HIGHLIGHTS OF THE YEAR

Research

Genomics and Bioinformatics

By using a powerful and sensitive genome research method they initially developed for cancer gene discovery, Mike Wigler and his colleagues have uncovered what is likely to be one of the most significant sources of normal genetic variation in the human genome. They are now using the same method to begin to study the genetic basis of mental illness and brain disorders including autism, schizophrenia, and Parkinson's disease.

Mike Wigler

The method, called ROMA (for representational oligonucleotide microarray analysis), was developed by Rob Lucito and Mike Wigler. When used in cancer research, ROMA compares the DNA harvested from normal cells and tumor cells. Such "normal-to-tumor" comparisons have already revealed several chromosomal amplifications (excess copies of DNA segments) and deletions (missing DNA segments) associated with breast, ovarian, and pancreatic cancer, as well as leukemia and lymphoma. The identification of these genetic alterations provides the basis for a better understanding of cancer biology and for developing improved diagnostic and therapeutic measures.

In the course of that work, when "normal-to-normal" comparisons of DNA from different individuals were carried out as an experimental control, Mike's lab uncovered several large-scale variations in the human genome that they dubbed copy-number polymorphisms or CNPs. We are all supposed to have two copies of each gene in the vast majority of cells in our body—one from mom and one from dad. But it is now clear that we all have alterations to this Mendelian pattern: Some people have only one copy of a gene due to a deletion, and others have more than two copies due to amplifications of a particular part of a chromosome. In part to aid their cancer gene discovery efforts, Mike, CSHL Senior Fellow Jonathan Sebat, and their colleagues have mapped more than 80 such CNPs in the human genome and found that, on average, the genomes of two individuals differ by about a dozen CNPs. Many more of these CNPs will be discovered.

Mike believes that many CNPs are likely to be associated with inherited susceptibility to neurological and cardiovascular diseases, diabetes, cancer, obesity, or other disorders. His lab has recently set out to use ROMA to search directly for the genetic basis of autism, schizophrenia, and Parkinson's disease. Dr. Scott Powers, once a postdoctoral fellow at Cold Spring Harbor Laboratory, returned as a faculty member this year from industry to ramp up the applications of ROMA to cancer gene discovery.

Molecular and Structural Biology

RNA interference (RNAi) has emerged as a widespread biological regulatory mechanism, as a powerful tool for both basic and applied research, and as a therapeutic strategy of enormous potential. In organisms from fungi and flies to plants and humans, RNAi has an essential multifaceted role in controlling gene expression. Small endogenous RNA molecules produced in the cell, or similar RNAs designed and introduced into cells by scientists, shut off the expression of genes either by blocking transcription of the gene or by blocking the trans-

Leemor Joshua-Tor

lation of the genetic code into protein. One of the best-studied RNAi mechanisms is the quashing of gene expression through the cleavage and destruction of templates for protein synthesis called messenger RNA, a biochemical process worked out in Greg Hannon's laboratory.

Until recently, however, the identity of the molecular scissors that actually cut messenger RNA during RNAi has remained elusive. A collaborative effort led by molecular biologist Greg Hannon and X-ray crystallographer Leemor Joshua-Tor has solved this puzzle by revealing that a protein called Argonaute2 provides the cutting action or "Slicer" activity of RNAi.

Greg and his colleagues focused on sorting out the functions of four distinct yet related mammalian Argonaute proteins (Argonaute1, 2, 3, and 4). With a biochemical approach, they found that only Argonaute2 is part of the multisubunit molecular machine that comprises Slicer activity. To extend these findings, Greg's group showed that messenger RNA cleavage by RNAi is abolished in mouse cells lacking Argonaute2 and that DNA encoding human Argonaute2 could restore Slicer activity in mouse cells lacking Argonaute2. These results were consistent with the idea that Argonaute2 itself provides the Slicer activity of RNAi. However, the possibility that a different protein provides Slicer activity could not be ruled out.

The work of Leemor Joshua-Tor's group clinched the case that Argonaute2 provides the Slicer activity of RNAi. Leemor and her colleagues were studying an Argonaute protein from the archaebacterium, *Pyrococcus furiosus*, by using X-ray crystallography (a method that reveals the three-dimensional structure of molecules at the atomic level). Determining a protein's structure by X-ray crystallography frequently provides valuable, if not decisive, clues about how that protein functions.

When the three-dimensional structure of *P. furiosus* Argonaute emerged from their data and was compared to other proteins of known structure and function, Leemor's group soon noticed that part of *P. furiosus* Argonaute was the spitting image of the "RNase H" family of proteins, whose members were known to cut RNA. With guidance from Leemor, Greg's lab did a final experiment based on the *P. furiosus* Argonaute structure that confirmed Argonaute2 as the protein that provides the Slicer activity of RNAi in mammals. Other information led Leemor to propose a model that explains precisely how Argonaute binds and cuts messenger RNA during RNAi.

The discoveries by Greg, Leemor, and their colleagues are a significant advance toward a comprehensive understanding of one of the most intriguing biological phenomena to be uncovered in recent years.

Cell Biology

In 1958, five years after he helped discover the double helix structure of DNA, Francis Crick coined the term "Central Dogma" to characterize the cellular processes whereby DNA is transcribed into RNA and RNA is translated into protein. Since then, researchers have typically explored individual aspects of these processes in isolation by developing separate systems for studying transcription and translation. David Spector and his colleagues have developed the first system for viewing how the Central Dogma unfolds in its entirety, from DNA to RNA to protein, within living cells.

David and postdoctoral fellow Susan Janicki developed a multicomponent, fluorescence microscopy imaging system in which the DNA near an inducible gene is labeled green, the

messenger RNA encoded by the gene is labeled yellow, and the protein encoded by the messenger RNA is labeled blue. The system was then used to capture time-lapse images in live cells as the inducible gene was switched on: First, the DNA architecture in the region of the gene became less compacted. Next, RNA appeared, was spliced in the nucleus, and subsequently exported to the cytoplasm. Finally, the protein appeared.

David Spector

Although scientists know that protein production involves regulated interactions among many molecules that carry out transcription, RNA splicing, translation, and other processes, they have been unable until now to simultaneously track all of the products of these processes as they are produced and move within living cells.

David and his colleagues have used their system to detect specific events that transform the architecture of chromosomes from a transcriptionally silent state to an actively transcribed state. This work has revealed fundamental information about how genes are switched on and off in the context of living cells. The system is being used by many researchers to explore how a variety of dynamic processes involving DNA, RNA, and protein are regulated in normal cells, as well as how those processes or their regulation might be altered in cancer or other diseases.

Neuroscience

The ability to form long-lasting memories shapes who we are and most often enriches (but sometimes impairs) our lives. Understanding the molecular and cellular principles that underlie learning and memory is one of the principal goals of our neuroscience program. This year, faculty members Roberto Malinow and Tony Zador collaborated in a study of a form of associative, "Pavlovian" learning known as fear conditioning.

Roberto Malinow

In humans, fear conditioning involves the association of an otherwise neutral stimulus (e.g., a particular place or sound) with an unpleasant experience. In experimental animals, in which a tone might be paired with a foot shock, a "freezing" response is used to measure fear. In both humans and animals, long after the initial learning period, the neutral stimulus alone elicits fear.

Roberto's group—in collaboration with Hollis Cline, Karel Svoboda, Linda Van Aelst, and others—has previously uncovered several of the molecular "rules" that govern long-term potentiation (LTP), a process whereby synpases become strengthened, that has emerged as a leading candidate mechanism for long-term memory.

Tony Zador

Those studies focused on a brain region called the hippocampus. They revealed that the controlled movement of neurotransmitter receptors called AMPA (α-amino-3-hydroxy-5-methyl-4-isoazole) receptors into synapses is likely to be a key event in the formation of memory. Importantly, these studies also led to the development of a number of powerful tools that Roberto and Tony used in their recent work.

A region of the brain called the amygdala is known to be required for learning and memory formation during fear conditioning. By using a recombinant version of AMPA receptors that specifically tags newly strengthened synapses, Roberto and Tony first tested whether fear conditioning in rats

leads to the strengthening of synapses in the amygdala. They found that as many as one third of the neurons in the amygdala strengthen synapses in response to fear conditioning.

This finding indicates that rather than being restricted to a comparatively small proportion of neurons, long-term memories are widely distributed among a large proportion of neurons. However, on the basis of other evidence (see below), Roberto and Tony do not believe that this wide distribution of memory-associated synaptic changes serves to make memories resistant to being disrupted (e.g., by brain damage or other perturbations). To test whether the strengthening of synapses in the amygdala is required for learning, the researchers used a different recombinant version of AMPA receptors—one that blocks the strengthening of synapses. They found that blocking synapse strengthening in the amygdala during fear conditioning disrupts the learning process that leads to memory formation.

Interestingly, Roberto and Tony also discovered that blocking synapse strengthening in as few as approximately 10–20% of the relevant neurons was sufficient to impair memory formation. This finding contradicts the conventional view that widely distributed memories are tolerant to perturbation and will change the thinking of many neuroscientists in this field.

Short-term or "working" memory is also an important process that enables us to interact in meaningful ways with others and comprehend the world around us on a moment-to-moment basis. A classic, albeit purely practical, example of short-term or "working memory" is our ability to look up a telephone number, remember it just long enough to dial it, and then promptly forget it. However, working memory is believed to be fundamental to many other cognitive processes, including reading, writing, holding a conversation, playing or listening to music, decision-making, and thinking rationally in a general sense.

Carlos Brody

Carlos Brody is exploring how neurons interact with one another to form neural networks that underlie working memory and other rapid and flexible cognitive processes. As part of an ongoing collaboration with Ranulfo Romo (Universidad Nacional Autónoma de México), Carlos' group is developing mathematical models for interpreting data collected by his collaborators, who use animals (macaque monkeys) to perform a simple task that involves working memory. In one version of the task, Romo's animals were trained to compare an initial stimulus (a vibration applied to a fingertip) with a second stimulus applied a few seconds later and to immediately provide a "yes" or "no" answer to the question: Was the first vibration faster than the second?

This behavior requires the animals to load the initial stimulus into their working memory ("loading phase"), hold information about that stimulus in their working memory ("memory phase"), compare that information to the second stimulus, and then make a decision based on the comparison ("decison phase").

At the outset of the study, Carlos and postdoctoral fellow Christian Machens hoped to develop a mathematical model—based on known properties of "spiking" neurons—that would explain how the brain carries out just the memory phase of the behavior. To their surprise, the simple "mutual inhibition" model they developed yielded a neural network architecture that explains not only the memory phase, but also the loading phase and the decision phase of the behavior. The model makes several predictions about the neurological basis of working memory that can be tested to confirm the likelihood that the model is a significant advance toward understanding fundamental properties of brain structure and function.

The human brain is estimated to contain 100 billion neurons (the number one followed by 11 zeros). Because a typical neuron forms approximately 1000 synaptic connections to other neurons, the total number of synapses in the brain is estimated to be 100 trillion (the number one followed by 14 zeros). The thin projections from neurons that form connections

with one another (axons and dendrites) can be thought of as the biological "wiring" of the brain.

Neuroscientists already know that brain neurons can and do form specific rather than random connections with one another to generate the observed wiring diagram of the brain. However, the precise patterns of such nonrandom connections, how the patterns are formed, and how these patterns underlie the brain's extraordinary information processing capacity are important questions that CSHL researchers are addressing in various ways.

Dmitri Chklovskii and his colleagues are using statistical analysis and mathematical modeling—coupled with in vivo, experimental observations—to search for recurrent, nonrandom patterns of local connectivity within the vast thickets of brain wiring diagrams. Finding such patterns would be strong evidence for the presence of functional modules (e.g., local cortical circuits) that process information. This year, Dmitri and his colleagues have potentially uncovered such functional modules by using two complementary approaches.

Dmitri Chklovskii

In one study, they chose the nematode worm *Caenorhabditis elegans* as a relatively simple model system. Previous studies had determined that this organism has 302 neurons and had partially mapped which neurons connect with which. However, these studies did not characterize nonrandom patterns of connectivity in a rigorous way. When Dmitri and his colleagues completed the worm's wiring connectivity map and considered all 13 possible patterns of connectivity that can occur among three neurons (one such "triplet" pattern being "neuron A connects to B, B connects to C, and A connects to C"), they found that three particular patterns, including the one above, stood out as appearing far more frequently in the *C. elegans* nervous system than they would by chance. They also discovered that some triplet patterns were *less* common than predicted by chance. Taking the analysis a step further, Dmitri and his colleagues found that among all 199 possible quadruplet patterns of connectivity that can occur among four neurons, one particular pattern stood out in *C. elegans* as appearing more frequently than it would by chance.

Significantly, Dmitri and his colleagues considered whether the frequent connectivity patterns or "motifs" that they discovered might be accounted for by previously known principles of neurobiology. They found no such explanation for the existence of the motifs, indicating that further analysis of the motifs may reveal important information about nervous system structure and function.

Because it was based purely on anatomical data collected by electron microscopy, Dmitri's *C. elegans* study did not include information about the strengths of connections between neurons. Therefore, to extend his findings into the physiological realm, Dmitri collaborated with researchers at Brandeis University. The Brandeis group had previously collected one of the largest electrophysiological data sets of its kind ever recorded—measurements of the connectivity of some 3000 individual neurons in the rat visual cortex.

Dmitri recognized that the Brandeis data could be used to explore his ideas concerning functional modules in the brain. He and his colleagues detected some of the very same nonrandom patterns of connectivity in the rat brain that they had observed in *C. elegans*. More importantly, they found that most connections formed by neurons in the rat visual cortex are weak and that the stronger connections (~17% of all connections) account for as much as half of the total synaptic strength of a particular network. In part because more strongly connected neurons fire more reproducibly, Dmitri proposes that strong cortical synapses—with particular connectivities—act as a network "scaffold" that is likely to generate reproducible patterns of activity and have an important role in brain function.

Cold Spring Harbor Laboratory Board of Trustees

At our November Board of Trustees meeting, we traditionally honor those who are concluding their service with us. This occasion was notable this year, since we said a special goodbye and thank you to our chairman William R. Miller, who led the Board through two 3-year terms. He will now join us at future Board meetings as our newest honorary trustee.

Charles Harris

Susan Hockfield

William R. Miller

Charles J. Sherr

Howard Soloman

Following Bill's departure, the Board unanimously elected Eduardo G. Mestre as our new Chairman, Lola Grace as our vice chair, and Edward Travaglianti as our secretary/treasurer. Their vision and experience will help CSHL to expand its research and educational goals, especially in the fields of cancer and neuroscience. Eduardo, a member of the CSHL Board of Trustees since 2001, is currently vice chairman of Evercore Partners, a leading investment and advisory firm, where he is responsible for the firm's corporate advisory practice. Lola, managing director of Sterling Grace Capital Management, previously served as the treasurer and secretary of our Board as well as chair of the finance and audit committees and a member of the Dolan DNA Learning Center committee. Ed, President of Commerce Bank Long Island and a 34-year veteran of commercial banking in the metropolitan New York market, joined the CSHL Board of Trustees in 2003.

Susan Hockfield, a scientific trustee since 1998, concluded her term as a scientific trustee of the Laboratory after being named the 16th President of Massachusetts Institute of Technology—the first woman in the institution's history. Although it is sad to see her leave, we are proud of Susan, who first came to know CSHL as a research scientist here in the 1980s. Scientific trustee Charles J. Sherr, M.D., Ph.D., and individual trustees Charles Harris and Howard Solomon also concluded their terms in November.

We welcomed new scientific trustees Laurence Abbott, Ph.D., of the Volen Center at Brandeis University, and Robert E. Wittes, M.D., physician in chief at Memorial Sloan-Kettering Cancer Center. Laurie Landeau, V.M.D., Nancy Marks, and Jerome Swartz, Ph.D., joined the Board as individual trustees this year.

Watson School of Biological Sciences Commencement Convocation

Founded with the mission to bestow the Ph.D. degree in biology in an unprecedented 4 years, the Watson School of Biological Sciences achieved its goal on April 25, 2004 when Amy A. Caudy, Ira Hall, Patrick J. Paddison, Emiliano Rial Verde, Elizabeth E. Thomas, and

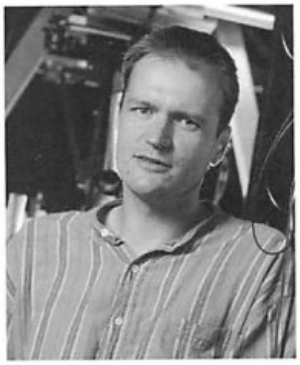
Niraj Harish Tolia became the first graduates of the School. This outcome is owed to the generosity of our benefactors and to the dedication of the faculty, administration, and the outstanding students we successfully recruited.

Patrick Paddison, Ira Hall, Elizabeth Thomas, Niraj Tolia, Amy Caudy, and Emiliano Rial Verde

Awards and Honors

CSHL Professor Lincoln Stein was named the 2004 laureate of the Benjamin Franklin Award in Bioinformatics. The Benjamin Franklin Award in Bioinformatics is a humanitarian award presented annually by *Bioinformatics.org* to an individual who has, in his or her practice, promoted free and open access to the methods and materials used in the scientific field of bioinformatics. Recipients are chosen based on nominations and votes by his/her peers—the more than 8000 members of the organization.

CSHL neuroscientist Karel Svoboda was the 2004 recipient of the Society for Neuroscience Young Investigator Award. The prize is awarded each year at the Society's annual meeting to an outstanding neuroscientist who has received an advanced professional degree within the past 10 years. He was also selected by *Popular Science* magazine as one of its "Brilliant Ten" young scientists in the United States for 2004.



Karel Svoboda

Recognized for his "promise of becoming a leader in research in the cure and treatment of cancer, cerebral palsy, and multiple sclerosis," Senthil Muthuswamy was named a Rita Allen Foundation Scholar. The Rita Allen Award is only awarded to a handful of researchers annually—all of whom have been on a tenure track for no more than three years.

The CSHL Press book, *George Beadle, An Uncommon Farmer: The Emergence of Genetics in the 20th Century,* by Paul Berg and Maxine Singer, was selected by the American Library Association for inclusion in its "Outstanding Academic Titles" (OAT) list for 2004. Outstanding Academic Titles are chosen from among more than 7000 books reviewed "for their excellence in scholarship and presentation, the significance of their contribution to the field, and their value as important—often the first—treatment of their subject." Comprising less than 3% of the 23,000 plus titles submitted, Outstanding Academic Titles have been called "the best of the best."

DNA Interactive (DNAi) DVD, produced by the Dolan DNA Learning Center (DNALC) in association with The Red Green and Blue Company (RGB) and Windfall Films, was named "Best Offline Factual" at the British Academy of Film and Television Arts (BAFTA) Interactive Entertainment Awards ceremony—the British version of the Oscars—in February. In its sixth year, the BAFTA Best Offline Factual award is given to "the most imaginative and effective use of offline interactivity to explore the factual world." The *DNAi* DVD was recognized as "an unusually rich and deep experience, stimulating personal exploration of the history, science, issues, and future of the genome from the unique perspective of the people involved in its research."

DNA Interactive DVD

In April, my colleague and friend Tom Kelly of the Memorial Sloan-Kettering Cancer Center and I were awarded the Alfred P. Sloan, Jr. Prize, one of three awards given annually by the

General Motors Cancer Research Foundation (GMCRF). The Sloan Prize recognizes the most outstanding recent contribution in basic science related to cancer research.

The Sabin Vaccine Institute honored CSHL Chancellor James D. Watson, Ph.D., with the Sabin Humanitarian Award at their *Salute to Lifesaving Discoveries* benefit dinner in May. The awards program is a yearly tradition for the Institute and extols the contributions made by scientists, philanthropists, and humanitarians who share in some aspect of the goals of advancing vaccine science for the benefit of humanity.

The United States Rice Genome Consortia, Cooperative State Research, Education, and Extension Service (Tucson, Arizona)—of which Cold Spring Harbor Laboratory is a principal member—were honored with the U.S. Department of Agriculture (USDA)'s Secretary's Award, presented by Agriculture Secretary Ann M. Veneman at the 58th Annual Secretary's Honor Awards Ceremony on June 25. Considered the highest award the USDA can bestow, the members of the United States Rice Genome Consortia were honored in the "Enhancing Economic Opportunities for Agricultural Producers" category for leading the United States partnership in the multinational achievement to decode the rice genome to advance knowledge, improve nutrition, and alleviate world hunger. W. Richard McCombie, Melissa Kramer, Lance Palmer, Robert Martienssen, Maureen Bell, Sujit Dike, Lidia Nascimento, Andrew O'Shaughnessy, and Lori Spiegel are among the members of the CSHL staff involved in this project.

Development

Capital and Program Contributions

Private funding is essential to our research programs, enabling successful and innovative projects not yet eligible for public funding. For this reason, we are especially grateful to those supporters who made major gifts in 2004 to our cancer and neuroscience research programs. We gratefully acknowledge donors of $100,000 or more to our cancer program: the DeMatteis Family Foundation, a first-time grant for colon cancer research; The Miracle Foundation; The Breast Cancer Research Foundation; and one anonymous donor.

Our neuroscience program was also generously supported, and we acknowledge donors to that program, including Jo-Ellen and Ira Hazen, The Seraph Foundation, The Dart Foundation, The G. Harold and Leila Y. Mathers Charitable Foundation, and the St. Giles Foundation. We also received a special gift this year from Trustee Jerome Swartz, and his Swartz Foundation, which provided more than $215,000 for the establishment of the The Swartz Center for Computational Neuroscience and additional research support in brain structure and neuroscience research. The Swartz Center has become an integral part of our strong neurobiology program, supporting both research and neuroscience programs. The Thomas Hartman Foundation for Parkinson's Research also pledged $4.4 million over the next 5 years to support Parkinson's research at CSHL and to establish The Thomas Hartman Parkinson's Research Laboratory. We also received significant and continued support from The Simons Foundation, to fund autism research at CSHL.

Robertson Research Fund

The Robertson Research Fund has been the primary in-house support for our scientists for more than three decades. During 2004, Robertson Funds supported research in the labs of Josh Dubnau, Masaaki Hamaguchi, Leemor Joshua-Tor, Alexei Koulakov, Adrian Krainer, Yuri

Lazebnik, Wolfgang Lukowitz, Bud Mishra, Partha Mitra, Scott Powers, Cordula Schulz, and Michael Wigler.

Watson School of Biological Sciences

Now in its second phase of funding and led by Robert D. Lindsay, the Watson School has received additional support in 2004 for the Dean's Chair, fellowships, and lectureships, enabling the Watson School to continue to grow and influence the field of biological sciences. We appreciate new gifts of $100,000 or more made this year by Mr. and Mrs. Robert D. Lindsay and Family, Curt Engelhorn, and The Seraph Foundation, as well as ongoing support received from Bristol-Myers Squibb Company, Mr. and Mrs. Alan E. Goldberg, the Florence Gould Foundation, and the Lita Annenberg Hazen Foundation.

The Dolan DNA Learning Center

Thanks to a very generous gift from The Dana Foundation, the Dolan DNALC has embarked on creating *Genes to Cognition (G2C) Online: A Network-driven Internet Site on Modern Brain Research,* an Internet portal exploring the genes of cognition and learning. In addition, the Dolan DNALC received significant support from the Pfizer Foundation to continue its Pfizer Leadership Institute in Human and Genomic Biology.

Carnegie Building

We are continuing plans to renovate the existing Carnegie Library to enhance its ability to serve the Laboratory community. This project received significant support this year from alumni Philip A. Sharp, Ph.D.; Drs. Joan Brooks and James Garrels; and Thomas P. Maniatis, Ph.D.; and from The Koshland Foundation and The Lehrman Institute.

Capital Campaign

As CSHL prepares to embark on a capital campaign to raise funding for new research space, we are very grateful to significant gifts received to support the buildings intended for the southwest corner of our campus. In 2004, we received pledges from Mrs. Leslie C. Quick, Jr., for a cancer research facility named for her husband, and a pledge from the Wendt Family Charitable Foundation of Community Foundation Sonoma County for a neuroscience research facility. Mrs. William L. Matheson made a significant gift in 2003 for this project, to name a facility for her late husband. CSHL also received significant support for these projects from Gillian and Eduardo Mestre and Mrs. George N. Lindsay. We will continue to plan this campaign throughout 2005.

Additional Support

The Laboratory was fortunate to receive support for many ongoing projects in 2004. The Joseph G. Goldring Foundation made a significant gift to support research, and the Louis Morin Charitable Trust made a significant contribution to support the work of Drs. Leemor Joshua-Tor, Josh Dubnau, and David Spector. We received support from the Estates of Elisabeth S. Livingston, Florence Strelkowski, and Adele C. Diaz to complete our housing

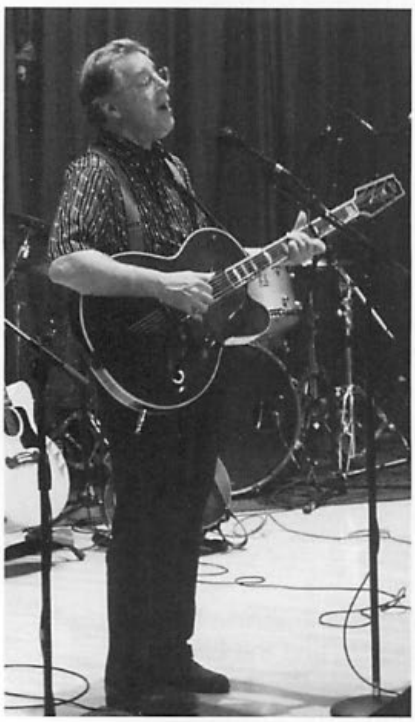
project at Uplands Farm, and Dr. and Mrs. Walter C. Meier, through the Banbury Fund, made a significant gift to restore and renovate Robertson House on our Banbury campus. Mr. and Mrs. Charles E. Harris II made a gift this year to support capital projects, and the Roy J. Zuckerberg Family Foundation provided support for consultants in fund-raising and development. We are very grateful to these close supporters for their continued generosity.

Breast Cancer Groups

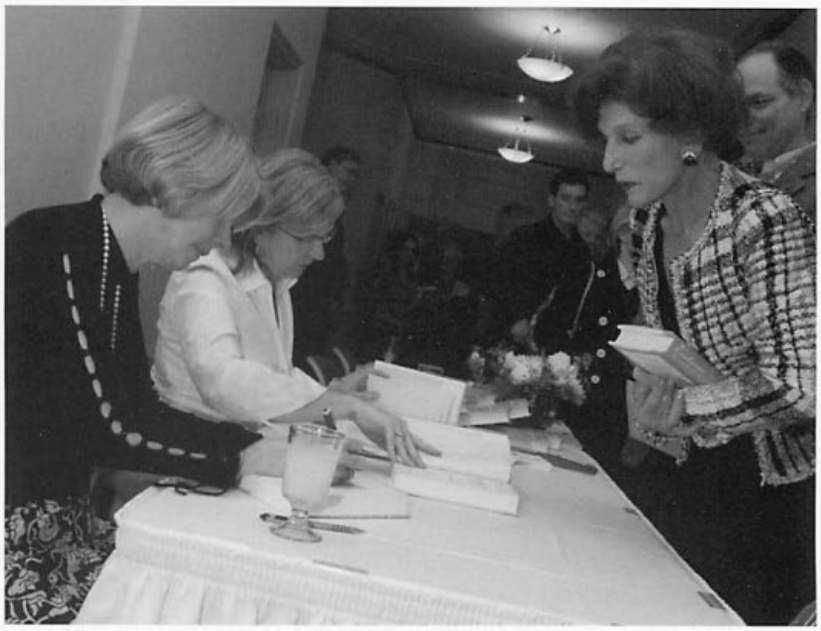
A crucial component to our breast cancer research program is the support we receive from local grassroots breast cancer groups who provide direct research support for our program, in addition to a myriad of patient care and educational services to thousands of constituents. This year, we were fortunate to receive support from Long Islanders Against Breast Cancer (L.I.A.B.C.); 1 in 9: The Long Island Breast Cancer Action Coalition; Breast Cancer H.E.L.P., Inc.; the New York State Grand Lodge Order Sons of Italy; F.A.C.T. (Find a Cure Today); The Elisabeth McFarland Fund; The Long Island 2 Day Walk to Fight Breast Cancer; The Judi Shesh Memorial Foundation; the Long Beach Breast Cancer Coalition; and The WALK for Women Breast Cancer Fund. We also gratefully acknowledge continued support from The Breast Cancer Research Foundation. The generous support we receive from these groups, year after year, is truly propelling our breast cancer research.

Benefit for the Brain

John Sebastian and the J-Band played to a packed Grace Auditorium on October 30, 2004 at the first "Benefit for the Brain." The event realized a net profit of more than $225,000 for



John Sebastian



Kay Jamison signing a copy of *Exuberance* for Joan Spiro.

CSHL's Alzheimer's and Parkinson's research, thanks to the efforts of William S. Robertson and the Banbury Fund, who underwrote the event, and event co-chairs Edward Travaglianti and Kathy DiMaio and their committee. The event honored Monsignor Thomas J. Hartman, founder of The Thomas Hartman Foundation for Parkinson's Research.

Exuberance: The Passion for Life

On December 5, Dr. Kay Redfield Jamison, best-selling author and internationally renowned authority on mood disorders, discussed the feeling of exuberance and how it fuels our most important creative and scientific achievements at the Dolan DNALC. Sponsored by Arthur and Joan Spiro, this event benefited the educational opportunities hosted annually at the DNALC.

Library and Archives

The Library and Archives enjoyed a very exciting year in 2004. A major goal of the Library is to provide scientists with digital access to all publications vital to their research. In response to the expanding scope of science research performed at the Laboratory, the Library subscribed to many new journal titles this year. In addition, the Library purchased an electronic book collection composed of 134 e-books. In 2004, an SFX system was installed that electronically interconnects the Library's resources so that patrons can navigate the entire Library collection through one interface. Within the past year, the Interlibrary Loan office implemented *Ariel*, an advanced electronic delivery service that allows the Library to receive requested articles as PDFs via e-mail.

The Library's Advisory Committee, composed of professors, postdocs, and Watson School students, convened this year to discuss library services and resources. In 2004, the Library collaborated on particular projects with other medical and academic libraries at The Rockefeller University, Harvard University, and the Marine Biological Laboratory at Woods Hole. The Library, represented by director Mila Pollock, was also invited to the Annual Nature Publishing Group International Library Committee to take part in discussions of interest to today's library market.

In 2004, the Archives were fortunate to acquire the personal collection of Elof Carlson, a prominent geneticist and professor at Stony Brook University. The *Oral History Office* has also continued to expand, now comprising more than 100 scientific interviews, half of which are already accessible online. In 2004, the Sloan Foundation formally recognized the digital archives project, the *Memory Board*, an online forum in which the lab community documents the history of the Laboratory by contributing first-hand accounts, reminiscences, original materials, photos, and video clips. The Sloan Foundation will support the redesign of the Memory Board and advocate its use as a model that other institutions could adapt for documenting their own history. Conceived by librarian and archivist Mila Pollock, the Memory Board has attracted much attention and many interesting anecdotes. The exhibition *Building Blocks of CSHL* was created this year and will be on display at Blackford Hall for two years and online in digital format. This project explores the history of the buildings at CSHL (and the life of its community) through documents, photos, and personal memories. This year, the Library's exhibit *Honest Jim: Watson the Writer* moved to the Charité Universitätsmedizin in Berlin, Germany and will be exhibited in Moscow, Russia next year.

Building Projects

The Laboratory continues to improve and expand its facilities and, during 2004, undertook several construction and renovation projects. Several projects were completed in the Demerec building, including alteration and renovation of laboratory spaces and the construction of a new tissue culture laboratory. Grace Auditorium received attention as well, with a complete remodeling of the bookstore to accommodate *DNA Stuff*—the Laboratory's bookstore and nonprofit retail operation. The Laboratory also continued its project to replace the HVAC systems in Grace and Harris and to update the emergency power system that supplies those buildings.

A major renovation of the James building was begun in 2004, updating laboratory, support, and office spaces to meet the increased demands on the building's facilities the Laboratory has experienced in recent years. Work was begun on the Banbury pool, which had been leaking badly for years. The entire pool has been reconstructed, and final work is to be completed by the spring of 2005.

The Laboratory has continued to improve its student and scientist housing program. The housing project at Uplands Farm is nearing completion and will provide much-needed housing close to the main campus. The last of the apartments in the Hooper building was renovated, and the Weghorn House, which lies at the northern tip of the campus, was purchased and will be renovated in 2005.

A major milestone in 2004 was the approval of the Laboratory's updated Master Plan and its Upper Campus project by the Village of Laurel Hollow. This approval came at the end of a 2-year process and has paved the way for the Laboratory to break ground on the largest construction project it has ever undertaken in Spring 2005.

100 Years of Genetics at Cold Spring Harbor

In 1904, the Carnegie Institution of Washington founded a Station for Experimental Evolution at Cold Spring Harbor, launching a century of genetics that placed CSHL at the forefront of biomedical research. The occasion was marked by a very special 2004 Cultural Series filled with engaging lectures and inspiring music and art.

Public Lectures

April 19 Mark Hallett, Vice President of the American Academy of Neurology: *How Your Brain Recovers from a Stroke.*

May 11 Vincent Li, Director of the Angiogenesis Foundation: *Prevention and Reversal of Skin Cancer and Other Skin Diseases.*

May 18 Carter Burwell, award-winning composer: *From Cold Spring Harbor to the Coen Brothers: A Composer's Journey.*

May 24 Andrew Solomon, award-winning author of *The Noonday Demon: An Atlas of Depression*: *Depression Too, Is a Thing with Feathers.*

Sept. 28 Zach Mainen, CSHL Associate Professor, and Sharron McCarthy, Director of the Society of Wine Educators: *Demystifying the Sommelier: The Art and Science of Wine Tasting.*

Sylvia Nasar

Antoine Tamestit

October 5 Sylvia Nasar, author of *A Beautiful Mind: Genius, Madness, Recovery*.

December 7 Richard Stone, Britain's youngest royal portrait artist: *Painting England's Queen and DNA's Dean*.

Concerts

April 24	The Molinaro-Levy Project, piano and harmonica
May 1	Yunjie Chen, piano
May 8	Mikhail Simonyan and Alexei Podkorytov, violin and piano
May 22	Hsing-ay Hsu, piano
September 11	Dmitri Berlinksky and Elena Baksht, violin and piano
October 2	Vassilis Varvaresos, piano
October 9	Alexandre Bouzlov, cello
October 16	Antoine Tamestit, viola

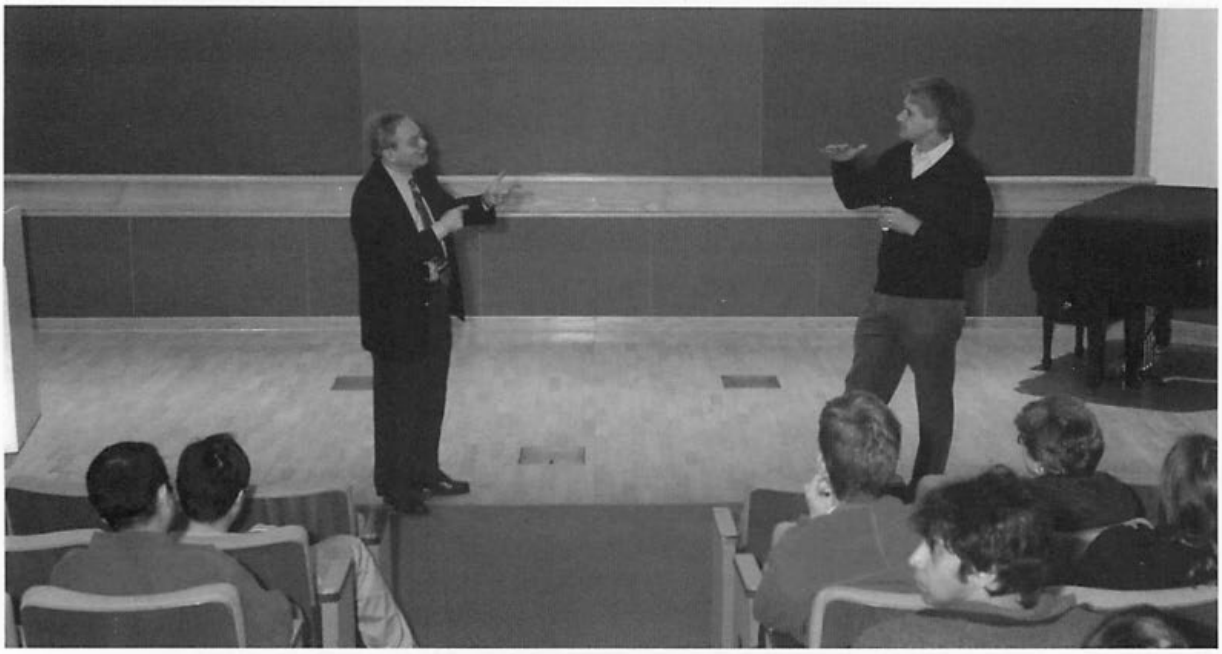
Exhibits

From July 9 to August 1, 2003–2004 Artist-in-Residence Eduardo De Soignie displayed his work, *Paintings From Another Domain*, in Bush Lecture Hall. Inspired by his Cuban roots, De Soignie's work is influenced by artists such as Jose Bedia and Tomas Esson.

Events

Gavin Borden Visiting Fellows

The 10th annual Gavin Borden Fellow Lecture, created by Jim Watson in memory of Gavin Borden, publisher of *Molecular Biology of the Cell*, was held on March 17 in Grace



Richard Losick and Bruce Stillman at the Gavin Borden Lecture

Auditorium. Dr. Richard Losick, the Maria Moors Cabot Professor of Biology at Harvard University, spoke on "Cell fate, polarity, and cannibalism in bacteria." Dr. Losick is internationally acclaimed for his research on microbial development and is developing computer-based animations and video for teaching introductory molecular biology.

Symposium

The 69th Annual Cold Spring Harbor Laboratory Symposium, "Epigenetics," was oversubscribed again this year with nearly 500 scientists from around the world in attendance. The Dorcas Cummings Lecture, in memory of long-time Laboratory friend and former Director of the Long Island Biological Association Dorcas Cummings, was given by David Haig of Harvard University on the subject of "The Divided Self—Brains, Brawns, and the Superego." This endowed lecture is traditionally open to friends and neighbors of the Laboratory and is followed by dinners generously hosted in the homes of our neighbors for our visiting scientists and faculty and staff.

Other Lectures

Winship Herr ("Why Our Cells Multiply") and Nick Tonks ("Plague, Pox, and Phosphatases") participated in our lecture series for fourth- to sixth-grade students and their parents, co-hosted with the Cold Spring Harbor School District, at the Dolan DNALC.

Huntington Hospital continued to host their fall/spring lecture series on cardiovascular health and related diseases in Grace Auditorium.

Laboratory Employees

New Staff

Scott Powers returned to CSHL in October as Associate Professor and Director of the Human Cancer Genome Center in the Cancer Genome Research Center. Scott came from Tularik Genomics Division, which was initially a company spun out from the Laboratory to use RDA (representational difference analysis) technology to identify cancer genes. Scott received his graduate degree from Columbia University and performed seminal work as a postdoc with Mike Wigler on the study of *RAS* genes in yeast.

David Wu joined Scott as a Research Investigator at the Human Cancer Genome Center. David received his graduate degree from Berkeley and as a postdoc with Aziz Sancar developed the first biochemical system for mammalian DNA repair with purified proteins.

Promotions

Dr. Lilian Clark Gann became Dean of the Watson School of Biological Sciences on July 1. Lilian joined the Laboratory in March 1999 as Assistant Dean of the Watson School and was promoted to Associate Dean in January 2002. She received her Ph.D. from the University of St. Andrews, Scotland in 1988, for her studies on DNA–protein interactions in transcriptional control elements of DNA tumor viruses, and her M.B.A. from the University of Westminster, London in 1996. Since her arrival at CSHL, Lilian had played a crucial role in the development of the School's innovative Ph.D. program, while also enhancing the educational and training environment of CSHL for students and postdoctoral fellows in general. Her unique background in science, education, and business made her an obvious choice to develop and oversee the programs of the Watson School. She was joined by Dr. Bill Tansey who was appointed as director of graduate studies in the Watson School of Biological Sciences and Lita Annenberg Hazen Professor of Biological Sciences on the same day.

A number of other faculty members were promoted in 2004, including Dmitri Chklovskii to Associate Professor, Zachary Mainen to Associate Professor, Ravi Sachidanandam to Senior Computer Scientist, Lincoln Stein to Professor, Karel Svoboda to Professor, Yi Zhong to Professor, and Anthony Zador to Associate Professor. Ira Hall and Patrick Paddison were both named CSH Fellows.

Departures

Dr. Winship Herr stepped down as Dean of the Watson School of Biological Sciences effective July 1 to concentrate his efforts on his research. Beginning in 1995, Winship spearheaded the effort that resulted, in September 1998, in the Laboratory's accreditation as a Ph.D. degree-granting institution by the Board of Regents of the University of the State of New York, on behalf of the State Education Department. This enabled the establishment of the Watson School of Biological Sciences. Soon thereafter, Winship became the Founding dean of the Watson School. During the last 5 years, we have seen the School grow and become one of the most innovative programs in the country, attracting outstanding students. Winship has nurtured and shaped the Watson School in its first formative years, culminating in our first commencement convocation this spring. In the coming year, he and Nouria Hernandez will move to Nouria's native Switzerland to become professors at a new institute in Lausanne. I thank Winship for his remarkable effort in establishing a graduate school at Cold Spring Harbor and for his sound advice to me. The establishment of a graduate school

has transformed Cold Spring Harbor Laboratory and will have a long-lasting effect on the intellectual environment here.

Neilay Dedhia, Research Investigator; David Helfman, Professor; Terence Strick, CSH Fellow; and Jerry Yin, Associate Professor, all departed the Laboratory in 2004. David spearheaded the understanding of cancer progression through his research on the cell biology of cell architecture and I wish him the best as he continues his research at the University of Miami Cancer Center.

Long-term Service

The following employees celebrated milestone anniversaries in 2004:

30 years	Lane Smith
25 years	Maureen Berejka, Judith Cuddihy, Katya Davey, James Hope, John Meyer, James Parsons, Susan Schultz, Bruce Stillman
20 years	Carmelita Bautista, Dessie Carter, Robert Gensel, Mary Ellen Goldstein, Daniel Miller, Robert Pace, Steven Tang
15 years	Leslie Allen, James Bense, Sharon Bense, Charlene De Poto, Janice Douglas, Jan Eisenman, Helena Johnson, Robert Martienssen, Jacqueline Matura, Alison McDermott, Eleanor Sidorenko, Halina Swidzinski, Ryszard Swidzinski, Spencer Teplin

1st row, left to right: Eleanor Sidorenko, James Bense, Sharon Bense, Charlene De Poto, Susan Schultz, Carmelita Bautista, Jan Eisenman, Katya Davey
2nd row, left to right: Rob Gensel, James Parsons, Mary Ellen Goldstein, Alison McDermott, Maureen Berejka, Daniel Miller
3rd row, left to right: John Meyer, James Watson, Spencer Teplin, Helena Johnson, Dessie Carter
4th row, left to right: Bruce Stillman, James Hope, Steve Tang

CSHL team at the Long Island Walk to D'Feet ALS.

Community Outreach

In May, Laboratory employees Sandy Neuwald, Lisa Manche, Carla Margulies, Barbara Misk, Kathryn Borowski, Barbara Purcell, and Theresa Saia served dinner at the Ronald McDonald House in nearby New Hyde Park, which provides temporary housing to families of seriously ill children at the Schneider Children's Hospital. In June, Shuly Avraham, Jason Evans, Kim Gronachan, Jo Leonardo, Jianli Li, Erin Maroney, Liya Ren, Theresa Saia, and Doreen Ware planted six flats of flowers at Haven House, a homeless shelter in Huntington Station, purchased with money donated by CSHL employees. A CSHL Team also participated in the *Long Island Walk to D'Feet ALS* (Lou Gehrig's disease) for the The ALS Association Greater New York Chapter at Eisenhower Park in East Meadow on September 26.

Cold Spring Harbor Laboratory is a vibrant and dynamic institution, and like all such institutions involved in the increasingly expensive research in the genomic age, we are even more dependent on support from individuals and foundations to enable us to remain one of the leading research centers in the world. As we move forward, we need the type of support that can be used to ensure that our scientists have the facilities and resources to achieve their goals. Increasingly at Cold Spring Harbor, our research focuses on how to use all the accumulated knowledge to develop new ideas for diagnosing and treating human disease. I thank all those who have supported our efforts to date, helping us to make Cold Spring Harbor Laboratory a truly unique education and research center.

Bruce W. Stillman, Ph.D., F.R.S.
President