HIGHLIGHTS OF THE YEAR

Research

Research at Cold Spring Harbor Laboratory continues to flourish. This will surprise no one in the community of scientists, within which our reputation ranks among those of the very best life science research institutions worldwide. This fact was reflected once again in an annual survey by Thompson Scientific's *Essential Science Indicators*, which reported in 2008 that CSHL is in the top 1% of institutions most cited in published research and that our faculty is ranked by peers among the top three in terms of its influence in shaping the fields of molecular biology and genetics. Much of this is due to the sound guidance of our research administration, which consists of a very effective team headed by Director of Research David L. Spector and includes Research Executive Committee members Greg Hannon, Scott Lowe, and Tony Zador, who receive outstanding administrative assistance from Sydney Gary and Walter Goldschmidts.

The Laboratory's achievements in 2008 are particularly noteworthy when considered in the context of the current funding environment. Against a backdrop of limited resources and a contraction in federal grant funding, scientists in all of the areas in which CSHL concentrates—cancer, neuroscience, and plant biology—reported a steady stream of significant research results throughout the year. Although these are comprehensively described on our website, it is useful to briefly review a few among the many to illustrate the richness of our scientists' cumulative achievements in 2008 and the continuing overall success of our research program.

Compensating for a Missing Gene in SMA

The neuromuscular disease called spinal muscular atrophy (SMA) can lead to death in children before the age of two. It is traced to a protein deficiency caused by mutations in the gene *SMN1*, which in turn leads to serious damage in growing nerve cells and the muscles that these cells control. This past year, Adrian Krainer and colleagues at CSHL and Isis Pharmaceuticals induced cells to replenish the deficient protein by activating a poorly expressed relative of *SMN1* called *SMN2* that resides in the human genome. This was done by inducing alternative splicing of a second copy of the *SMN2* gene so that it now included a missing piece that makes it more active and able to prevent disease progression. Adrian and his team sought to change the splicing by introducing synthetic molecules called anti-

sense oligonucleotides (ASOs). The team injected their most potent ASOs into mice that had an added, human version of *SMN2*. As they had hoped, the gene produced much more of the RNA for the critical protein, including the section that is usually omitted in *SMN2*, in tissues where the ASOs accumulate. They now seek to determine whether the ASOs really benefit growing animals with SMA and how and when they should be administered to affect the nervous system. This research follows a decade or more of fundamental research by Adrian and his colleagues regarding the understanding of control mechanisms of RNA splicing. Without this knowledge, the advances in therapeutic strategies would not be possible.



A. Krainer

Causal Link between a Tumor-suppressor Gene and Liver Cancer



S. Lowe

In a project that attests to the spirit of cooperation among our laboratories, no fewer than five CSHL teams joined forces in 2008 to confirm that a gene called *DLC1* is a tumor suppressor. In an effort spearheaded by Scott Lowe, they demonstrated in living mice that deletion, loss, or inactivation of the gene precipitates events culminating in an aggressive type of liver cancer closely related to common human epithelial cancers of the liver. Tumor suppressor genes have a vital role in intracellular signaling networks that protect against uncontrolled cell growth and proliferation. Such genes can be rendered inactive by a variety of DNA alterations. *DLC1*, a gene whose acronym reflects prior suspicions that it was "deleted in liver cancer," was known to be located in a region of chromosome 8 that has been observed to be missing in past studies of mammalian liver cancer cells. Importantly, the team's success in tracing the pathway by which *DLC1* func-

tions in both healthy and pathological states suggests a highly specific new target for future anticancer drugs. Using a mechanism called RNA interference (RNAi) to control the expression of specific genes, the team effectively turned off the DLC1 "switch" in living mice cells and, in so doing, was able to isolate one particular signaling intermediary whose presence was both necessary and sufficient to set the cell on an uncontrolled growth path. This essential molecular intermediary, a potential drug target, is called RhoA.

Role of Rare Gene Mutations in Schizophrenia



J. Sebat

In 2008, Jonathan Sebat and colleagues from the University of Washington and the National Institute of Mental Health contributed an important finding to our rapidly growing knowledge about the genetics of schizophrenia. They identified multiple, individually rare gene mutations in individuals with this devastating illness that may help to explain its causation in at least a subset of cases. Jonathan and the team screened the genomes of patients and healthy controls for gene copy-number variations (CNVs)—a type of structural variation in the genome characterized by the presence of either too many or too few copies of particular genes. They found that deletions, disruptions, and duplications of normal genes were three to four times more frequent in patients compared with controls. The study suggested that rare mutations not only are common in schizophrenia, but are also often quite powerful. In a preliminary effort to discover the role of these rare muta-

tions in disease etiology, the team found, intriguingly, that more than half of the disrupted genes were involved in pathways involved in neuronal development and regulation.

Rethinking the Neural Code

Anthony Zador, a neuroscientist who is interested in how neural circuitry in our brains gives rise to astonishing system properties such as consciousness and perception, performed a simple yet powerful experiment this past year that produced a surprising and important result. Tony wanted to determine the shortest possible time interval between neuronal signals or "spike trains" that an animal's cortex could distinguish and use to make a decision. The remarkable answer, observed in the auditory cortex of living rats, proved to be



A. Zador

three one-thousandths of a second (3 ms). These data provide support for an alternative theory of how information is processed in the brain, sometimes called the "neural code." The prevailing theory is based on the observation that neurons spike more quickly when they are transmitting information. This supports a "rate code" model, which stipulates that information is contained within the spiking rate of the neuron. However, Tony's experiment lends credence to a "timing code" model, wherein information is encoded within the precise pattern of spiking, which can be deduced by examining how spikes are distributed over time.

How the Brain Decides What to Believe

The laboratory of Adam Kepecs is also making important and original contributions to the study of the brain's system properties. Adam and his colleagues point out that even the simplest decisions involve the integration of sensory and memory information with emotional and motivational attributes, requiring the concerted action of millions of neurons across brain regions. Their current work seeks to elucidate the neurocomputational principles of decision making and attempts to capture elusive attributes such as emotion, motivation, or confidence. This past year, Adam, with Zachary Mainen and colleagues at CSHL, discovered neural signals for confidence in decision making in the rat prefrontal cortex. Their study suggests that confidence estimation is a fundamental information-processing mechanism in the brain, not a complex function specific to humans but a core component of decision making.



A. Kepecs

They speculate that it is found throughout the animal kingdom, shared widely across species, and not strictly confined to those, such as humans, that are self-aware.

Epigenetic "Reprogramming" of Plant Cells

Transposons are bits of DNA that can jump around in the genome and disrupt normal gene function and regulation. Under normal conditions, genomic chaos, found to occur in cancer and other diseases, is prevented in various ways, among which are a series of mechanisms that scientists call epigenetic. These mechanisms modify the expression of genes without altering their DNA sequence. Among the pioneers in the study of epigenetics is Robert Martienssen, a worthy successor to the late Barbara McClintock, the Nobel Laureate who, in discovering "controlling elements," vividly demonstrated at CSHL what we could learn about genetics by studying plant systems. This past year, Rob's team continued their ambitious project to map the changing epigenetic landscape of "immortalized" or continuously dividing

plant cells. They succeeded in describing epigenetic alterations that allow transposons to escape normal regulatory controls. Transposons in plant genomes are normally rendered inactive via RNAi, which is orchestrated by small interfering RNAs (siRNAs) that target heterochromatin (densely packed, genetically inactive regions of DNA). In immortalized plant cells, Rob's team found that epigenetic changes resulting in a loss of heterochromatin and transposon "reactivation" are not due to a loss of proteins regulating heterochromatin. They found instead that they were due to a change in the population of siRNAs produced in the continuously dividing cells. This suggests that siRNA-driven heterochromatin restructuring may lead to the formation of "epialleles"—epigenetic variations in gene expression patterns that stem from the creation of particular states in the chromosomes of cells, thereby changing the patterns of gene expression in related cells.



R. Martienssen

Small RNAs Involved in Transmission of Epigenetic Information: Genome Defense



G. Hannon

One way in which epigenetic information is known to be passed from parent to offspring is through the pattern of chemical "caps" added onto certain "letters" of the DNA sequence, ensuring that the sequence is "silenced." In some cases, enzymes that add these caps are guided to DNA by small RNA molecules. Gregory Hannon, a leader in the study of small RNAs, discovered (in part, with Leemor Joshua-Tor at CSHL) the cellular machinery that "dices" and "slices" double-stranded RNAs into gene-regulating single-stranded miand si-RNAs. Greg's team has now discovered that a class of small RNAs carries epigenetic information and has demonstrated how, in one instance, they pass on the trait of fertility from mother to offspring in fruit flies. This was only one of several discoveries made by Greg's team this year, most involving small RNAs, which, he has observed, are far more diverse as a class than initially suspected and act in more ways than anyone imagined when they were

first described about a decade ago. In 2008, the Hannon team described a new class of small RNAs that partner with the protein Argonaute 2. Using advanced sequencing technology, they found that these small RNA partners modify gene activity and suppress transposable elements, thus serving as a genome defense mechanism in cells that are destined to become the germ line for the next generation. These studies have helped to explain old and intriguing observations that when certain strains of animals are mated, their offspring are not fertile, a process called hybrid dysgenesis.

New Perspectives on "Noncoding" Portions of the Genome

Discovering where and how functional information is stored in genomes represents a frontier of research that underlies all life sciences and clinical research. Without this information, the biological and clinical effects of disease-causing mutations in humans and other organisms can only be partially understood. Recently, detailed analyses regarding which genomic segments are transcribed into RNA and the functional roles of these RNAs have revealed the fact that our current models of how genomes are organized and regulated remain rudimentary. As one of the leaders of the National Institutes of Health's project ENCODE (*ENC*/clopedia *Of DNA Elements*), Thomas Gingeras—who rejoined our faculty in 2008—has determined that almost all of the human genome can be transcribed into RNA and that most of these RNA products are not made to be translated into pro-



T. Gingeras

teins. Rather, non-protein-coding RNAs are used in a variety of functions ranging from regulation of expression of protein-coding genes to acting as scaffolds upon which large protein complexes are assembled. As reported in a front-page feature in the *Science Times* section of *The New York Times* on November 11, Tom's research is helping scientists to significantly revise long-standing notions about such basic questions as what constitutes a gene.

Histone Modifications with "Personality"

Michael Zhang's group has developed a series of computational tools that make use of statistical pattern-recognition techniques to identify exons, promoters, and posttranslational modification signals in large genomic DNA sequences. They also study alternative splicing of exons and collaborate with other labs to characterize splicing enhancers and silencers. This past year, Michael's group was part of a team that published a comprehensive analysis of modification patterns in histones. Using a new technology called ChIP-Seq, they identified 39 histone modifications, including a "core set" of 17 modifications that tended to occur together and were associated with genes observed to be active. The various modifications showed distinctive "personalities," each preferentially associating with particular regulatory regions of genes. They developed a better promoter prediction algorithm by taking into account such epigenetic information. They also worked with Professors Li at the University of Chicago and Krainer at CSHL to discover that one of the steps in turning genetic information into proteins leaves genetic fingerprints, even on



M. Zhang

regions of the DNA that are not involved in coding for the final protein. They estimated that such fingerprints affect at least a third of the genome and suggested that although most DNA does not code for proteins, much of it is nonetheless biologically important enough to have persisted during evolution. In addition, with Adrian Krainer, Michael's team succeeded in defining the regulatory networks of two related tissue-specific (brain and muscle) splicing factors, Fox-1 and Fox-2.

Three CSHL Studies Appear in Cell—in a Single Issue

Three separate research teams each led by our faculty reported results in the November 26 issue of the journal Cell—a reflection of the caliber and relevance of the work that is routinely performed at the Laboratory. It is unusual for multiple, unrelated studies emanating from the same institution to appear in a single issue of this prestigious journal, and it is truly remarkable for three teams to report on different projects in the pages of a single issue, given the relatively small size of our faculty, now at 47. A team consisting of Scott Powers, Gregory Hannon, W. Richard McCombie, Michael Wigler, and corresponding author Scott Lowe reported 13 new tumor-suppressor genes in liver cancer, which they revealed using a powerful new approach to validate linkages between suspect genes and their functional contributions to cancer. A second CSHL study in the same issue of *Cell* by Senthil Muthuswamy and colleagues demonstrated that normal function of the protein Scribble allows breast epithelial cells to form duct-like structures and resist cancer formation. They were also able to show that when Scribble stops functioning, the tissue loses its shape and the earliest stages of cancers ensue. The results constitute first steps toward identifying a new class of molecules and pathways that can be targeted by anticancer therapies to prevent precancerous lesions from turning into malignant tumors. In the third CSHL paper, a team in David Spector's lab shed light on possible functions of noncoding RNA molecules, announcing the discovery of a previously unknown mechanism in the nucleus that sends different parts of the noncoding RNA molecule MALAT1 to different cellular destinations.

Cold Spring Harbor Laboratory Board of Trustees

The Board of Trustees welcomed five new members: Leo A. Guthart, founder and manager of Topspin Partners, a venture and private equity firm based on Long Island; Thomas Lehrman, president and founder of Boliven, LLC, an internet start-up focusing on innovation, consulting, and venture investing in technology businesses; Marilyn Simons, Ph.D., president of the Simons Foundation, which funds basic research and education programs in mathematics and physical and life sciences; and Paul Taubman, managing director of Morgan Stanley. Charles L. Sawyers, M.D., Howard Hughes Medical Investigator and head of the Human Oncology and Pathogenesis Program at Memorial Sloan-Kettering Cancer Center, was elected a Scientific Trustee. In addition, the ranks of our honorary trustees grew with the addition of Norris Darrell, Senior Counsel, Sullivan & Cromwell LLP and CSHL Chancellor Emeritus James D. Watson, Ph.D.

On behalf of CSHL and the Board of Trustees, I thank departing Scientific Trustee Robert E. Wittes, M.D., for his service. Dr. Wittes was elected to the Board of Trustees as a Scientific Trustee in February 2004 and served on the Tenure and Appointments Committee from 2004 to 2008 and the Research Committee from 2004 to 2008. He stepped down in November 2008.

We are grateful to members of the Cold Spring Harbor Laboratory Association (CSHLA), who came together often in 2008, cultivating new friends and raising funds to support the research of scientists who are at the early and most innovative stages of their careers in research at CSHL. Despite the difficult economy, CSHLA members raised more than \$1.1 million for the annual fund.

Highlights from the CSHLA this past year included dancing to the latest Latin rhythms, an evening of education about skin stem cells, and a special thank you to major donors. The April *The Lab Goes Latin* dinner and dance event was a lively change from our traditional spring jazz benefit. We applaud co-chairs Lisa and Tim Broadbent and Kate and John Friedman for the tremendous energy and creativity that they put into this successful event. In early June, many of our new association members hosted dinner parties in their homes for visiting and CSHL scientists as part of the annual CSHL Symposium's Dorcas Cummings public lecture. Researchers and guests from the local community enjoyed the presentation on skin stem cells given by Elaine Fuchs, Ph.D., head of the Laboratory of Mammalian Cell Biology and Development at The Rockefeller University.

The rain did not dampen attendance by a record number of Association members and major donors at a lovely reception held in their honor at the home of CSHL Trustee Stephen Lessing and his wife Sandra in nearby Lloyd Harbor, New York.

I thank Pien Bosch, who served with exceptional dedication and success as President of the CSHL Association in 2007 and 2008. I look forward to the continued involvement of Pien and her husband Hans at CSHL and welcome all of the new friends that the Association directors and members introduce to the CSHL community.

Research and Education Management

We are proud of our continuing commitment to strategic and fiscal management of our research and education programs, which must evolve constantly to meet the challenges of contemporary science and society. This year, we established an independent Scientific Advisory Council (SAC) that is comprised of scientific leaders from top research universities and institutes. SAC will advise this institution on important issues related to research and education that will be necessary to maintain CSHL as a world leader. The nine-member SAC is chaired by Frederick W. Alt, a Howard Hughes Medical Investigator, member of the National Academy of Sciences, Professor of Pediatrics at Children's Hospital Boston, and Professor of Genetics and Scientific Director of the Immune Disease Institute at Harvard Medical School. Fred taught the influential molecular cloning course at CSHL in the 1980s. Other SAC members include Cornelia Bargmann, The Rockefeller University; David Botstein,

Princeton University; Joanne Chory, Salk Institute for Biological Studies; Carol Greider, Johns Hopkins School of Medicine; Leonid Kruglyak, Princeton University; Markus Meister, Harvard University; Tony Pawson, Samuel Lunenfeld Research Institute; and Max Wicha, University of Michigan.

CSHL hosted the inaugural conference of the iPlant Collaborative, a National Science Foundation-funded \$50 million project to create a virtual center in cyberspace for plant sciences, researchers, and students. The kickoff conference, entitled "Bringing Plant and Computing Scientists Together to Solve Plant Biology's Grand Challenges," took place April 7–9, 2008. In addition to CSHL, institutions in the iPlant Collaborative include the University of Arizona, Arizona State University, the University of North Carolina at Wilmington, and Purdue University.

CSHL Education Programs Expand

This year, through the skillful leadership of David Stewart, Executive Director of the Meetings and Courses program, we established a wholly owned subsidiary called Cold Spring Harbor Conferences Asia, to develop and operate an annual program of scientific conferences modeled after the CSHL meeting format. Our own in-house legal counsel John Maroney and his staff have been instrumental in this initiative.

Located on a 25-acre campus beside Dushu Lake in the eastern part of the city of Suzhou, which is in the Golden Triangle region of Shanghai on the lower reaches of the Yangtze River, the 600,000-square-foot ultramodern conference center and hotel currently under construction is funded by the Suzhou Industrial Park.



Cold Spring Harbor Conferences Asia appointed a distinguished Scientific Advisory Board of 20 academic scientists from Asia, Europe, Canada, and the United States, which held its inaugural meeting in Suzhou in October 2008. Cold Spring Harbor Asia plans to begin a program of international scientific conferences at the Suzhou Dushu Lake site in 2010.

Our foray into Asia recognizes the global nature of advanced science and builds on existing strengths of the CSHL Meetings and Courses program, which currently attracts more than 8000 scientists to our campus each year for exceptional scientific exchange and discussion, free of commercial or regional/national bias. We have a successful record of international educational partnerships and collaborations in Europe that include programs with the European Molecular Biology Organization in Germany and the Wellcome Trust in England.

The year 2008 was an inaugural one for the CSHL Personal Genomes meeting, whose time had finally come, thanks to advances in technology that are now making economical and efficient sequencing a reality. Our Chancellor Emeritus James D. Watson was one of only four whose individual genome had been sequenced and assembled at the time of the meeting. He and J. Craig Venter were honored at CSHL's third annual Double Helix Medals Dinner on November 6 for making their personal genome sequences available to the public. As more genomes are sequenced and analyzed, the CSHL Personal Genomes meeting will surely become an increasingly important venue for discussion linking personal genome data of humans and the genomes of many other species, as well as the societal issues associated with the accumulation of such personal data.

In September 2008, together with New York City Department of Education Chancellor Joel I. Klein, we officially opened an important extension of our DNA Learning Center, called the Harlem DNA Lab, at the John S. Roberts Education Complex in East Harlem. The Harlem DNA Lab is CSHL's first New York City–based education facility. It is amazing to think that it was only 20 years ago this year that we opened the Dolan DNA Learning Center facility in the village of Cold Spring Harbor. Since then, CSHL has provided hands-on educational experiences in genetics to more than 325,000 children and teachers on Long Island. During



Chancellor Joel Klein was a featured speaker at the Harlem DNA Lab opening in September.

the last two decades. Dolan DNA Learning Center Executive Director David Micklos and his team have profoundly influenced the way in which biology and genetics are taught in schools, not only in New York, but around this country and around the globe.

The Harlem DNA Lab is now bringing the latest knowledge and cutting-edge tools and techniques of modern biology to New York City's middle and high school students and teachers. With generous funding from the Howard Hughes Medical Institute (HHMI) and initial support from the Dana Foundation, Jerome L. Greene Foundation, The Goldman Sachs Foundation, and William Townsend Porter Foundation, New York City's 8th and 9th grade science teachers will receive professional development in genetics and biotechnology in order to boost student performance in science.



Landeau Multimedia Studio to support the next phase in the development of the

DNALC's Biomedia Group as a world leader in biology education. The studio contains the latest equipment for high-quality video production and is designed with separate sets for interviews, news reporting, and lab demonstrations. Many thanks to CSHL Trustee, Education Committee chairperson, and long-time friend Laurie J. Landeau, V.M.D., for making this possible.

The year 2008 was a multiple anniversary year for our Chancellor Emeritus James D. Watson, who not only celebrated his 80th birthday and 40-year wedding anniversary with Liz Watson, but also marked 40 years of dedicated contributions to the Laboratory. His imprint on CSHL spans every aspect of the Laboratory's life, ranging from financial stability, to beautiful landscapes, an expanded research program, the growth of professional education programs, and the establishment of the Watson School of Biological Sciences and the Dolan DNA Learning Center.

Liz Watson marked the year with the release of her new book Grounds for Knowledge, published by CSHL Press, which, under the leadership of John Inglis, continues in its commitment to publishing excellence. The publication coincided with the designation by the Public Gardens Association of America of the CSHL Bungtown Road campus as a botanical garden. Liz's book, filled with beautiful prose and the stunning photography of CSHL Director of Facilities Peter Stahl, showcases the landscapes of our shoreline location. As a campus community, we celebrated and joined with friends in the international scientific community to reminisce with Jim and Liz on several occasions this year, including an employee picnic honoring the Watsons in August 2008. Groundbreaking on the Hillside Campus expansion project began in 2005, but this year, we witnessed the most dramatic progress yet in this monumental capital project that will increase our research capacity in cancer, neuroscience, and bioinformatics by nearly 40%. At the beginning of the year, only the foundations for the six-building research complex were in place. By year's end, all of the internal piping and wiring were installed; the concrete superstructure was complete, exterior block walls were erected, and the roof structure and sheathing were in place, enclosing the buildings and ensuring that interior work continued through the winter months.

All the work on building structures could readily be seen at a glance as it progressed. Much less obvious was the enormous amount of work taking place inside the structures. Electricians and steamfitters worked hard, installing electrical and mechanical systems, including the two high-pressure boilers that will ultimately heat the six-building complex. These two areas were by far the most complex components of the project, and the impressive progress made in these areas is essential to the timely completion of the Hillside Campus.



Students get hands-on education in genetics at the Harlem DNA Lab.

The final touches were also put on the new chiller plant, and much of the underlying infrastructure—drainage systems, electrical conduit and wiring, water and sewer piping—was installed underground.

The Nassau County Chapter of the New York State Society of Professional Engineers presented CSHL with the Project of the Year Award for the engineering and innovative environmental design of the storm water management system for the Hillside Campus. CSHL was recognized for achieving a balance between development and the environment. The unique and functional storm water management system not only is effective at protecting the surrounding ecosystems, but also provides a visually pleasing backdrop for the Laboratory.

We thank Vice President and Chief Facilities Officer Art Brings and the Facilities Department for all of these great results and the minimal disruption to our daily operations and quality of life on campus as the work has proceeded.

Awards and Honors



L. Joshua-Tor



D. Ware

CSHL professor and Dean of the Watson School of Biological Sciences Leemor Joshua-Tor was one of 56 newly named HHMI Investigators in 2008. She joins approximately 300 HHMI Investigators in the Institute's flagship program, who lead HHMI laboratories at 64 institutions. In addition to Leemor, HHMI Investigators at CSHL include Gregory J. Hannon, Ph.D. and Scott Lowe, Ph.D.

For leadership in computational approaches and leveraging emerging sequence technology to link candidate genes and their function with agricultural traits and germplasm improvement, CSHL adjunct assistant professor Doreen Ware received the 2008 Scientist of the Year Award for the North Atlantic Area from the United States Department of Agriculture.

CSHL postdoctoral fellow Alexei Aravin was a 2008 finalist in the second annual New York Academy of Sciences Blavatnik Awards for Young Scientists. Sixteen young scientists from the New York tristate area were selected for their outstanding work as postdoctoral fellows and young faculty members. Five winners were chosen after three rounds of review of the 16 finalists, who represented a wide scientific and institutional spectrum in engineering, physics, and biology at nine different institutions in New York, New Jersey, and Connecticut.

Thompson Scientific's *Essential Science Indicators* ranked the research conducted at CSHL among the most cited in the world. The analysis, reported in the January/February issues of *Science Watch*, placed CSHL in the top 1% of institutions most cited and identified our research as having significant impact on molecular biology and genetics research from 2002 to 2006. This follows the previous ranking of CSHL by *Science Watch* as the top institution in the world in molecular biology and genetics during the decade from 1993 to 2002, based on citation impact.

I was honored to be elected this year to the American Academy of Arts and Sciences, joining other inductees who included CSHL friend and science philanthropist James H. Simons.

At the 2008 Watson School of Biological Sciences Commencement Convocation on April 13, we conferred the degree of Doctor of Philosophy to Hiroki Asari, Rebecca Bish, François Bolduc, Monica Dus, Angélique Girard, Christopher Harvey, and Wei Wei. Claire Biot and Adrienne Jones received the Master of Science degree. The Watson School also bestowed honorary degrees on three distinguished recipients. The first is one of the world's most successful entrepreneurs, who established the Allen Brain Institute that has mapped the gene architecture of the brain—Microsoft



Watson School Commencement Convocation

cofounder Paul G. Allen. The remaining two include the Nobel Prize-winning neuroscientist Dr. Eric Kandel and a clinician whose ability to translate the complexities of the brain's biology into house-hold concepts has made him a cultural icon: Dr. Oliver Sacks.

The 2008 incoming class is the 10th of the Watson School and represents a record number of students—a total of 15—who come to Long Island from Australia, France, Germany, Italy, South Korea, Russia, and Turkey, in addition to the United States. This year, we also established the Gonzalo Rio Arronte Fellowship, to be held by a qualified Mexican graduate student. Candidates for the fellowship will be preselected by the Universidad Nacional Autónoma de México and the Fundación Gonzalo Río Arronte and presented to the Watson School Admissions Committee, which will make the final decision on admission. The fellow will be expected to have a role in the development of genomic sciences in Mexico upon completion of his or her graduate and post-doctoral training.

For the seventh consecutive year, CSHL received the highest possible rating from Charity Navigator for its financial organizational efficiency and capacity.

As a private nonprofit research and education institution, we are proud to be recognized for achieving the highest standards of financial responsibility. These standards distinguish CSHL as an institution prepared to meet the expectations of public and private donors, who demand accountability, transparency, and quantifiable results from their contributions to nonprofit organizations. Thank you to CSHL Chief Operating Officer Dill Ayres and Comptroller Lari Russo for their commitment to ensuring the highest standards for CSHL.

Development

With the hard work of the Development department, led by Charlie Prizzi, Cold Spring Harbor Laboratory's fund-raising efforts saw much success in 2008. The \$200 million goal for the Hillside Campus Campaign was surpassed and more than \$41 million was raised in unrestricted and program support. Generous philanthropic gifts resulted in the establishment of the Center for Quantitative Biology at Cold Spring Harbor Laboratory, which will be based in the newly constructed David H. Koch Laboratory. The Simons Foundation and The Stanley Medical Research Institute have continued to fund programs aimed at uncovering the genetics behind autism, schizophrenia, and bipolar disorder. Additionally, a generous commitment was made by HHMI to help expand the laboratory space for the CSHL Meetings and Courses program so that more scientists will have the opportunity to participate in our world-renowned educational programs.

On behalf of CSHL, our Board of Trustees, and our Development department, I would like to acknowledge all those who helped us to achieve our goals. Please refer to the back of this Annual Report for a complete list of our generous supporters.

The Robertson Research Fund

The Robertson Research Fund continues to serve as a vital internal resource of support for our scientists. In 2008, it supported research in the labs of Grigori Enikolopov, Josh Huang, Leemor Joshua-Tor, Rob Martienssen, Senthil Muthuswamy, Bill Tansey, Anthony Zador, and Yi Zhong. Start-up research support was also provided by the Fund to four new investigators: Hiroyasu Furukawa, Raffaella Sordella, Lloyd Trotman, and Glenn Turner. In addition, the Robertson Research Fund continues to support the annual CSHL In-House Symposium and our programs for postdoctoral fellows and graduate students, the laboratory seminar program, and faculty recruitment.

Library and Archives

History of Biotechnology Meeting

While renovations progressed on schedule to the Carnegie Building, the home of the CSHL Library and Archives, there was also much progress in the expanded mission of this vital CSHL resource. Under the aegis of The Genentech Center for the History of Molecular Biology and Biotechnology at CSHL, Library and Archives, in cooperation with the Banbury meetings program that is run by Jan Witkowski, hosted a milestone meeting entitled "Biotechnology: Past, Present, and Future." From September 21 to 23, scientists, entrepreneurs, and venture capitalists discussed the academic discoveries that gave rise to our modern biotechnology industry, and along with distinguished sociologists, economists, and historians, they discussed the importance of gathering and preserving primary documentary source materials that will enable historians of today and tomorrow to study the emergence of a field that has transformed the life sciences, business, and health care since its advent in the 1970s. I am pleased to note that our own Library and Archives department, under Ludmila Pollock, has already established a valuable repository for materials of lasting historical value, including an extensive and growing oral history archive.

Building Projects

Hillside Research Laboratory Campus

Progress on the construction of the six new research buildings of the Hillside Research Complex has been excellent. The Nancy and Frederick DeMatteis, David H. Koch, and William L. and Marjorie A. Matheson Laboratory buildings have progressed substantially toward their anticipated completion by the spring of 2009. The Donald E. Axinn, Leslie and Jean Quick, and Wendt Family Laboratory buildings are expected to be ready for occupancy by mid-2009. The landscaping surrounding the complex was significantly enhanced this year, and much-needed parking facilities have already been put to use.



The Hillside Research Laboratory Complex (top)

Access to the new complex is now possible via a roadway connecting to the Grace parking lot. As part of this project, we made the decision to reconfigure the lot for improved traffic flow and safety. Despite adding an additional traffic lane to better accommodate bus and van traffic associated with the Meetings and Courses program, we were able to increase green space in the area by more than 5000 square feet.

Renovation was also begun on teaching facilities in the Delbruck Laboratory. Structural problems necessitated reconstruction of the building's circa-1927 center section, requiring the entire top floor and roof section to be completely removed and rebuilt. Generous funding from HHMI allowed CSHL to completely modernize the entire historic teaching suite that is used for courses to train scientists on the latest technologies and techniques. These renovations and improvements are expected to be complete by the spring of 2009.

As noted above, we have made significant progress on the Carnegie Building renovation. Although we had originally hoped to complete the project by the end of 2008, design alterations and the challenges of working within an existing, historic structure made that impossible. The project is expected to be completed and ready for occupation in 2009.

We also undertook renovation and improvement of the circa-1937 Robertson House, located on the Banbury estate and primarily serving participants invited to high-level meetings at the Banbury Conference Center. Principal among the planned renovations was the replacement of the house's original electrical system in preparation for the installation of central air conditioning. The torrid weather of recent summers has made the house all but uninhabitable during the hottest part of the year. When completed in 2009, the house will have been completely freshened with new washrooms, refurnished, air-conditioned, and equipped with telephones and internet connections in each room. I thank Art Brings and Peter Stahl and all who worked on this difficult project to maintain Robertson House as a grand residence and doing so under budget.

CSHL has also continued its long-standing program of general campus improvements. The four-year project to upgrade and replace the building management system is now half complete. The Jones Laboratory was renovated for course use during the Delbruck Laboratory renovations. Updates and changes were also made to various office areas to better suit the needs of the Laboratory's staff.

Special Events

National DNA Day

We celebrated the sixth annual congressionally designated National DNA Day on April 25, with walking tours of CSHL and festive signs on campus and throughout the village of Cold Spring Harbor. We thank the Cold Spring Harbor Library and Environmental Center and the Cold Spring Harbor Main Street Association for their participation.

Emerson String Quartet Concert

Cold Spring Harbor Laboratory, Stony Brook University, and Brookhaven National Laboratory hosted an evening of "Perfect Harmony" on April 1 to celebrate music, partnerships, and possibilities for increased research collaboration among the three scientific institutions on Long Island. Guests listened to the Emerson String Quartet and were treated to an appearance by pianist Gilbert Kalish.

Gavin Borden Visiting Fellows

The 14th Annual Gavin Borden Visiting Fellow Lecture, in memory of the publisher of *Molecular Biology of the Cell*, was held on April 14. The lecture was presented by Tania Baker, who in addition to being an alumna of the CSHL Undergraduate Research Program is the Edwin C. Whitehead Professor of Biology at the Massachusetts Institute of Technology and an HHMI Investigator.

The Lab Goes Latin

This year's *The Lab Goes Latin* event marked the 10th anniversary of the Cold Spring Harbor Laboratory Association's spring benefit. Held on May 10 at the Nature Conservancy in Cold Spring Harbor, it featured a packed dance floor with music by the urban salsa band Yerba Buena. The event raised more than \$200,000 for CSHL's cancer and neuroscience research programs.



Symposium

The urban salsa band Yerba Buena entertains at *The Lab Goes Latin.*

The 73rd Symposium, on "Control and Regulation of Stem Cells," brought more then 300 researchers from around the world together at CSHL to discuss the latest findings in stem cell biology.

During the Symposium, the traditional Dorcas Cummings Memorial Lecture for scientists and guests from the community was delivered by Elaine Fuchs, Rebecca C. Lancefield Professor and head of the Laboratory of Mammalian Cell Biology and Development at The Rockefeller University.

Women's Partnership for Science

This year's event attracted 150 women from the surrounding community, New York City, and Connecticut to the home of Mr. and Mrs. Daniel P. Davison on June 22. They gathered to promote and support women pursuing careers in biomedical research. Guests participated in their own tabletop experiments on organic and genetically modified foods. The instructors were young educators from Cold Spring Harbor Laboratory's Dolan DNA Learning Center (DNALC); Erin McKechnie, a plant and soil specialist; and Elna Gottlieb, an earth science specialist.

Topping Ceremony

On July 22, CSHL celebrated the topping of the highest structure in the soonto-be-opened Hillside Research Complex. Distinguished guests, elected officials, colleagues, friends, and members of Long Island's talented construction trades gathered to commemorate the occasion. They proudly observed as a 10-foot-6-inch square by 13-foot-high 5000-pound stainless steel pyramid was lifted by crane and secured to its new home atop an 85-foot tower that is called the Laurie and Leo Guthart Discovery Tower. In addition to the pyramid, a steel beam autographed by hundreds of CSHL staff and visitors is part of the foundation for the crown.



The Laurie and Leo Guthart Discovery Tower at the Hillside Research Complex

Paul Liam Harrison Exhibit

Paul Liam Harrison exhibited his artwork at CSHL during the Dynamic Organization of Nuclear Function meeting on September 16. For several years, his practice has become increasingly collaborative and has engaged with developments in and around the biosciences and, in particular, cell and gene research. The exhibit was a collection of works entitled "Designs for Life."

Harlem DNA Lab Opening

On September 23, New Yorkers celebrated the opening of the Harlem DNA Lab, a state-ofthe-art education facility located in the John S. Roberts Educational Complex in East Harlem, New York. Joel I. Klein, New York City Department of Education Chancellor, and Peter Bruns, Vice President for Grants and Special Programs at HHMI, joined school principal Maria Aviles, DNALC Executive Director David Micklos, myself, and local leaders in opening remarks followed by a community tour of the teaching lab.

DNALC 20th Anniversary

On November 1, The Dolan DNA Learning Center celebrated the accomplishments of Executive Director David Micklos and his staff in transforming science education during the last two decades. The event included the dedication of the Laurie J. Landeau Multimedia Studio.



The Double Helix Medals Dinner

The Double Helix Medals Dinner was held on November 6 at the Mandarin Oriental, New York. Medals were presented to Drs. Marilyn and James Simons for corporate leadership, Sherry Lansing for humanitarianism, and James D. Watson, Ph.D. and J. Craig Venter, Ph.D. for scientific research. A total of \$3.6 million was raised at the gala, which was cochaired by the Hon. and Mrs. Alan J. Blinken, Mr. and Mrs. Alan C. Greenberg, Dr. Arthur D. Levinson, Mr. and Mrs. David M. Rubenstein, Mr. and Mrs. Herbert J. Siegel, and Mr. and Mrs. Erwin P. Staller.

CSHL's Double Helix Medal

CSHL Public Lectures

January 21

Bruce Stillman, CSHL President: The Future of Molecular Medicine at The Secret Science Club public science and art lecture series in Brooklyn, New York.

August 4

Scott Lowe, Professor and HHMI Investigator: *The Latest from the Frontlines of Cancer Research* at The Secret Science Club public science and art lecture series in Brooklyn, New York.

October 21

WLIW-TV "Healthy Minds" host Dr. Jeffrey Borenstein; Josh Huang, CSHL Professor; Jonathan Sebat, CSHL Assistant Professor; Linda Van Aelst, CSHL Professor; and Anthony Zador, CSHL Professor: Autism: The Latest Genetic and Neuroscience Research and What it Means for Patients and Families.

October 28

Jonathan Sebat, CSHL Assistant Professor and Anil K. Malhotra, Director, Psychiatry Research, Zucker Hillside Hospital and Associate Professor of Psychiatry, Albert Einstein College of Medicine: *Bipolar Disorder: Cracking the Code*.

November 11

CSHL trustee and poet Don Axinn: *Travel in My Borrowed Lives*.

CSHL Public Concerts

April 12

Jennifer and Angela Chun with Nelson Padgett, violins and piano

May 3

Soukhovetski and Vassily Primakov, piano duo



Harlem DNA Lab announcement

May 17 Anastasia Khitruk and Elizaveta Kopelman, violin and piano

August 30 Martin and Kristina Kasik, piano duo

September 20

Alexander Fiterstein and Steven Beck, clarinet and piano

September 27 Soyeon Lee, piano

October 4

Krista River and Judith Gordon, soprano and piano

Laboratory Employees

New Staff

Thanks to a superb recruiting effort led by CSHL Director of Research David L. Spector, we were pleased to introduce the following new faculty into the CSHL community this year.

Tom Gingeras, Ph.D., CSHL professor, is an established leader in the field of functional genomics who has developed high-throughput microarray technologies and powerful computation approaches to understand how genomes are organized and regulated. Before joining CSHL, Tom was Vice President for Biological Research at Affymetrix, Inc., California.

Assistant Professor Gurinder "Mickey" Atwal, Ph.D., is the first faculty appointment for the new Center for Quantitative Biology at CSHL. He will integrate computational, analytical, and experimentally derived data to approach several questions concerning the evolution and diversity of genomes. His projects include identifying changes in the genome that modify risk in cancer and autism; developing statistical tools for the analysis of interactions among genetic polymorphisms identified in large-scale genetic and epidemiological studies; and developing computational methods to detect networks of genes that have responded to evolutionary selection pressures.

Assistant Professor Bo Li, Ph.D., who completed his postdoctoral training at CSHL and at U.C. San Diego with Robert Malinow, studies neural synapses, specifically focusing on how synaptic dysfunction contributes to psychiatric disorders such as schizophrenia and depression. He uses a number of methodologies, including electrophysiology, genetics, and behavioral analyses, with a long-term goal of developing methods that allow for the manipulation of activity in specific brain circuits to correct disease-related behaviors.

Assistant Professor Zachary Lippman, Ph.D., studies the molecular mechanisms controlling reproductive fitness in plants. He uses genomic approaches to determine what controls flower, fruit, and seed production in tomato and *Arabidopsis*. His research will not only provide insights into plant evolution and domestication, but will also develop new tools for plant breeding. Zach joins us from the Faculty of Agriculture at Hebrew University of Jerusalem and is a Watson School graduate.

Associate Professor Pavel Olsten is both an M.D. and a Ph.D., whose research will provide a critical bridge connecting CSHL's genetics and neuroscience programs. He has developed a high-throughput approach involving cutting-edge imaging technology to monitor brain function at the level of synaptic circuits. He is studying how specific genetic mutations and variations affect neural circuits in mouse models of schizophrenia and autism. Pavel was previously an Assistant Professor at Northwestern University.

Associate Professor Darryl Pappin, Ph.D., comes to CSHL to head the proteomics core facility on our campus. Proteomics is the large-scale study of proteins, and Darryl brings an impressive record of developing new methods for identifying and analyzing proteins in complex biological samples. Before joining us, he was a Scientific Fellow at Applied Biosystems, Applera Corporation.

Florin Albeanu, Ph.D., is a CSHL Fellow who received his doctorate from Harvard Medical School. Florin is an expert in imaging neuronal circuits in awake behaving rodents. Working in the olfactory system, he plans on using fiber-optic imaging and electrophysiological recordings to understand how neuronal circuits code information from the environment and how these circuits are shaped by sensory experience.

Ivan lossifov, Ph.D., is a CSHL Fellow in Quantitative Biology from Columbia University. Ivan has devised computational methods to reliably extract knowledge about molecular interactions from the biomedical literature and combine this data with results from high-throughput biological experiments. In this way, he has built a framework to predict pathways or networks of interacting genes that contribute to common hereditary disorders. He is interested in applying his methods to improve conventional genetic analyses to detect correlations between specific mutations and common complex hereditary disorders such as schizophrenia, bipolar disorder, and autism.

CSHL Fellow Christopher Vakoc, M.D., Ph.D., is interested in how changes to the structure and organization of chromatin are related to cancer progression. He uses biochemical approaches to study specific modifications associated with leukemia and colon carcinoma. He did his doctoral training at Children's Hospital of Philadelphia.

Joining the administrative leadership of CSHL this year was Hans-Erik Aronson, Director of Information Technology. Hans-Erik was previously at the Center for Computational Biology and Bioinformatics at Columbia University. His own training in biochemistry and molecular biophysics, combined with his experience in design, implementation, and delivery of emerging technologies, will be critical to the success of individual scientific research projects as well as to the operations of the entire Laboratory, which increasingly depends on the strength of our information technology infrastructure and dedicated staff.

Promotions

Congratulations to Zhenyu Xuan, Ph.D., who was promoted this year to Assistant Research Professor and to Jim Hicks, Ph.D., who is now a CSHL Research Professor.



Departures

During the course of the year, several faculty members took on new challenges at other institutions. Hollis T. Cline holds the position of Professor in

J. Hicks

both the Department of Cell Biology and Chemical Physiology at the Scripps Research Institute. Roberto Malinow is a Professor, Section of Neurobiology, and Professor, Neurosciences at UC San Diego. Zachary Mainen is Principal Investigator at the Champalimaud Foundation. Vivek Mittal is currently Associate Professor, Cardiothoracic Surgery, and Director, Lehman Brothers Lung Cancer Laboratory at Weill Cornell Medical Center.

Community Outreach

CSHL employees continue to actively participate in local and national community service events, including lab-wide blood drives in February, August, and December and the American Cancer Society's Daffodil Days in the spring. This year, CSHL employees donated 400 pounds of food to the Long Island Cares Harry Chapin Food Bank. Our campus also participated in the national campaign to donate used cell phones for conversion to 911 emergency-use cell phones that will be distributed to those in need by the Secure the Call Foundation. These efforts are organized by our dedicated Human Resources Department ably led by Katie Raftery. In addition to participating in local Long Island school activities, every year CSHL is proud to sponsor Cold Spring Harbor Library and Environmental Center kickoff festivities for the children's summer reading program.

CSHL campus walking tours were open to the public most Saturdays from March through November. Our specially trained team of tour guides, which includes CSHL graduate students and postdoctoral fellows, provides guests with scientific insights and personal perspectives that enrich the public's understanding of CSHL.

Looking Forward

The year 2008 was notable for the many accomplishments that I have highlighted here. The year was perhaps even more notable for the ability of this institution to manage its research and education programs in the face of significant external economic uncertainty. I credit the Laboratory's Principal Investigators, who are committed not only to scientific excellence but to the responsible management of their laboratory budgets and staff. The research administration team that we have built has succeeded in establishing a new standard for meshing the creativity required in scientific pursuit with the realities of fiscal and regulatory requirements.

CSHL's education programs have never been as strong and broad, reaching from middle and high school ages to undergraduates, graduates, postdoctoral students, and professional development for accomplished scientists. None of this would be feasible if not for the operational efficiencies and accomplishments of the Laboratory's administrative departments and their staff who provide critical support to our scientists and educators. In addition to those departments already mentioned, let me thank the entire Facilities Department, the Office of Sponored Programs, the Office of Technology Transfer, the Public Affairs Department, and the Purchasing Department for their great work. Despite a tough external environment, CSHL thrived as an institution and a community in 2008.

Thank you to our Trustees, faculty, staff, and many supporters for your hard work. As I look to the future, I remain confident that scientific research and education are a source of strength for the troubled national economy—a source that has yet to be tapped to its fullest potential. CSHL stands ready to push biomedical research forward to reach its fullest potential. With a sharp focus on our core mission, CSHL is poised to do even more for the future of science and society than we have in the many years of our very fruitful past.

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