HIGHLIGHTS OF THE YEAR

The research and education programs at Cold Spring Harbor Laboratory continue their strong momentum. The Watson School of Biological Sciences recruited its third class of students this year, and the DNA Learning Center expanded both its physical plant and its educational objectives. The Meetings and Courses program and Banbury Center continue to be invaluable resources for scientific information, and the Cold Spring Harbor Laboratory Press added several new projects and properties to its long list of titles. Cold Spring Harbor Laboratory was once again a bustling center of scientific activity, discovery, and education.

Research

Bioinformatics

On February 15, 2001, some 20 genome research centers around the world, including W. Richard McCombie's group at Cold Spring Harbor Laboratory, jointly published the first draft of the complete human genome sequence and made it freely available to researchers throughout the world. The finished sequence is scheduled to be released in 2003, coincident with the 50th anniversary of the discovery of the structure of DNA. The complete human genome sequence can be used in a great many ways (see below) and has already fueled an explosion of biological and biomedical research—much of it directed toward improving human health.

Analysis of the raw DNA sequence through the use of various bioinformatics (computer-based) methods revealed several interesting features of the human genome, including the preliminary finding that our genome contains approximately 30,000–40,000 protein-coding genes. A similar analysis of restricted raw data by a private concern revealed most of the same features.

In a companion study that accompanied the publication of the human genome first draft, Lincoln Stein, his CSHL colleagues, and other members of the International SNP Map Working Group identified some 1.4 million *s*ingle *n*ucleotide *p*olymorphisms (or SNPs) distributed throughout the human genome. The high-density map of human DNA sequence variation will become useful for identifying disease-related genes, for tailoring therapies to those patients who are most likely to respond, and for several other applications. Importantly, this project was jointly funded by a consortium of pharmaceutical companies, private foundations, and the federal government, providing a model for future ways of funding large projects and making the data freely available to the broader scientific community.

Lincoln Stein

To study and manipulate genes for a wide variety of research, diagnostic, or therapeutic purposes, scientists need to determine the precise fine structure of genes against a backdrop of what is frequently a vast and complex genetic landscape. Conventional bioinformatics software fails when it comes to detecting two important features of genes—the very first segments of genes, and the nearby "on" switches of genes called promoters.

Michael Zhang and his colleagues have developed a computer program called First Exon Finder (or FirstEF) that is especially good at finding these first segments and "on" switches of genes. The program is tailored toward detecting these features in the human genome sequence, but it is also useful for annotating other mammalian genomes. Although the total number of genes in an organism's genome depends on subtle, nonuniversal definitions of what constitutes a gene, on the basis

of his analysis of the human genome using FirstEF, Michael believes that there are 50,000–60,000 fundamental protein-coding human genes and that the preliminary estimate of 30,000–40,000 human genes is too low.

We will test these computer predictions and have established a joint research initiative involving the laboratories of Michael Zhang, Greg Hannon, and Dick McCombie. These laboratories will experimentally verify the new predicted genes. Greg will incorporate the findings into a project whose goal is to determine the function of human genes that have heretofore not been assigned a function.

Michael Zhang

Cancer

Michael Wigler, Robert Lucito, and their colleagues are developing a reproducible, high-resolution technique for detecting changes in gene copy number that are associated with the initiation of breast, ovarian, and prostate cancer or with the progression of these cancers from a noninvasive to an invasive or metastatic state.

Michael Wigler

The technique, called *r*epresentational *o*ligonucleotide *m*icroarray *a*nalysis, or ROMA, combines DNA microarray technology with a method Michael previously invented to simplify the search for differences between two sets of DNA (representational difference analysis). Using ROMA, Robert and Michael can scan the entire genomes of both normal cells and cancer cells taken from the same patient and can detect the genetic differences between the two. To apply ROMA to the study of breast cancer, a needle biopsy of as few as 1,000–10,000 cells from breast tissue (followed by isolation of the normal and cancer cell DNAs) provides sufficient material.

Genes that are amplified (potential oncogenes) or deleted (potential tumor suppressor genes) in cancer cells—or in invasive/metastatic versus noninvasive tumors—are prime targets for improved methods to diagnose and treat cancer. A strong team has been established to develop this project: Robert and Michael are joined in several of their studies by clinical colleagues at Memorial Sloan-Kettering Cancer Center (Larry Norton), bioinformatics colleagues at CSHL (Bud Mishra, who holds a joint appointment at the Courant Institute of Mathematical Sciences at New York University), and Jonathan Melamed (also at the Courant Institute), and the local division of Tularik, Inc., a biotechnology company (Scott Powers). To date, these researchers have identified some 20 candidate genes associated with cancer by using ROMA and other genomics approaches.

Rob Lucito

Remarkably, the major limitation at this stage in the development of ROMA is neither theoretical nor technical, but economic. Robert and Michael estimate that the cost of synthesizing sufficient numbers of DNA oligonucleotides to reliably detect small deletions in the genomes of cancer cells is on the order of $2 million. However, once these oligonucleotides are available, they will be sufficient to fabricate 40,000 individual ROMA microarrays, enough to study many human cancers.

Epigenetics

Epigenetics is commonly defined as the study of heritable changes in chromosome structure or gene function (e.g., transcriptional activity) that occur without changes in DNA sequence. As work

at CSHL and elsewhere has shown, proper functioning of epigenetic mechanisms of inheritance, such as maintaining stable gene silencing over many cell divisions, is essential to many aspects of normal biology. Moreover, CSHL researchers have linked abnormal silencing of tumor suppressor genes to cancer.

In the past year, work in my own laboratory (in collaboration with Rui-Ming Xu), as well as studies by Greg Hannon, Shiv Grewal, David Spector, and Rob Martienssen, has revealed several molecular features of epigenetic phenomena.

Working with yeast, worms, flies, plants, and mammals, CSHL researchers are establishing comprehensive models for different aspects of epigenetic inheritance, including RNA interference, the modification of histone proteins and DNA (e.g., by methylation), and importantly, how these processes work together to establish and maintain silent versus active chromatin (DNA plus protein architecture). These models unify many genetic and biochemical observations and have a significant impact on how we view the biology of DNA.

RNA Interference: Double-stranded RNA triggers potent, specific gene silencing through a process called RNA interference (RNAi). A central component of RNAi is a nuclease, composed of both RNA and protein, which Greg Hannon and his colleagues first characterized and dubbed RISC (*R*NA-*i*nduced *s*ilencing *c*omplex). This nuclease seeks and destroys other RNA molecules (e.g., messenger RNA) homologous to the short guide RNAs or "siRNAs" (small *i*nterfering *RNA*s) it carries.

Greg Hannon

In 2001, members of Greg's lab reported two significant RISC-related observations. First, they showed that the siRNA molecules within RISC are derived from longer, double-stranded RNA through the action of an enzyme they aptly named Dicer. They noted that Dicer is evolutionarily conserved in yeast, worms, flies, plants, and mammals. Second, through biochemical purification of RISC, they showed that RISC itself contains a different RNA-cleaving enzyme, plus a protein called Argonaute2, which Greg believes is one of several such components that targets RISC-mediated inhibition of gene expression to various biochemical pathways. These findings are among several links being forged at CSHL between the genetics and biochemistry of RNAi, and between RNAi (post-transcriptional silencing) and other epigenetic phenomena such as transcriptional silencing and transposon activity.

As often happens, basic research on biology opens doors that are unexpected. It is now possible to synthesize RNAi molecules and to use them to individually and specifically shut off the expression of virtually every human gene. Greg Hannon and his colleagues have developed some of these technologies and have established a large project to use RNAi to investigate the function of human genes. The technology has spread like wildfire around the Cold Spring Harbor campus, and rightly so, because it has the potential to change how we study mammalian biology.

Transcriptional Silencing: By studying transcriptional silencing of mating-type genes in fission yeast, Shiv Grewal and his colleagues have shown that seemingly small differences between two varieties of histone H3 have profound effects on chromatin structure, gene expression, and recombination. They found that silent regions of chromatin—where genes are kept off and DNA resists genetic recombination—contain a particular variety of histone H3 (H3 Lys-9-methyl). In contrast, they observed that active regions of chromatin—where genes can be easily switched on and DNA can readily recombine—contain a different variety of histone H3 (H3 Lys-4-methyl). Through this and other work, Shiv has defined a highly conserved pathway wherein enzymes that modify histones (deacetylases and methyltransferases) act cooperatively to establish a "histone code" leading to epigenetic silencing.

In addition, Shiv showed that deleting "boundary elements" that mark the transition between silent and active chromatin allows the spreading of H3 Lys-9-methyl, and hence a silent chromosome architecture, into neighboring DNA normally occupied by H3 Lys-4-methyl. This finding has important implications for genetic disease caused by abnormal gene silencing. Indeed, in 2001, Scott Lowe, Yuri Lazebnik, and colleagues found that abnormal silencing of the tumor suppressor gene Apaf-1 leads to malignant melanoma.

My own laboratory has uncovered mechanisms of inheritance of epigenetically determined states of gene expression and has provided links to DNA replication proteins. Recently, in collaboration with Rui-Ming Xu, we have determined the three-dimensional structure of part of the origin recognition complex (ORC) that recruits gene silencing proteins to specific loci in the yeast genome. ORC was discovered here 10 years ago as a key regulator of genome duplication.

Shiv Grewal

X Inactivation: In species such as humans, where females have two X chromosomes and males have one, the proper proportion of X chromosome gene expression ("dosage compensation") is maintained in females through the global inactivation of one of the two X chromosomes. X inactivation stems from the initiation (at a locus called the *X-i*nactivation center or *Xic*) and spread of an inactive chromatin state. Establishment of the inactive chromatin state begins with the coating of the X chromosome by "Xist" RNA molecules, followed by large-scale remodeling of chromatin structure.

Until recently, little was known about either the molecular partners of Xist RNA that enable it to coat the X chromosome, or the precise nature of the chromatin remodeling induced by this coating. Visiting scientist Edith Heard suspected that the same histone H3 variety that Shiv Grewal found to establish silent chromatin in fission yeast (H3 Lys-9-methyl) might also mediate X inactivation. Using mouse embryonic stem cells, Edith and David Spector showed this to be true by measuring when and where (relative to other events) H3 Lys-9-methyl appears on X chromosomes marked for inactivation. They found that Lys-9 methylation of histone H3 occurs immediately *after* the coating of the X chromosome by Xist RNA and *before* the silencing of X-linked genes. Thus, Edith and David could conclude that Lys-9 methylation of histone H3 is a definitive early event in the X inactivation process.

DNA Methylation and Transposon Activity: Rob Martienssen explores the role of transposable elements (transposons) in epigenetic regulation and genome organization using both maize and the mustard relative, *Arabidopsis*. In plants and many other organisms, the DNA of inactive transposons is generally methylated, whereas the DNA of canonical genes and active transposons is generally unmethylated. One of Rob's interests is to determine how these methylated and unmethylated regions of chromatin are established and maintained, and to explore the biological consequences of normal and abnormal states of DNA methylation.

Several years ago, Rob isolated an *Arabidopsis* mutant called *ddm1* (*d*ecrease in *D*NA *m*ethylation) in which methylation of DNA was decreased. In 2001, Rob and his colleagues showed that transposons become demethylated in *ddm1* mutants and that such transposons become both transcriptionally active and activated for movement from place to place in the genome. Next, Rob and visiting scientist Vincent Colot showed that inactive transposons are preferentially associated with (you guessed it) the same variety of histone H3 that Shiv found ito be associated with silent regions of chromatin in fission yeast, and which Edith and David found to be involved in X inactivation (H3 Lys-9-methyl). Rob and Vincent also showed that transposons activated in *Arabidopsis ddm1* mutants become preferentially associated with the variety of histone H3 that Shiv found to be associated with active regions of chromatin in fission yeast (H3 Lys-4-methyl).

Finally, working together, Rob, Shiv, and their colleagues showed that fission yeast homologs of the RNAi components Dicer and Argonaute are involved in silencing ancient relics of transposons known as centromeric repeats. Moreover, *dicer* and *argonaute* mutations in fission yeast, like *ddm1* mutations in *Arabidopsis*, lead to the replacement of the silent chromatin-associated variety of histone H3 (H3 Lys-9-methyl) by the active chromatin-associated variety (H3 Lys-4-methyl).

These observations suggest a model in which components of the RNAi machinery target histone-modifying enzymes to regions of chromatin to be silenced or kept silent (centromeric repeats, transposons, and possibly other regions such as inactive X chromosomes in female mammals). Furthermore, Rob suspects that in those situations where DNA methylation is involved in epigenetic inheritance, the silent chromatin-associated variety of histone H3 (H3 Lys-9-methyl) may indirectly recruit enzymes that methylate DNA.

Molecular Biology

In the United States, approximately 70,000 deaths from cancer per year are associated with genetic alterations in the *myc* oncogene. This gene encodes a protein—the Myc transcription factor—that is a potent stimulator of cell proliferation. Because Myc is a potent growth stimulator, the level of Myc within cells is normally tightly regulated. This level is determined by how much Myc is synthesized in a given time frame and by how quickly it is destroyed.

Bill Tansey

William Tansey and his colleagues are studying how the destruction of the Myc protein is regulated and how defects in this process lead to abnormally high levels of Myc and to cancer. In so doing, they have uncovered an intriguing connection between two seemingly unrelated processes—protein degradation and transcriptional activation. Bill's findings support a "licensing" mechanism in which a particular protein modification (ubiquitylation) simultaneously activates transcription factors that switch on gene expression and primes them for destruction. The net result of this licensing mechanism is to limit how long genes remain switched on. Bill suspects that this mechanism is an efficient way for the cell to limit the effects of many of its most potent transcription factors.

Moreover, work in Bill's lab indicates that a link between transcription and protein degradation has been conserved since the evolutionary divergence of yeast and mammals approximately 1 billion years ago. Thus, Bill and his colleagues appear to have uncovered a phenomenon of fundamental biological importance.

Tim Tully

Neuroscience

Learning & Memory: Josh Dubnau and Tim Tully have used a genetic strategy in fruit flies to switch electrical activity on and off at will in the "learning center" of the insect's brain called the mushroom body. In so doing, they have made the surprising discovery that switching off electrical activity in this part of the fly brain blocks memory recall but not the initial formation of a particular kind of memory.

In some respects, fruit fly brains work very much as do the brains of other animals, including humans. Both flies and humans are capable of the kind of "associative learning" made famous by Pavlov's dogs. (After ringing a bell and presenting dogs with food several times over a few days, the Russian physiol-

ogist Ivan Pavlov [1849–1936] found that eventually his dogs would display dinnertime behavior [drooling, excitement] upon hearing the sound of the bell alone.)

Josh and Tim study olfactory associative learning by training flies to avoid a particular odor and later measuring the flies' odor avoidance behavior. They found that memories based on olfactory associative learning can be acquired and stored in the absence of electrical activity in mushroom bodies. However, those memories cannot be recalled in the absence of such electrical activity. These results suggest that memories are acquired and stored by chemical processes in mushroom bodies, and that electrical activity in this part of the brain is necessary only to recall those memories. In some instances, when it comes to learning and memory, the fly brain (and perhaps ours) must function electrically to recall what is stored chemically.

Brain Imaging: Karel Svoboda continues to pioneer the application of a high-resolution, real-time imaging technique called two-photon microscopy to brain research. Recently, Karel and his colleagues have used two-photon microscopy to examine abnormalities during brain development in a mouse model of Fragile X syndrome. In humans, Fragile X syndrome is the most commonly inherited cause of mental impairment. The syndrome is typically caused by a mutation in the *FMR1* gene leading to absence of the *F*ragile X *m*ental *r*etardation *p*rotein or FMRP.

By using two-photon microscopy to compare the earliest stages of postnatal brain development in normal and *FMR1* knock-out mice, Karel and Esther Nimchinsky have detected dramatic differences in the density and length of all-important neuronal structures called dendritic spines. Such spines form the familiar connections between neurons called synapses. When examined 1 week after birth, the "barrel" cortex in the brains of Fragile X mice displayed significantly increased density and length of spines. (Barrel cortex interprets neurological signals from the whiskers of newborn animals as they explore their world for the first time.) However, by 4 weeks after birth, differences in the density and length of spines between normal and Fragile X mice were largely undetectable. The transient nature of the spine abnormality in Fragile X mice suggests that FMRP functions soon after birth during a critical window of opportunity for brain development. In addition, Karel's findings indicate that FMRP probably has a role in linking experience (e.g., whisker signals) to the growth of dendritic spines and that such links are required to specify the elaboration of a fully functional neuronal architecture in the brain.

Nick Tonks

Awards and Honors

Several members of the Laboratory community were honored in 2001 for their work and achievements.

Scott Lowe

CSHL Professor Nick Tonks was appointed a Fellow of the Royal Society of London, England's National Academy of Sciences. Since 1660, election to the Fellowship has been recognized as one of the highest honors in science. Dr. Tonks joins CSHL President Jim Watson and myself as CSHL's Fellows of the Royal Society.

Laboratory President James Watson received an honorary knighthood from the Queen of England in the New Year's Honours List. This is a rare honor for a United States citizen, and recognizes Dr. Watson's accomplishments from the double helix to the human genome, among others.

CSHL Professor Scott Lowe, the Deputy Director of the Cold Spring Harbor Laboratory Cancer Center, was honored this year with the Cornelius P. Rhoads Memorial Award of the American Association for Cancer Research (AACR). The

award recognizes groundbreaking contributions to cancer research and was established in 1979 to honor the memory of Dr. Cornelius P. Rhoads, the founder and first director of the Sloan-Kettering Institute for Cancer Research.

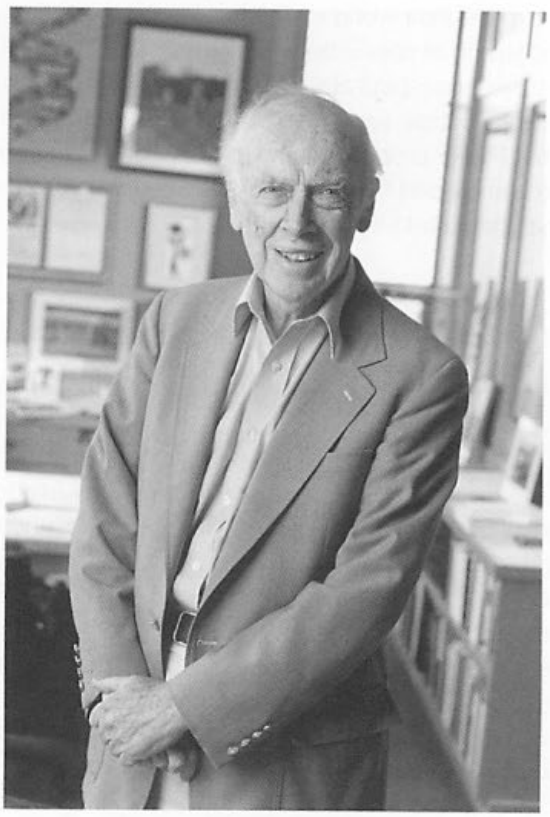
Song-Hai Shi

Song-Hai Shi, a 2000 graduate of the joint Genetics Program at Cold Spring Harbor Laboratory and Stony Brook University, was awarded the 2001 Amersham Biosciences and *Science* Grand Prize for work he carried out in the neuroscience lab of Robert Malinow at Cold Spring Harbor Laboratory. The award recognizes the most outstanding Ph.D. thesis among graduate students in molecular biology. He received the award in Stockholm at the time of the Nobel Prize ceremonies in December.

I was pleased this year to be elected as a foreign member of The European Molecular Biology Organization (EMBO), the organization that leads, guides, and promotes biological sciences in 24 European countries.

Symposium LXVI

From May 31 to June 5, an enthusiastic group gathered for the 66th annual CSHL Symposium, titled "The Ribosome." On Sunday, June 3, meeting attendee Dr. Venki Ramakrishnan, of the Laboratory of Molecular Biology, MRC, Cambridge, delivered the annual Dorcas Cummings Memorial Lecture to a scientific and public audience. This very successful annual event is hosted



"Sir" James Watson

Jim Watson and Venki Ramakrishnan

by the CSHL Association. Dr. Ramakrishnan's talk, "Protein Factories and Antibiotics," was timely and appealed to the broad range of interests represented in the audience. The Symposium celebrated recent, major breakthroughs in understanding how proteins are made in cells, a fundamental aspect of molecular biology.

William Maxwell Cowan

Robert J. Glaser

David L. Luke III

Watson School of Biological Sciences

CSHL's graduate school—the Watson School of Biological Sciences—welcomed its third class of students this fall. On August 28, six new students joined the Watson School's ranks. Hailing from across the country and around the world, the students dove quickly into their rigorous programs, enrolling in the core courses and beginning the laboratory rotations that mark their first year of study.

On November 2, Cold Spring Harbor Laboratory held its 2001 Convocation in Grace Auditorium to celebrate service to science. Before an audience of nearly 300 people, the Watson School bestowed honorary degrees upon William Maxwell Cowan, Robert J. Glaser, and David L. Luke III, in recognition of their continuing service to science. All three honorees have made a vast difference to the world of scientific education and research, and the convocation provided an excellent opportunity to honor these individuals. Gail Mandel, a professor of Neurobiology and Behavior at Stony Brook University and an investigator for the Howard Hughes Medical Institute, gave the keynote address.

Lilian Gann, the Assistant Dean of the Watson School of Biological Sciences, was also appointed this year to Associate Dean, in recognition of her work in developing the programs and offerings of the Watson School.

James D. Watson, president of CSHL, spent a busy year promoting his newest book, *Genes, Girls and Gamow*. The book, a follow-up to the critically acclaimed *Double Helix*, profiles Jim's life after the landmark discovery.

Banbury Center

From time to time, Banbury Center holds a meeting on what might be called "science policy," i.e., discussions of topics that affect the way biomedical research is done. One of the most interesting, held in 2001, was on the ways in which the Internet is making, and provoking, changes in the dissemination of scientific information and data. *Electronic Access to the Scientific Literature* examined the initiatives intended to lower the barriers to electronic access to the scientific literature, for example, by providing free access to the full collection of scientific papers within a short period of publication. This is a highly controversial topic, and although no resolution was reached at the meeting, the discussions involving scientists, publishers of society journals, and commercial publishers were useful.

Cancer figured strongly in the Banbury Center program in 2001, with four meetings dealing with important issues in cancer treatment. Two discussed the current status of interferon therapy in cancer and were particularly interesting in that they reviewed the actions of interferon in virus infections as well as in multiple sclerosis. The third meeting on *New Concepts for Clinical Cancer Trials* discussed new findings indicating that the manner in which cancer treatments are given is important. It seems that different dosing schedules combined with lower doses could increase the efficacy and reduce the toxicity and side effects of traditional cytotoxic drugs, and perhaps also of radiotherapy and some investigational drugs. These topics were so interesting that we decided to make *Controlling Cancer* the subject of the 2001 Executives Conference. It was a great success, and we are very grateful to David Deming and JPMorgan H&Q for their continuing support of the meeting.

We turned to a neuroscience topic with strong psychological and philosophical underpinnings with *Can A Machine Be Conscious?* A wealth of new experimental information about the brain has been gathered by neuroscientists, and participants discussed how these data require a revision of classic thinking on consciousness. The participants were a most interesting mix, from philosophers and neuroscientists, to builders of robots, to robots themselves!

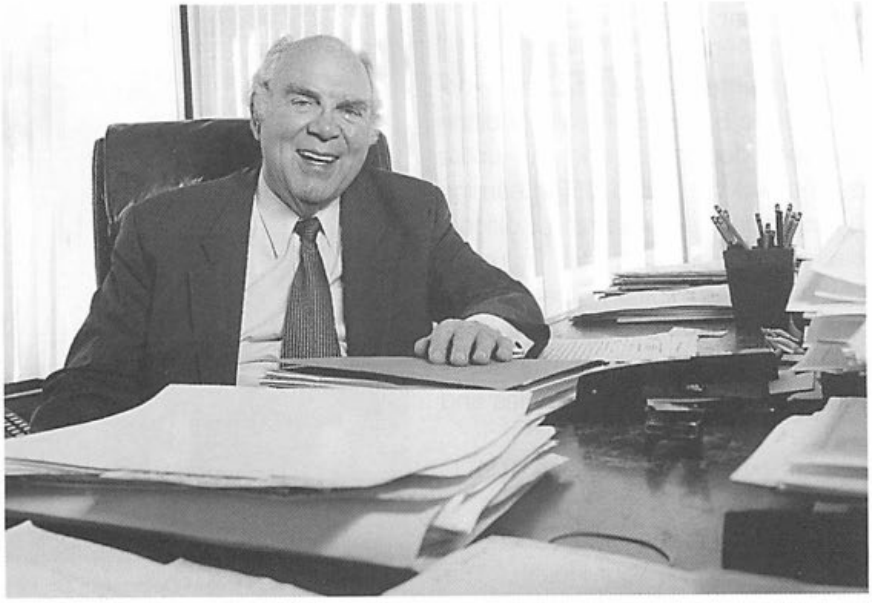
Robertson Research Fund

Since 1973, the Robertson Research Fund has been the primary in-house support for our scientists. The fund has grown from its original 1973 total of $8 million to more than $95 million. During 2001, Robertson funds supported cancer research in the labs of Shivinder Grewal, David Helfman, Winship Herr, Tatsuya Hirano, Yuri Lazebnik, Dick McCombie, Jacek Skowronski, William Tansey, and Rui-Ming Xu; neurobiology research in the labs of Grigori Enikolopov, Dimitri Chklovskii, Josh Huang, Roberto Malinow, Zachary Mainen, Anthony Zador, and Yi Zhong; and plant research in the labs of Robert Martienssen and David Jackson. Robertson funds also supported several new investigators, including Carlos Brody, Alea Mills, Bud Mishra, and Senthil Muthuswamy.

The Marie H. Robertson Memorial Fund, devoted to neuroscience, provided support for Grigori Enikolopov and Zachary Mainen, and also for a neurobiology seminar program and Banbury Meeting.

Cold Spring Harbor Laboratory Board of Trustees

Cold Spring Harbor Laboratory's Board of Trustees led the Lab through another challenging and eventful year, continuing to shape the direction and vision of this institution.



William E. Murray

This year, the Board welcomed the addition of three new trustees to its ranks: Eduardo G. Mestre, Vice Chairman of Salomon Smith Barney and Chairman of its Investment Banking Division; Douglas P. Morris, Chairman and CEO of Universal Music Group; and Thomas C. Quick, Vice Chairman of Quick & Reilly/Fleet Securities, Inc.

William E. Murray and Whitney D. Pidot both reached the end of their allotted terms as trustees and were honored at the board's November meeting for their outstanding service to the Laboratory. In early 2002, William E. Murray was elected as Honorary Trustee.

Whitney D. Pidot

CSHL Association

The CSHL Association (CSHLA) continues to support the wide range of research and education programs at Cold Spring Harbor Laboratory. The CSHLA is particularly important in funding the research of junior scientists in the formative years of their careers, when it is most difficult to obtain federal grants. Through its fund-raising efforts and community interaction, the CSHLA is vital to the Laboratory's success.

The CSHLA held its annual meeting on February 4, featuring a lecture by Dr. Shirley Tilghman on "Genomic Imprinting." Dr. Tilghman, at that time a professor at Princeton University, is a former trustee of Cold Spring Harbor Laboratory and has since been appointed as President of Princeton University. We extend congratulations to our former trustee and good friend.

I encourage you to closely review the report of the Cold Spring Harbor Laboratory Association, found later in this Annual Report, for a more comprehensive view of the many functions and successes of this special group. I extend my thanks to David H. Deming, President of the CSHLA, and Annette Gangitano, Executive Director of the CSHLA, for their hard work in making this another banner year for our Association.

Shirley Tilghman

DNA Learning Center

Charles and Helen Dolan with Dr. Peter Bruns (Right)

The DNA Learning Center (DNALC) had an exhilarating year. On June 8, the BioMedia Addition to the Center was dedicated, and the entire building was renamed the Dolan DNA Learning Center. The expanded administrative offices, additional teaching lab, computer lab, a lunchroom, and additional exhibition space were made possible primarily through the generosity of the Dolan Family Foundation, established by former and current CSHL Trustees Charles and Helen Dolan.

In addition to its expansion, the Dolan DNALC continued its heralded "Great Moments in Science" lecture series this year, and launched a new Web Site, "Your Genes, Your Health." The comprehensive Site profiles genetic diseases and explains their intricacies on an easy-to-understand level. The Site, which receives thousands of visitors each month, is quickly becoming a valuable resource for families and patients with genetic diseases. I encourage you to review the Dolan DNALC report in its entirety, later in this Annual Report.

CSHL Press

For Cold Spring Harbor Laboratory Press, 2001 was a year of new beginnings. The entirely rewritten, third edition of its classic *Molecular Cloning: A Laboratory Manual*, by Joe Sambrook and David Russell, recaptured its place as a best-selling, essential information tool in experimental biology. David Mount's *Bioinformatics* captured the suddenly burgeoning interest in this topic at the undergraduate level to become the textbook of choice at over 50 schools in the United States. A second textbook, the idea-driven *Genes & Signals*, by CSHL Trustee Mark Ptashne and staff member Alex Gann, was published to high praise in December. Among the other successes in a list of unusually interesting new titles was Elof Carlson's *The Unfit*, a history of the concept of eugenics, and Kathy Barker's *At The Helm*, a unique source of guidance for newly appointed leaders of research teams. Among the journals, *Genome Research* advanced strongly in circulation and manuscript submission, and the newly acquired *Protein Science*, being published for The Protein Society, was relaunched very successfully, with substantial increases in subscriptions and advertising sales. Amid all this activity, 40 members of the Press staff relocated to handsome new offices on the Woodbury campus, where for the first time in its history, all its key functions could be conducted under one roof, with ease and efficiency.

CSHL Library and Archives

In 2001, the CSHL Library continued its work toward creating a "virtual" library. To that end, it has maintained and substantially increased its digital library that includes all the necessary publications, software, and databases for the multidisciplinary research of the Laboratory's scientific staff. The Library continues its membership in consortia with two other major research institutions that began

in 2001: Rockefeller University and Memorial Sloan-Kettering Cancer Center. Membership in these consortia provides our scientists electronic access to many journals from these institutions. In addition, the *BioInformation Synthesis Collaborative Consortia* was formed with the libraries of the Woods Hole Marine Biological Laboratory, The Rockefeller University, and the American Museum of Natural History. The purpose of the consortia is to share human and information resources so that the collective strengths support and advance the research and learning of the members' constituents.

The Library enjoyed the second year of its automated cataloging system called *Sirsi*, which provides the Library's electronic catalog called *WebCat*, containing the library collection. Work on creating a new comprehensive database of all of the scientific laboratory's publications began this year. It will cover the period from its inception in 1890 to 1965 (pre *PubMed*). Two new digital projects were initiated this year: James D. Watson's Photo Archives and the CSHL Symposium photo collection. This collection contains a remarkable history of biology in the latter two thirds of the 20th century and into the new millennium.

New Major Gifts

2001 was a challenging year for fund-raising. Several major campaigns continue to be successful, despite the changed economy and the aftermath of the tragic events on September 11. The campaign to fund the Genome Research Center, the BioMedia Addition to the Dolan DNA Learning Center, and a continuing campaign for the Watson School of Biological Sciences were our major concerns, as was the ongoing effort to fund the cancer gene discovery program. We are very fortunate to have such generous and supportive friends at Cold Spring Harbor Laboratory, but for us to remain at the forefront of all areas of research and education, we need to increase support. Cold Spring Harbor Laboratory appreciates the major investment for these campaigns that provide the basis for many innovative initiatives. Through private funding, the Laboratory is changing the way we think about disease to provide a better future.

Institutional Advancement

The thoughtful commitment of $750,000 from Helen and Charles Dolan has enabled the planning and execution of initiatives to advance our education and research programs.

Watson School of Biological Sciences

The main focus of fund-raising for 2001 was the continuing campaign for the Watson School of Biological Sciences led by Laboratory Honorary Trustee David L. Luke III. New support was secured this year to fund student fellowships, lectureships, and courses. We are grateful for new gifts from Mr. and Mrs. Norris Darrell, Jr. for $200,000; The William Stamps Farish Fund for $200,000; the Annette Kade Charitable Trust for $100,000; Pfizer Global Research & Development for $300,000; Mr. and Mrs. Julian H. Robertson for $100,000; The Seraph Foundation for $75,000; and the Ziering Family Foundation for $300,000. A generous challenge gift of $350,000 was also made to the Watson School by an anonymous donor.

The Genome Research Center

This year heralded the completion of the 65,000-square foot Genome Research Center in Woodbury. The Center, just occupied in the middle of this year, is now running at close-to-full capacity, housing a Bioinformatics Center, a Cancer Research Center, the Genome Sequencing

Center, the Plant Genomics Center, the Cold Spring Harbor Laboratory Press, and the Laboratory's Purchasing Department. We are grateful for major new contributions to the facility in nearby Woodbury from the Goldfield Family Charitable Trust for $100,000 and the William and Maude Pritchard Charitable Trust for $280,000. The largest gift to date for this facility and its programs was $3,500,000 received from a generous donation of real estate by Kenyon Gillespie.

Dolan DNA Learning Center

Major support to fund the new BioMedia Addition continued this year with gifts from The Booth Ferris Foundation for $150,000 and $165,000 from the estate of Mrs. Dorothy H. Hirshon. Rotating exhibit space in *The Genes We Share* installation was made possible by a generous $150,000 pledge from Dr. Laurie J. Landeau. Once again, Brinkmann Instruments, Inc./Eppendorf AG has donated new lab equipment, this year valued at $75,000. We are also grateful to Arrow Electronics for their generous gift of $30,000; to Fisher Scientific International for $27,000 worth of equipment; and to Mr. and Mrs. Stephen A. Paolino/JPC Contracting for their gift of $10,000.

Private Research Support

Private funding in 2001 facilitated important research initiatives in cancer, neuroscience, and other areas, with major gifts in the $100,000 and above category, including the Oliver and Jennie Donaldson Trust for $250,000; the Louis Morin Charitable Trust for $125,000; the David and Lucille Packard Foundation for $970,000; the St. Giles Foundation for $183,000; Ann and Herb Siegel for $1,000,000; and the Whitehall Foundation for $225,000. The generosity of these and numerous other major private benefactors of Cold Spring Harbor Laboratory is crucial to our mission to perform the highest-quality basic research.

Breast Cancer Support

We greatly appreciate the support received in 2001 for breast cancer research from a number of breast cancer groups, including The Breast Cancer Research Foundation; the Long Beach Breast Cancer Coalition; Long Islanders Against Breast Cancer (L.I.A.B.C.); the Michael Scott Barish Human Cancer Grant sponsored by 1 in 9: The Long Island Breast Cancer Action Coalition; and the proceeds from Breast Cancer Awareness day in memory of Elizabeth McFarland. We remain grateful to and inspired by the dedicated individuals who donate their time and energy to advance cancer research through these organizations.

CSHL Planned Giving Advisory Board

The Cold Spring Harbor Laboratory Planned Giving Advisory Board was convened in 2001. Its members—drawn from the financial services, accounting and legal professions—total more than 20. The Board consists of bank officers, trust officers, investment advisors, investment bankers, accountants, tax advisors, and lawyers, representing 13 firms located on Long Island, in New York City, and in Connecticut. The purpose of the Board is to report to this influential group the Laboratory's activities and accomplishments and to engage Board members in the support of the Laboratory's goals. We welcome the board members to the Laboratory community.

President's Council

As in previous years, Jim Watson invited members of the President's Council to a 1-day meeting at the Laboratory, to meet the young scientists supported by the Council members and to hear about interesting advances in biomedical research. The topics for these meetings are carefully chosen for a combination of high-quality research and general interest, and for 2001 we selected a topic of importance to everyone—Nutrition: Facts and Myths.

The Council began with a talk by Nancy Etcoff (Massachusetts General Hospital) on "The Evolutionary Basis of Beauty," discussing why we find certain body forms attractive and showing that there are some fundamental forms that are cross-cultural. She was followed by Walter Willett (Harvard School of Public Health) who spoke on "Nutrition and Health" and gave us many good suggestions for improving our health through our diet—including some suggestions that were against our current wisdoms. Diet and cancer is a very controversial topic, but Bruce Ames (University of California, Berkeley) presented convincing data that micronutrients really do have a protective effect against cancer. With "Diets: Reality and Hype," Marc Jacobson (North Shore-Long Island Jewish Health System) reviewed diets and what does and does not work, and George Roth (National Institute on Aging) described how diet affects life span. This was a truly fascinating meeting and one that had a lasting impact on all participants.

Bruce Ames

Gavin Borden Visiting Fellow

Joan A. Steitz, Ph.D., Sterling Professor and Chair of Molecular Biophysics and Biochemistry at Yale University, was the Laboratory's 7th Gavin Borden Visiting Fellow. A former Trustee of CSHL, Dr. Steitz presented a lecture titled "Mechanisms of mRNA Export and Stability" on April 23 in Grace Auditorium. The Gavin Borden Lecture series was named in memory of Gavin Borden, a publisher whose *Molecular Biology of the Cell* and other books made a lasting impression on many scientists, both old and new.

Joan A. Steitz

Building Projects

Cold Spring Harbor Laboratory obtained some much-needed space this year, with the completion of two major projects.

On June 8, the Laboratory dedicated the Dolan DNA Learning Center, named for Helen and Charles Dolan. The Center is significantly expanded, with new administrative, laboratory, auditorium, and lunchroom space for school-aged visitors. In addition, the Learning Center nearly doubled its existing exhibit space and is in the process of designing new exhibits related to the history and future of biology.

Renovations were completed this year on the Genome Research Center in nearby Woodbury. The building, a 65,000-square-foot facility, now houses four research components: a

The Genome Research Center (*top*) and the Dolan DNA Learning Center (*bottom*).

Bioinformatics Center, a Cancer Research Center, a Genome Sequencing Center, and a Plant Genomics Center, as well as new administrative space for the CSHL Press and other administrative departments.

Community Outreach

Grateful for the overwhelming support that CSHL receives, a number of employees set out this year to "give back" to the Long Island community.

- CSHL was well-represented at the annual Chase Corporate Challenge, held at Jones Beach on July 31. More than 32 Laboratory runners were on hand at the event. The CSHL Men's team placed 12th and the Women's team placed 59th in the 3.5-mile race. Top performers included Holly Cline, Linda Van Aelst, and Ivo Grosse.
- CSHL "road-runners" were also on hand at the Cigna 5K Walk/Run, to support 1 in 9: The Long Island Breast Cancer Action Coalition, held at Eisenhower Park in East Meadow on August 23. The CSHL group—grateful for more than 10 years of support from 1 in 9—performed well despite the rain. In all, the event raised more than $60,000.

Special Events

Harbor Lecture Series

Francis Collins

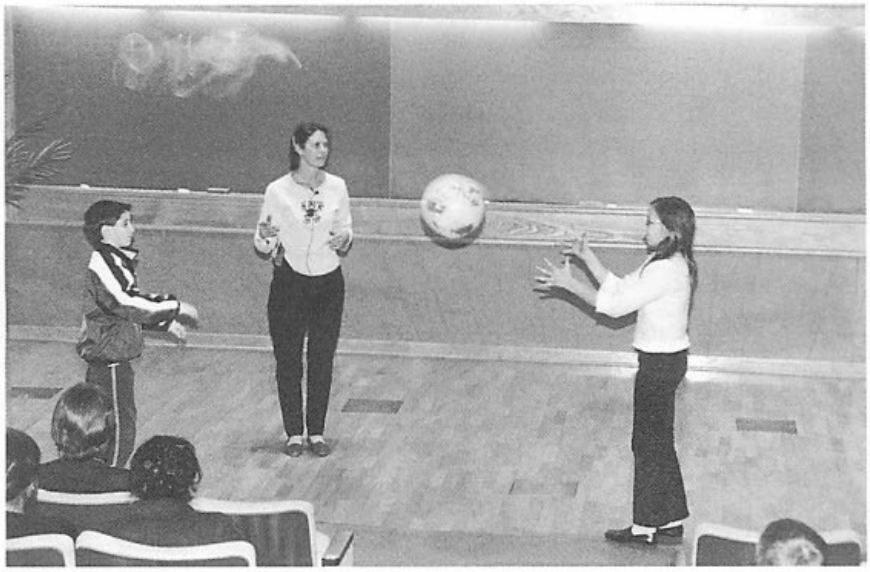
This year, the Laboratory hosted its first Harbor Lecture Series, three public lectures that attracted more than 900 visitors to Grace Auditorium. The first lecture was given by Dr. Francis Collins, M.D., Ph.D., Director of the National Human Genome Research Institute, on May 8. Dr. Collins's lecture, "Medical and Societal Consequences of the Human Genome Project," was well attended and much enjoyed. On May 21, John Coffin, Ph.D., the Director of the HIV Drug Resistance Program at the National Cancer Institute and the American Cancer Society Research Professor at Tufts University School of Medicine in Boston, delivered a lecture titled "HIV: Can This Disease Be Controlled or Cured?" The timely topic was fascinating for all participants. The final lecture, delivered on September 10, was by Jeffrey M. Friedman, M.D., Ph.D., a professor at The Rockefeller University in New York and an investigator for the Howard Hughes Medical Institute. Dr. Friedman addressed the audience about weight and body mass in an appealing lecture titled, "Molecular Mechanisms Regulating Body Weight."

Other Lectures

CSHL continued to host the Huntington Hospital Lecture Series, which ran from February to June. This year's topic was "Cardiac Health," part of Huntington Hospital's Heart Health Lecture program.

Cold Spring Harbor Laboratory expanded its popular West Side School Lectures Program, designed for students in local schools in grades four through six. Four CSHL Professors—Holly Cline, Eli Hatchwell, Yuri Lazebnik, and Robert Malinow—delivered entertaining and informative lectures to the budding scientists. The lectures, already a success, will again be expanded in 2002.

On March 23, Dr. Tom Kirkwood, a professor at the University of Newcastle in the United Kingdom, delivered a fascinating lecture on aging and genetics titled "Thread of Life: The Role of DNA in the Aging Process."


Holly Cline delivering a West Side School lecture.

Concerts and Exhibits

As part of the Laboratory's Music of the Harbor Concert Series, several concerts were held this year. Attended by the participants of CSHL's Meetings program and the public, the concert series was a huge success. The concerts included:

March 9	Cathie Ryan, Traditional Irish Female Vocalist
May 5	Stella Simakova, Pianist
May 19	Melvin Chen, Pianist
May 26	Jonathan Biss, Pianist
August 18	Anna Stoytcheva, Pianist
August 25	Alexis Pia Gerlach, Cellist
September 1	Antonio Pompa-Baldi, Pianist
September 8	Claremont Trio
September 22	Anthony Molinaro, Pianist
October 6	Eric Johnson, Jazz Guitar/Donald Axinn Poetry Reading

The Claremont Trio (*top*) and Cathie Ryan, Vocalist (*bottom*)

In addition to the concert series, the Laboratory hosted "FotoLab I," a collection of works from Laboratory staff and students. The event, inspired by Watson School student Rebecca Ewald, included Doug Fogelson, a Chicago-based photographer, as the "official" photographer in residence. Doug helped the staff and students select and capture their best work for the exhibit. Doug also gave special lectures and master classes during the exhibit, which ran in the Bush Auditorium from June 30 through August 5.

Laboratory Employees

Long-term Service

On June 22, employees celebrating milestone anniversaries with the Laboratory were honored at a special dinner at Robertson House, on the Banbury Center property. Congratulations to all! Honorees included:

30 Years	William Keen and John Maroney
25 Years	Guy Cozza, Joseph Ellis, Roberta Salant, Peter Stahl, Margaret Wallace, and Patricia Wendel
20 Years	Dorothy Brown, Rodney Chisum, David Helfman, Patricia Kurfess, Joseph Pirnak, and Philip Renna
15 Years	Russell Allen, Jennifer Blovsky, Mary Cozza, Nouria Hernandez, Christopher Hubert, Adrian Krainer, Susan Lauter, Carol Marcincuk, Vincent Meschan, Timothy Mulligan, Jacek Skowronski, and Diane Tighe

Back row (left to right): David Helfman, Russell Allen, Patricia Wendel, Adrian Krainer, Joseph Ellis, Peter Stahl, Jacek Skowronski, Bruce Stillman, Dill Ayres

Middle row (left to right): Susan Lauter, Nouria Hernandez, Roberta Salant, William Keen, Timothy Mulligan, John Maroney

Front row (left to right): Philip Renna, Carol Marcincuk, Margaret Wallace, Mary Cozza, Dorothy Brown, Guy Cozza, Jennifer Blovsky, Chris Hubert

Not pictured: Diane Tighe, Rodney Chisum, Patricia Kurfess, Joseph Pirnak, and Vincent Meschan

Carlos Brody

Alea Mills

Senthil Muthuswamy

New Faculty and Staff

Carlos Brody, Alea Mills, and Senthil Muthuswamy joined the Laboratory this year as assistant professors.

Promotions

Michael Myers and Marja Timmermans were both promoted to assistant professor this year. Shiv Grewal, David Jackson, and Andrew Neuwald were promoted to associate professors, and Dick McCombie was promoted to professor.

Departures

Departures this year included Ryuji Kobayashi, an associate professor; Edward Stern, a senior fellow; and Clifford Yen, a research investigator.

Visiting Scientists

Three visiting scientists joined us this year: Ann-Shyn Chiang joined the lab of Tim Tully; Xiaomin Wang joined the lab of Grigori Enikolopov; and Tilak Sharma joined the lab of W. Richard McCombie. Four scientists also wrapped up their stays at Cold Spring Harbor Laboratory: Antonius Holtmaat, Vincent Colot, Edith Heard, and Mary Sabatini.

Concluding Remarks

Science moves at a rapid pace at Cold Spring Harbor Laboratory—perhaps faster than at many places—for three principal reasons. First, our focus has always been on nurturing young scientists who are in the formative years of their scientific careers, giving them the reins and letting them go where they will. We are constantly surprised by what they achieve. Second, we teach in our courses program the latest research technologies to active scientists who visit from all over the globe. Third, administration and support staff are solely geared to the support of science. When combined, these factors make CSHL a center for truly innovative research. This is one of the reasons I decided to stay at CSHL after arriving as a postdoctoral fellow (not too long ago). Scientific research, by its very nature, is always moving into the unknown, trying to explain the ways of nature and how it can go wrong in diseases that afflict so many. I am confident that our approach will win the fight against some of the most important problems in biology and biomedicine.

With the slowing economy and the ever-increasing cost of high-technology-based science, our ability to support all that we need to do is a challenge that keeps me constantly worrying how we might "make ends meet" at the end of each year. The opportunities are significant, and I hope that as we move forward into a new year, we might feel more comfortable that at least the *very best of* what we do will receive the necessary funds. Ultimately, it is the fruits of this science that will benefit us, our children, and our children's children.

Bruce Stillman