivek Mittal, Marja Timmermans, Linda Van Aelst, and Yi Zhong. It also provided support to new investigators Alexei Koulakov, Cordula Schulz, Partha Mitra, and Wolfgang Lukowitz.

### **Awards and Honors**

On February 14, Terri Grodzicker was honored by the American Association for the Advancement of Science (AAAS) for her distinguished contributions to scientific discourse and standards as editor of *Genes & Development* (published by the Cold Spring Harbor Laboratory Press) and as Assistant Director for Academic Affairs at Cold Spring Harbor Laboratory. Since 1974, the AAAS Council has been electing those members to the rank of AAAS Fellow whose “efforts on behalf of the advancement of science or its applications are scientifically or socially distinguished.”



Terri Grodzicker

*DNA Interactive* ([www.DNAi.org](http://www.DNAi.org)), the newest addition to the Dolan DNA Learning Center Web site family, was selected as a winner of a *Scientific American* 2003 SciTech award for being one of the best scientific resources on the Web for biology. The Web site was described as “ultra-sophisticated” and the award mentioned “the folks at Cold Spring Harbor Laboratory, the brains behind the site, are to be congratulated for giving the fabric of our lives the rich treatment it deserves.”

Scott Lowe, Deputy Director of the Cold Spring Harbor Laboratory Cancer Center, was awarded a \$5 million, 5-year Specialized Center of Research (SCOR) grant from The Leukemia & Lymphoma Society® on October 1. With this grant, he will collaborate with researchers at the University of Minnesota, the University of California, San Francisco, and the University of Chicago to create leukemia treatments that are more effective and less toxic to patients.

On October 6, Zhejiang University in China dedicated the “James D. Watson Institute of Genome Sciences” on the Zijing Campus. It is their hope to create an “Oriental Cold Spring Harbor Laboratory” by basing it on our model as an international institute integrating scientific research and academic exchanges. It will be operated jointly between Zhejiang University



Building Dedication Ceremony in China

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

after the death of the filmmaker John Grierson, and has been run by the Grierson Memorial Trust since its establishment in 1974. Grierson 2003 is an international event with awards in nine categories. This year, there were a record number of entries: a shortlist of 76 titles, and a final 36 nominations.

Dr. Roberto Malinow was selected to receive the 2003 MetLife Foundation Award for Medical Research. The award, consisting of a personal prize to the researcher and an institutional award to Cold Spring Harbor Laboratory, was established by MetLife in an attempt to treat and eventually cure Alzheimer’s disease, which already affects 4 million Americans and has the potential to affect as many as 14 million by 2050. It is awarded yearly to a “smart, successful, dedicated researcher who has made significant contributions to the understanding of Alzheimer’s disease” and “provides them with the means to continue their work.”

Z. Josh Huang, Assistant Professor, was awarded a 2003 EJLB Foundation Scholar Research Award, totaling CAN\$300,000 over three years. Up to seven outstanding young researchers are awarded each year. The EJLB Foundation was established in 1983 as a charitable corporation with an interest in medical and scientific research in all areas of neuroscience that pertain directly or indirectly to schizophrenia and mental illness.

Two papers published in *Science*, “Regulation of Heterochromatic Silencing and Histone H3 Lysine-9 Methylation by RNAi” (13 September 2002) and “Establishment and Maintenance of a Heterochromatin Domain” (27 September 2002) were recipients of the AAAS Newcomb Cleveland Prize this year. Laboratory employees Ira M. Hall, Catherine Kidner, Robert A. Martienssen, and Ken-ichi Noma, former Laboratory scientists Shiv Grewal, Gurumurthy D. Shankaranarayana, and Thomas A. Volpe, and colleagues Grace Teng, Nabieh Ayoub, and Amikam Cohen were all recognized as establishing “a new landmark in epigenetic control” through these papers. This is the oldest and largest of the AAAS awards, and it recognizes outstanding papers published in the research articles or reports section of *Science*. Each recipient receives a bronze medal and a share of the \$25,000 prize.

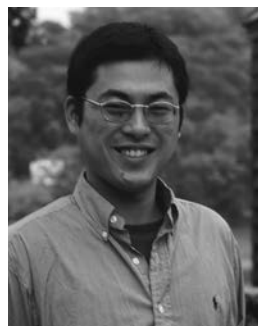
Cold Spring Harbor Laboratory was named “Institute of the Year” in the November/December issue of *Genome Technology*, which called the Laurel Hollow research and educational powerhouse “Long Island’s Genomics Gem.” The honor was determined based on Cold Spring



Ira Hall



Rob Martienssen



Ken-ichi Noma



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.



Rare red-tail hawk watching construction at Uplands Farm.

## Education

### Meetings and Courses

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-



Charlie Boone and Brenda Andrews on Bungtown road after the Blackout of 2003.

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 without power and had 300 visiting biologists, all here for the *Yeast Cell Biology* meeting, on campus. Posters and platform sessions were rearranged, and Food Services found enough charcoal to barbecue the evening's meal. The Facilities staff worked through the night to pump fuel from the local gas station to keep the emergency generators running.

Finally, a December 5th snowstorm dumped more than a foot of snow on the area and, again, the staff ensured that disruptions to the *Molecular Approaches to Vaccine Design* meeting were minimal.

### **Banbury Center**

The year 2003 marked the 25th anniversary of Charles Robertson's gift of his Lloyd Harbor estate of some 45 acres, the buildings on it, along with an endowment to contribute to the upkeep of the estate to Cold Spring Harbor Laboratory, creating what is now known as Banbury Center. The Silver Anniversary was celebrated with a small party on September 12. Guests included Bill Robertson and Anne Meier (two of Charles and Marie Robertson's children), former directors Victor McElheny (1978–1982) and Michael Shodell (1982–1986), and

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.

### **Dolan DNA Learning 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.

### **CSHL 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.

### ***CSHL Library and Archives***

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 Cavendish Laboratory at Cambridge University. His goal: To have a large, flat surface on which to explore how cardboard cutouts representing the building blocks of DNA might fit together to form the basic structure of the molecule of life. Although years of work by many scientists laid the chemical and intellectual foundations for the discovery of the double helix, the principal features of the now familiar DNA structure came together for Jim and Francis Crick over a short period in 1953.

To mark the 50th Anniversary of the double helix, Cold Spring Harbor Laboratory hosted or participated in several scientific, cultural, and celebratory events in 2003. Many of those events explored how the discovery of the double helix has transformed science, medicine, and society and rightly recognized the tremendous strides that were made in biology since that time (see pages 31–46).

## **Events**

### ***Symposium***

The 68th Annual Cold Spring Harbor Laboratory Symposium, “The Genome of *Homo sapiens*,” set a new attendance record, attracting nearly 500 scientists from around the world, and represented a remarkable bookend to half a century. Fifty years prior, at a Cold Spring Harbor Laboratory meeting in 1953, Jim Watson made the first public presentation of the double-helix model for the structure of DNA. In 1986, Jim organized a Cold Spring Harbor Laboratory meeting on “The Molecular Biology of *Homo sapiens*,” during which arguments for and against a proposal to sequence the entire 3-billion-letter human genome were presented. This year, that sequence was completed.

Marking this occasion, Dr. Francis Collins, who directed the United States’ later efforts to sequence the human genome, gave the 2003 Dorcas Cummings Memorial Lecture. Francis, one of the leaders of the sequencing effort, escorted the audience on a brief tour of the human genome and explained the surprises scientists found as they sequenced, namely, that the genome is much more similar between individuals than expected and the genome turned out to be much shorter than expected. CSHL Association President Trudy Calabrese welcomed the audience, where meeting participants were joined by friends from the local community, as tradition dictates. The endowed lecture is in memory of Dorcas Cummings, a longtime Laboratory friend and former Director of the Long Island Biological Association. After the lecture, scientists visited the homes of Laboratory neighbors to enjoy dinner and the chance to learn from one another.





Audience at 2003 Dorcas Cummings Memorial Lecture

### **Gavin Borden Visiting Fellows**

On March 26, Dr. Randy Schekman, Howard Hughes Medical Institute, University of California, Berkeley/ Department of Molecular and Cell Biology, delivered the ninth annual Gavin Borden Visiting Fellows Lecture titled "How proteins are sorted in the secretory pathway." The annual Gavin Borden Lecture was started by Jim Watson in 1995 in memory of Gavin Borden, a publisher whose *Molecular Biology of the Cell* and other books made a lasting impact.



Randy Schekman

### **Public Lectures**

This year's lectures, part of *The Double Helix 50th Anniversary Cultural Series*, focused on the practical uses of the double helix and how it has benefited humanity for the past 50 years.

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|----------|--|
| April 27 | David Gallo, director of special projects, Woods Hole Oceanographic Institution: <i>Origins—Evolution Destiny: Clues from the Deepest Sea</i> .                                  |
| May 5    | Oliver Sacks, renowned neurologist and best-selling author of <i>Uncle Tungsten</i> and <i>The Man Who Mistook His Wife for a Hat</i> : <i>Oliver Sacks: A Life of Science</i> . |

- 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: *A Composition of Memory: From Literature to the Brain.*
- October 7 Robert Shaler, director of forensic biology for the Medical Examiner's office of New York City: *Questions Answered: DNA Identification at the World Trade Center.*



Oliver Sacks

### **Other Lectures**

The West Side School lecture series moved to a new venue: the Arthur and Joan Spiro Auditorium at the Dolan DNA Learning Center. Nouria Hernandez ("How We Read Our Genes"), Senthil Muthuswamy ("Cells Gone Wild: A 3-D Approach to Studying Cancer"), Elizabeth Thomas ("Why Two Is Better Than One: Gene Duplication in Evolution"), and Shirley Chan ("Biology on the Web") delivered these lectures, which are geared toward 4th–7th graders and their families.

As in the past, Cold Spring Harbor Laboratory hosted the Huntington Hospital Lecture Series on cardiovascular health and related diseases in both the spring and the fall in Grace Auditorium.

### **Concerts**

Accompanying the lectures in *The Double Helix 50th Anniversary Cultural Series* was a comprehensive lineup of concerts that included an eclectic mix of musical styles from classical cello to piano duets to singers and postmodern chamber music performed by renowned young artists from around the world. They were all equally enjoyed by Meetings participants, CSHL Association members, and the general public.

- April 26 Vassily Primakov, piano
- May 3 Viviane Hagner, violin
- May 10 Thomas Carroll, cello
- May 17 Anton Belov, baritone
- September 6 Ken Noda and Jennifer Frautschi, piano and violin
- September 13 Antonio Pompa-Baldi and Emanuela Friscioni, piano
- September 20 Tin Hat Trio, postmodern Chamber Music
- October 4 Robert Belinic, guitar



Emanuela Friscioni and Antonio Pompa-Baldi

## **Exhibits**

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.

## **Spend a Day with DNA**

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 first-known attempt to relate how the discovery of DNA has served as an inspiration to artists and filmmakers throughout the world.

## **Community Outreach**

Once again, Betsy Panagot, Special Events Coordinator, organized our annual blood drive on April 14, which collected 42 pints of blood for the New York Blood Center.

Cold Spring Harbor Laboratory was well represented at the *6th Annual 1 in 9: the Long Island Breast Cancer Action Coalition 5K Walk/Run* sponsored by Cigna Healthcare on August 6. Forty-six employees participated, several of them placing, including Charles



CSHL Team at 1 in 9 Walk/Run

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

## **Institutional Advancement**

### ***Capital and Program Contributions***

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, Many 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.

Equally important to our research are the gifts with which we build and maintain our laboratories. Shortly before former Trustee William Matheson passed away in late 2002, he and his wife Marjorie announced their plans to make a gift for a future cancer building. With the gift we received this year, we are sure to build a fitting tribute to Mardi and Bill's dedication to the Laboratory's mission. Howard Solomon also gave \$1 million to help fund new science buildings.

We appreciate the Starr Foundation and the anonymous donor who made gifts of \$100,000 or more for the Cancer Genome Research Center. With these gifts, we will be able to continue to make advances in cancer, neuroscience, and plant genomics research at our outstanding Woodbury facility.

It is my pleasure to thank Jim Watson for his most generous donation of funds from lectures that he has presented. The resulting "2003 Fund" is an important source of unrestricted funds to further our research and education programs.

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

Now in its second phase of fund-raising, led by Robert D. Lindsay, the Watson School received more than \$2.4 million in gifts this year. These monies support the Dean's Chair, fellowships, and lectureships so that the Watson School can continue to grow and influence the biological sciences field. We appreciate the gifts of \$100,000 or more made by the Annenberg Foundation, Curt Engelhorn, Mr. and Mrs. Alan E. Goldberg, Mr. and Mrs. Robert D. Lindsay and Family, the Ziering Family Foundation, and Joy and George Rathmann/The Rathmann Family Foundation; the gifts of \$200,000 or more made by the Arnold and Mabel Beckman Foundation, the Lita Annenberg Hazen Foundation, the Florence Gould Foundation, the Miller Family Foundation, Bristol-Myers Squibb, and the William Stamps Farish Fund; and the gift in excess of \$300,000 from the Charles A. Dana Foundation, Inc.

### ***Carnegie Building***

We are initiating plans to make the Carnegie Building fit for the 21st century, and for the first time in 100 years, we are looking to renovate and expand the Library and Archives. To do



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, a new academic program to document research in the 20th and 21st centuries. We are grateful to Wacław Szybalski, Harold E. Varmus, Arnold J. Levine, Victor and Ruth McElheny, and Hiro Nawa for making the first contributions to this important campaign.

### ***Dolan DNA Learning Center***

Thanks to a generous gift from Joan and Arthur M. Spiro, the Dolan DNA Learning Center auditorium was dedicated as the Joan and Arthur M. Spiro Auditorium on September 9. Mr. Spiro is a member of the Cold Spring Harbor Laboratory Board of Trustees, an Executive Committee member, Chairman of the Dolan DNA Learning Center Committee, and Trustee Liaison for the DNALC's Corporate Advisory Board. We also thank Laurie J. Landeau, V.M.D., and Arrow Electronics for continued support of the DNALC's Biomedia addition. The Dolan DNA Learning Center was also able to contribute to the five-part television series on DNA and produce their *DNA Interactive* CD with a major grant from the Howard Hughes Medical Institute.

### ***President's Council***

Laboratory supporters who donated \$25,000 or more to the research of Cold Spring Harbor Laboratory Fellows Drs. Lee Henry and Terrence Stick were invited to a weekend retreat May



President's Council birdwatching at Shelter Island.



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. Fitzpatrick, Ph.D.); “The Wonders of Bird Migration” (Sidney Gauthreaux, Ph.D.); “Courtship and Mating in Birds” (Timothy Birkhead, Ph.D.); and “Developing Skills—Lessons from a Grey Parrot” (Irene Pepperberg, Ph.D.). On Sunday morning, participants went bird watching through the Mashomack Preserve on Shelter Island with our speakers, David Sibley (America’s premier birder and best-known bird illustrator) and James Watson, who retains an interest in ornithology he developed early in life.

### ***Planned Giving***

Bill Miller, Chairman of the Board of Trustees, and his wife, Irene, generously committed a substantial charitable remainder trust which, upon maturity, will be used to fund Watson School fellowships. We also received a further payment from the Estate of Elisabeth S. Livingston. This gift has provided the means to build much-needed housing for postdoctoral researchers at Uplands Farm.

In the fall, the benefits of estate planning were the subject of two seminars for the general public, held at our Cancer Genome Research Center in Woodbury. The sessions were oversubscribed and stimulated additional interest in the Laboratory. In November, we were pleased to welcome Peter Stehli to spearhead the Laboratory’s outreach for planned gifts, including bequests in wills, trusts, and other planned giving to benefit the education and research programs. A further meeting of the Cold Spring Harbor Laboratory Planned Giving Advisory Board was held in December. This board consists of accountants, tax advisors, trust officers, bank officers, investment advisors, investment bankers, and lawyers, representing firms located on Long Island, in New York City, and in Connecticut. The Board was briefed on the Laboratory’s activities and accomplishments and provided much-appreciated advice in support of the Laboratory’s goals.

### ***Breast Cancer Groups***

A crucial component to our breast cancer research program is the support we receive from hardworking local grassroots breast cancer groups such as Long Islanders Against Breast Cancer (L.I.A.B.C.); 1 in 9: The Long Island Breast Cancer Action Coalition; The Elisabeth McFarland Fund; and Long Beach Breast Cancer Coalition. This year, we were happy to become one of the beneficiaries of funds from F.A.C.T. (Find A Cure Today), a new fund-raising group based in Lloyd Harbor/Huntington. The Judi Shesh Memorial Foundation also made their first gift to us this year. We also gratefully acknowledge being chosen as one of the many recipients of funding from The Breast Cancer Research Foundation. The generous support we receive from these groups year after year is truly propelling our breast cancer research.

### ***Alumni Association***

This year, a Cold Spring Harbor Laboratory Alumni Association was formed, thanks to the efforts of Terri Grodzicker, Assistant Director for Academic Affairs, and the 18 alumni who agreed to serve on the board of the Alumni Association. The program aims to facilitate year-

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.

### ***Double Helix Gala and Exhibit***

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.

### ***Cultural Programs***

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*