Highlights of the Year

Research

In summing up the year's achievements in the annual "State of the Lab" presentation to Laboratory staff, I characterized 2011 as one in which research productivity was "truly exceptional." In fact, Cold Spring Harbor Laboratory remains at the very top of the list of scientific research institutions worldwide for its impact, as measured by science publisher Thomson Reuters. During the last decade, research papers in molecular biology and genetics published by CSHL investigators have been cited, on average, more frequently than those published by scientists in comparable institutions.

These statistics say something important about CSHL scientists beyond the general reputation of the institution, which has long been stellar. They tell us that work coming out of their laboratories is consistently important to their colleagues at other institutions, who trust, cite, and build upon their data. Notable about research at Cold Spring Harbor Laboratory is the highly collaborative nature of the research, which is focused on a few areas, including cancer, neuroscience, plant biology, and quantitative biology. Research results in 2011, highlighted below, indicate how studies in basic science, when pursued consistently over time, provide the basis for practical advances in medicine. Here is a sampling of a few of the many important results obtained by CSHL scientists in 2011.

Unconventional Hunt for Cancer Targets Yields a Drug Candidate of Unusual Potential

C. Vacok

Using an unconventional approach to discover new targets for anticancer drugs, a team led by CSHL Fellow (and now Assistant Professor) Christopher Vakoc along with Professor Scott Lowe pinpointed a protein called Brd4 as a novel target in the treatment of acute myeloid leukemia (AML). AML is an aggressive blood cancer that is incurable in about 70% of patients. In an early success for CSHL's new Cancer Therapeutics Initiative, Vakoc, Lowe, and their colleagues used a sophisticated screening method based on RNA interference (RNAi), developed in Greg Hannon's laboratory, to identify Brd4, a protein that helps regulate gene expression by reading chemical tags that attach to chromatin, the material in which the genetic material is bundled. They used short-hairpin RNAs to disable the gene that encodes Brd4 in mouse models of AML developed by Lowe, halting progression of the disease and bringing about significant remissions. In collaboration with physician and chemist Dr. James Bradner at the Dana-Farber Cancer Institute, the team was able to reproduce these antileukemic effects using a small-molecule drug called JQ1, previously characterized by Bradner to specifically inhibit the Brd4 protein. That drug is now being optimized for testing in human patients with AML, in trials that should begin within the next 18 months. Because Brd4 is a link in an intracellular signaling pathway that includes the major human cancer gene c-*Myc*, there is a chance that if successful, JQ1 or its analogs may be effective in treatment of other human cancer types in which c-*Myc* activation has an important role.

New Therapeutic Target for Liver Cancer and a Predictive Biomarker

S. Powers

In another research effort that highlights "next-gen" approaches in cancer research, Associate Professor Scott Powers and colleagues identified a strategy for targeted molecular therapy in liver cancer, which currently has limited treatment options and one of the worst one-year survival rates of any cancer type. Their experiments reveal that up to 15% of liver tumors are driven by the hyperactivity of a gene called *FGF19*, which is involved in various normal biological processes such as cell growth and tissue repair. Powers' collaborator, Dr. Dorothy French at Genentech, had previously developed a potent antibody that blocks the activity of the protein produced by the *FGF19* gene. Experiments showed that shutting down its activity with the antibody inhibited tumor growth. This work therefore provides

not only a potential treatment but also a biomarker—*FGF19* gene amplification—to predict whether treatment with the antibody is going to be effective. The research represents a new chapter in efforts to expand the current goals of large-scale cancer genome projects in which whole-genome sequencing of cancer genomes is pinpointing new therapeutic strategies and drug targets.

Relationship between Two Genes Mutated in Prostate Cancer Can Dictate Outcome and Aid Treatment Decisions

Prostate cancer is common, but only about 15% of newly diagnosed cancers progress to a malignant and lethal form. Identifying those patients who might progress is of high importance. Research by Associate Professor Lloyd Trotman and colleagues addressed this issue when they set out to discover what kind of gene deletions work together with the loss of a tumor suppressor gene called *PTEN* to trigger prostate cancer. The PTEN protein normally removes phosphate molecules from its molecular targets and tempers prostate cell proliferation by preventing activation of a cancer-causing gene called *AKT*. Focusing on another phosphatase, PHLPP1, that was recently identified as a deactivator of *AKT*, Trotman's team showed that the *PHLPP1* gene also functions as a suppressor of prostate tumors. Mice that lacked both copies of *Phlpp1* developed a premalignant form of prostate cancer. The team found that monitoring the activity of the two genes—*PTEN* and *PHLPP1*—in patients following prostate surgery can predict whether a patient is on a path to develop dangerous dual deletions and thus relapse following initial hormone therapy. This information could help identify the best patients for clinical trials testing a new class of prostate cancer drugs that inhibit the *AKT* pathway and could also influence which inhibitors of this type are used and when.

L. Trotman

New Method Reveals How Tumors Evolve and Spread

A new analytic method devised by Professor Michael Wigler, Research Professor James Hicks, and colleagues features a process called single-cell sequencing that enables accurate quantification of gene copy number within the DNA of a single cell. Gene copy number refers to the number of each gene in the cell, and normally it should be two (one inherited from each parent). In cancer, portions of the genome are amplified or deleted, giving rise to extra or missing copies of key genes and interfering with mechanisms that normally control cell growth and proliferation. Single-cell sequencing, the latest in a long line of technical innovations by the Wigler team, represents a major advance in our ability to understand how tumors evolve, uncovering the genetic complexity within a single tumor. The insights offered by this method have relied heavily on research within the new program of quantitative biology at CSHL that has expanded in the last several years. The analysis of breast cancers using single-cell sequencing methods suggests that tumors may not evolve gradually, but rather in punctuated bursts. It is a finding that has already shed new light on the process of tumor growth and metastasis and should help in the development of new methods to clinically evaluate tumors.

Powerful Quantitative and Clinical Study on Autism Causation and Gender Skew

Dan Levy, Michael Ronemus, and others investigators in the Wigler lab joined with CSHL Quantitative Biology Fellow, now Assistant Professor, Ivan Iossifov to complete a clinically extensive and mathematically powerful study of autism spectrum disorder (ASD). Using a newly assembled patient and family sample population called the Simons Simplex Collection—which at the time included about 1000 families comprising both birth parents and in most cases two children, one with ASD and the other unaffected—the team affirmed prior results stressing the importance of noninherited, spontaneously occurring copy-number variations (CNVs) as causal factors in autism. The team was able to consistently resolve much smaller genomic irregularities than previously possible. This analysis revealed a significantly greater number of genome areas where spontaneous DNA deletions and duplications affected genes thought to contribute substantially to ASD. The team estimates a minimum of 250–300 places in the genome harboring CNVs can give rise to ASD. Most of the CNVs detected

M. Wigler

were only seen once and are classified as rare gene mutations. This is a potential source of confusion because these rare events, taken in total, are possibly the source of at least half of all autism and, based on Wigler's previous studies, contribute to inherited forms of autism.

Mice Engineered with Chromosome 16 Deletion Seen in Humans Display Autism-Like Behaviors

A. Mills

Professor Alea Mills, together with Mike Wigler and colleagues, achieved an important milestone in 2011, proving that one of the most common genetic alterations in autism—deletion of a 27-gene cluster on chromosome 16—causes autism-like features. By generating mouse models of autism using a technique known as chromosome engineering, the Mills team provided functional evidence that inheriting fewer copies of these genes leads to features resembling those commonly used to diagnose children with autism. The behavior of mice with the deletion contrasted with that of normal mice; they were hyperactive, had difficulty adapting to a new environment, suffered from sleeping deficits, and displayed restricted, repetitive behaviors. Mice engineered to bear human gene aberrations associated with autism will be invaluable in pinpointing the disorder's genetic basis and elucidating how these alterations affect the brain. They could also be used for inventing ways to diagnose children before they develop the full-blown syndrome and for designing clinical interventions.

Overlooked Brain Area Found to Be an Important Locus of Depression

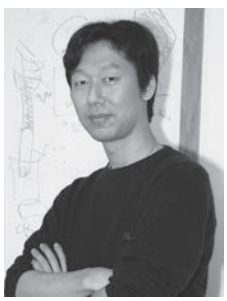
The scientific importance of animal models was also shown in experiments performed by Assistant Professor Bo Li, Professor Fritz Henn, and colleagues at Brookhaven National Laboratory and the University of California, San Diego. By implanting electrodes into a tiny area of the rat brain called the lateral habenula (LHb), they were able to deliver an analog of deep brain stimulation (DBS). This had the effect of reversing depression-like symptoms in the rats. The team's results point to DBS in the LHb as a potential therapy for depression. DBS is already an important treatment method for Parkinson's disease.

Precise Structural Maps of NMDA Receptors Will Aid Drug Discovery

In the search for the mechanisms that give rise to depression, scientists have a variety of clues, one of which is dysfunction of receptors in the brain's neurons called NMDA (*N*-methyl-D-aspartate) receptors. These widely expressed receptors are large, multiunit proteins found at the membrane of a subset of excitatory neurons. The way in which a neurotransmitter binds to the receptor determines the strength of neuronal electrical excitability. In 2011, Associate Professor Hiro Furukawa and his team of structural biologists published the results of two important studies. In one, they mapped the precise shape of the subunit of the NMDA receptor that binds excitatory neurotransmitters (notably glutamate, the brain's most prevalent excitatory neurotransmitter). In a second study, they obtained a precise molecular map of the binding site for an allosteric inhibitor of an NMDA receptor subtype. This site—a docking port within the receptor—is important because it is a potential target for drugs that can modulate NMDA receptors. Problems in these receptors have been linked not

B. Li

F. Henn



H. Furukawa

only to depression, but also to a number of other important disorders including schizophrenia, Parkinson's, and Alzheimer's diseases, as well as stroke-related brain injuries.

Stem-Cell-Related Changes that May Contribute to Age-Related Cognitive Decline

Why do our brains produce fewer and fewer neurons as we age—a phenomenon thought to underlie the process of age-related cognitive decline? Blood stem cells go through many cycles of self-renewal followed by quiescence, and their numbers do not decline with age. But Associate Professor Grigori Enikolopov's group, together with Associate Professor Alex Koulakov, has found, in contrast, that adult stem cells in the brain remain quiescent for a prolonged time before they are activated. Then, they undergo a series of rapid divisions, giving rise to progeny that differentiate into neurons. After that, the stem cells abandon their "stemness" by differentiating into astrocytes, a type of nonneural "helper" cell. This implies that each adult brain stem cell is used only once and hence is disposable. This in turns raises a fascinating question: Does activating neuronal production too much—say, with the use of neurogenesis-enhancing drugs such as the antidepressant Prozac—exhaust the stem cell pool prematurely? The answer depends on how the production of new neurons has been induced, according to Enikolopov. Whereas Parkinson's disease and traumatic brain injury, which activate stem cells directly, may result in a depletion of the stem cell pool, therapeutic deep brain stimulation of certain brain areas, as well as Prozac and exercise, stimulates the downstream progeny of stem cells and increases production of new neurons while keeping the stem cell pool itself safe and intact.

Paths to New Drugs from Basic Research on Protein Tyrosine Phosphatases

Professor Nicholas Tonks and his team have discovered how targeting an enzyme called PTP1B—which Tonks discovered in 1988—can provide a path to the discovery of new drugs to fight two major scourges, diabetes and obesity. As the "founding member" of a superfamily of enzymes called protein tyrosine phosphatases (all of which remove phosphate groups from tyrosine residues in proteins), PTP1B is known to be an important player in the intracellular signaling pathway that regulates the response to insulin. In type 2 diabetes, insulin molecules dock at cells but the cellular mechanism that sends their signal does not work properly. This year, Tonks and his colleagues found that PTP1B is regulated by hydrogen sulfide (H_2S). Tonks demonstrated reversible control of PTP1B activity by H_2S in cells by the addition of a sulfur molecule to the active-site cysteine residue in the enzyme, thereby inhibiting the enzyme activity. They also discovered a new allosteric mechanism that regulates PTP1B activity, offering the possibility of developing small-molecule drugs that could modulate PTP1B activity. Tonks' team generated a specific type of antibody that, when expressed in cells, selectively recognized and stabilized an oxidized state of PTP1B. In that mode, its role in suppressing insulin signaling is inactivated, resulting in increased insulin signaling. This had the effect of enabling insulin to transmit its signal in an enhanced and sustained fashion. It suggests a new way of targeting PTP1B in therapeutic efforts to address insulin resistance that occurs in diabetes. But this pathway that influences metabolic signaling may also influence how primary breast cancer cells switch to metastatic tumor cells and invade other parts of the body. In two separate papers, Tonks' team identified and characterized a novel allosteric inhibitor of PTP1B that indicates a unique mode of therapeutic intervention in HER2-positive breast cancers, and, using RNAi screening to test the role of PTP family members in controlling migration and invasion in mammary epithelial cell models of breast cancer, they discovered that PTPN23, another phosphatase family member, is among the regulators of such invasion, exerting its effects by regulating the well-known tumor-promoting SRC protein. Their research indicates that inhibitors of SRC might be useful in treating patients with inactivating mutations in the *PTPN23* gene.

N. Tonks

How Plants Are Able to Overcome Environmental Challenges in Order to Thrive

If an animal gets too hot or too cold, or feels pangs of hunger or thirst, it tends to relocate—to where it is cooler or hotter, or to the nearest place where food or water can be found. But what can a plant

do under similar circumstances? Plants cannot change the climate and are unable to uproot themselves to move to a more favorable spot. Yet they do respond successfully to changes in environmental conditions in diverse ways, many of which involve modifications of the way they grow and develop. Professor David Jackson and his team at CSHL have now discovered at the genetic level how one vitally important species of grass plant—maize—responds to the challenge to growth posed by shade. Central to this work is the team's identification of the role played by a gene called *grassy tillers1*, or *gt1*, whose expression, they confirmed, is controlled by light signaling. Maize plants produce very few tillers, or lateral branches, at their base. Plants with profuse tillers do not tend to grow well in close proximity because their branches and leaves tend to throw any close neighbors into shade, thus limiting access to sunlight, their common prime energy source. By severely limiting its lateral branching, maize is able to redirect its energy to the primary shoot, which grows taller and escapes the shade. A fascinating sidelight: Without any knowledge of genes or genetics, ancient Mesoamericans domesticated maize by selecting for genes that suppressed tillering and thus encouraged maize to grow upward to the sky, rather than outward into the neighboring stalk. We now know one molecular mechanism of how the corn that was selected by these early Indians grows to yield tall plants.

D. Jackson

Cold Spring Harbor Laboratory Board of Trustees

At the core of the success of Cold Spring Harbor Laboratory are the philanthropic organizations and generous individuals who recognize the significance of our biomedical research and education programs to the community and society at large. Investments in CSHL are driving scientific and medical progress as well as economic development. With more than 1100 employees, the Laboratory is one of the largest employers in the region. Technologies developed at CSHL have sparked new companies, some of which have grown to be players in the global economy. One example is OSI Pharmaceuticals, which was acquired by Astellas Pharma, but importantly remains on Long Island at the Broad Hollow Bioscience Park. CSHL helped found Broad Hollow at SUNY Farmingdale as an incubator for life science start-ups. More broadly, a new science cluster that includes CSHL, Brookhaven National Laboratory, Hofstra University, North Shore–LIJ Health System, and Stony Brook University could become a formidable engine for economic growth. Combined, the institutions represent a major economic force on Long Island and in New York State.

With an eye to the future, CSHL this year became a founding member of the New York Genome Center (NYGC), a nonprofit organization leveraging the collaborative resources of 11 leading academic medical centers, research universities, and hospitals in the vicinity of New York City. This consortium will generate data essential for the advance of personalized medicine, accelerate the development of new diagnostics and treatments for human disease, and promote life science commercialization. It will complement the strong genome research center that is currently the only genome center in New York State and that has contributed to major genome sequencing projects and investigation of the causes of human disease and cognitive disorders.

CSHL's leadership role in developing and using genomic technologies will provide the NYGC with expertise that will facilitate the genomic analysis of patient samples. This in turn will expedite the identification of mutations that drive disease processes, as well as critical prognostic and diagnostic markers for disease.

I am thankful for the active involvement and support that we receive from the Board of Trustees. In 2011, the Board elected George Sard, President of Sard Verbinnen & Co. The Laboratory community mourned the loss of Honorary Trustee Evelyn Lauder. Her leadership of the Breast Cancer Research Foundation, which supports research conducted at the CSHL Cancer Center and numerous breast cancer research centers throughout the world, has been invaluable in raising awareness and funds for research and treatment.

A. Harmon and J.C. Nicholls, CSHL Board of Trustees Chairperson

With newly elected president Sandy Tytel, the CSHL Association is the institution's grassroots connection to the community. In its "Science Never Sleeps" campaign, the CSHLA this year helped raise a record $5.9 million. "Labapalooza" was a unique fundraiser featuring scientist rock bands and tastings from Long Island's best restaurants and enabled our talented scientists to display their musical flair.

The 10th annual "Women's Partnership for Science" event featured Pulitzer-Prize–winning *New York Times* journalist Amy Harmon, who presented "Targeting Cancer: A Dose of Hope." During the last decade, the Partnership has raised almost $700,000. This year's luncheon drew nearly 150 women, who gathered on the scenic lawn of Airslie House.

Research Faculty

G. Hannon

Howard Hughes Medical Institute (HHMI) Investigator and CSHL Professor Greg Hannon, Ph.D., was honored on April 15 with the 2011 Northeastern Association of Graduate School Geoffrey Marshall Mentoring Award. Greg is among the original faculty of CSHL's Watson School of Biological Sciences, which opened its doors in 1999. Since then, he has mentored some 12 postdoctoral fellows and 17 graduate students. The achievements of his trainees have been outstanding. Four students completed their Ph.D. degrees in less than 4 years and two were recipients of the prestigious Harold M. Weintraub Graduate Student Award, which is presented to the top graduate students in life sciences in the United States.

Every mentee in Greg's laboratory has had at least one publication in a high-impact journal, and more than 60% of Greg's 200-plus scientific publications have had graduate mentee coauthorship. The training that he provides has resulted in the placement of 10 of his graduate students in prestigious postdoctoral positions, with four already holding independent faculty positions at Mt. Sinai School of Medicine, the University of Toronto, the Fred Hutchinson Cancer Research Center, and the Whitehead Institute.

R. Martienssen

The HHMI and the Gordon and Betty Moore Foundation in 2011 selected CSHL Professor Rob Martienssen as one of the nation's 15 most innovative plant scientists to become an HHMI Investigator. The honorees will share $75 million in research funding over 5 years. Rob is a trailblazer in unraveling epigenetic mechanisms, which help to regulate how genes work, and is an expert on transposons—sequences of DNA that jump around the genome, often altering gene activity.

The Brain & Behavior Research Foundation (BBRF) awarded CSHL Professor Josh Huang a NARSAD Distinguished Investigator grant to study how genetic alterations associated with behavioral symptoms of schizophrenia disturb the development and function of neural circuits. Using a genetically engineered mouse strain, Josh will study chandelier cells, which are key to inhibitory circuits in the brain's frontal areas. NARSAD Distinguished Investigators are selected by BBRF's 124-member Scientific Council.

CSHL Fellow Chris Vakoc was selected by the Burroughs Wellcome Fund to receive a 2011 Career Award for Medical Scientists. The 5-year $700,000 award helps M.D.-Ph.D.s—a unique set of scientists who are experienced in both research and patient care—to bridge postdoctoral training and the early years of faculty service. This award supports Chris' work in identifying epigenetic vulnerabilities in chemotherapy-resistant leukemia.

Professor W. Richard McCombie was named a Fellow of the American Association for the Advancement of Science (AAAS) "for distinguished contributions in the areas of molecular biology,


J. Huang


C. Vakoc


W.R. McCombie

computational biology, and genomics, including high-throughput genome sequencing, and as director of the CSHL Genome Center."

Assistant Professor Hongwu Zheng was selected by the V Foundation for Cancer Research as a 2011 V Scholar. Additionally, his proposal to study the genetic and functional characterization of epidermal growth factor receptor (EGFR)-targeted therapy resistance in malignant gliomas received special attention as the winner of the Martin Abeloff award for outstanding project submission.

CSHL and the National Institutes of Health (NIH) cohosted the "NIH New Investigator Regional Conference" on March 14. The brainchild of the head of our Office of Sponsored Research, Walter Goldschmidts, and supported by The Alfred P. Sloan Foundation, the event, held at Grace Auditorium, brought key NIH directors and scientific program leaders together with more than 250 new faculty from 56 universities and research centers to discuss national biomedical research priorities and issues facing new investigators. Despite NIH programs designed to facilitate the transition of new scientists to independently funded principal investigators, the average age at which an investigator first obtains an initial independent research grant remains unacceptably high.

CSHL's National Cancer Institute (NCI)-designated Cancer Center successfully competed for and secured a renewal of its NCI grant that provides more than $4 million annually for research during the next 5 years. CSHL has been an NCI-designated Cancer Center since 1987.

Promotions

Alea Mills was promoted to Professor and two of her colleagues, Raffaella Sordella and Hiroyasu Furukawa, are now Associate Professors. Former CSH Fellow Christopher Vakoc was appointed Assistant Professor.

NIH New Investigator Regional Conference

Administrative leaders of CSHL were also recognized with promotions. Lari Russo was named Chief Financial Officer and Damian Desiderio is now the Comptroller. Hans Erik Aronson, who heads our Information Technology Department, was promoted to Chief Information Officer.

In the Development Department, Diane Fagiola assumed a new role as Senior Director, Philanthropy, and Karen Orzel was named Director of Annual Giving and Donor Relations.

Departures

HHMI Investigator Scott Lowe took on a new position at Memorial Sloan-Kettering Cancer Center, continuing collaboration with CSHL as an Adjunct Professor and active collaborator on a program project grant from the National Cancer Institute.

Education Programs

The Watson School of Biological Sciences

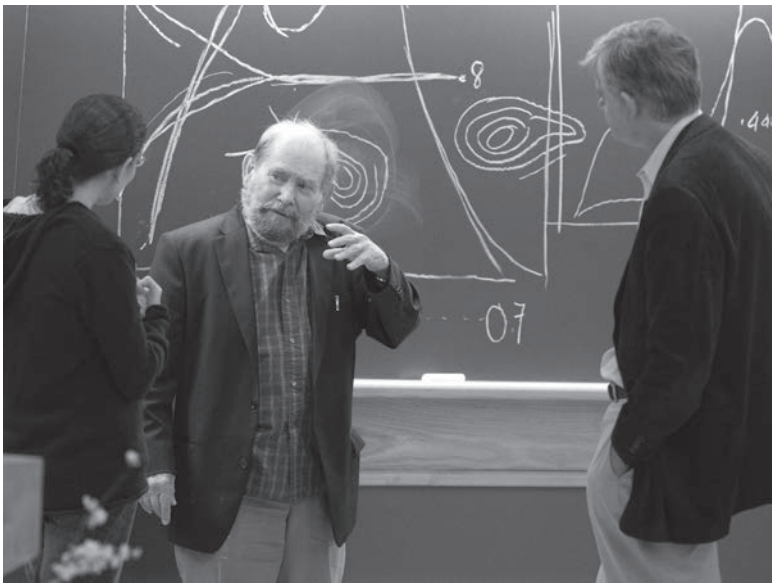
The School held its eighth graduation in 2011, with Amy R. Rappaport and Claudio Scuoppo joining the ranks of WSBS doctoral degree recipients, now numbering 49. Honorary degrees were bestowed on James H. Simons, Ph.D., Board Chair of Renaissance Technologies LLC, and James R. Lupski, M.D., Ph.D., Professor of Molecular and Human Genetics at Baylor College of Medicine.

Watson School graduates have thrived in the professional world. They publish in top scientific research journals and secure prestigious independent positions, fellowships, and awards. Eleven graduates to date have secured tenure-track faculty positions and are now receiving federal grants and publishing papers as independent researchers. At the end of 2011, WSBS students had published more than 185 research papers, a remarkable record since the school only started graduating students 7 years ago.

The 2011 entering class was composed of 10 accomplished students from the United States, Canada, the United Kingdom, France, Spain, and Switzerland. A significant number of additional students studying at CSHL are from Stony Brook University, via a program established between CSHL and Stony Brook more than 30 years ago.

The 10-week CSHL research program for undergraduate students—affectionately called "URP"—convenes in the summer and provides some of the finest college students in the nation a priceless opportunity to conduct sophisticated research at the side of a CSHL investigator. In 2011, URP's 53rd year, 727 college students competed for 28 slots, a continuing mark of the program's relevance and stellar reputation.

(*Left to right*) CSHL President B. Stillman, honorary degree recipients J.H. Simon and J.R. Lupski, and 2011 Watson School graduates A.R. Rappaport and C. Scuoppo



S. Brenner and B. Stillman at the Gavin Borden Lecture

The Gavin Borden Visiting Fellow Lecture "Reading the Human Genome" was presented on April 25 by Nobel laureate and long-time friend of CSHL Sydney Brenner, Ph.D., F.R.S.

Meetings and Courses Program

The world-renowned CSHL Meetings and Courses program attracted record attendance in 2011. More than 7750 people attended scientific meetings and more than 1300 (trainees, teaching, and support faculty) took part in courses. The Cold Spring Harbor Asia program based in Suzhou, China, meanwhile drew some 2700 participants to 13 conferences and a summer school held during 2011.

Our flagship meeting, the Cold Spring Harbor Symposium on Quantitative Biology, which each year focuses on a different topic, this year integrated classical biochemistry and modern molecular biology under the theme of *Metabolism and Disease*. This year's Symposium, the 76th in the historic annual series, featured 63 speakers from North America, Europe, and Asia. Steeped in the tradition of interactions between visiting scientists and the local community, the Dorcas Cummings Lecture opened the doors of the meeting to members of the local community, who were enthralled by Cyn-

Scene from the 76th CSHL Symposium

thia Kenyon's talk on "The Deadly Sweet Tooth." Dinner parties at local homes after the Lecture were the perfect venue to continue discussions of science and society.

New CSHL meetings in 2011 included *Stem Cell Engineering* and *Cell Therapeutics* and *The Biology of Cancer: Microenvironment, Metastasis, and Therapeutics*, both reflecting the increased interest in translational science. Basic bioscience meetings, such as those on *Eukaryotic Transcription* or *Neurobiology of* Drosophila, continued to flourish, whereas the *Eukaryotic RNA Processing* meeting was historic not least for beginning with an earthquake and ending with a hurricane.

CSHL offers ~25 high-level courses that attract more than 1000 scientists each year. Directed primarily at predoctoral-, postdoctoral-, and faculty-level scientists, these intensive courses allow practicing researchers to immerse themselves in new techniques and ideas that they can apply immediately to their own research. The HHMI awarded the Laboratory a new 4-year grant totaling $2.475 million to support current courses and to allow CSHL to start new courses.

HHMI

Banbury Center

In its 34th year of operation, the Banbury Center hosted 24 scientific meetings as well as six lecture courses, two Watson School courses, and a variety of third-party events in 2011.

The schedule centers around private scientific gatherings, and during the year, these were attended by ~686 participants from the United States and 25 other nations. Highlights of the science program included a series of meetings coorganized by James D. Watson. Dr. Watson and Joseph Schlessinger organized the meeting on *Curing Melanoma and Other Cancers by Targeted Therapies* that was well timed, coinciding with reports of exciting results in treatments with vemurafenib, developed by Plexxicon and Hoffmann La-Roche and now approved by the Food and Drug Administration. While the meeting was in session, the FDA approved ipilimumab for the treatment of metastatic cancer. Dr. James Allison, whose work helped lead to the development of the drug, was present at the meeting. Other timely cancer-themed meetings in the series included *Myc and the Pathway to Cancer* and *Metformin and Neoplasia*, both focusing on recent developments in discovering targeted therapies for cancer and dealing with cancer's unusual metabolism.

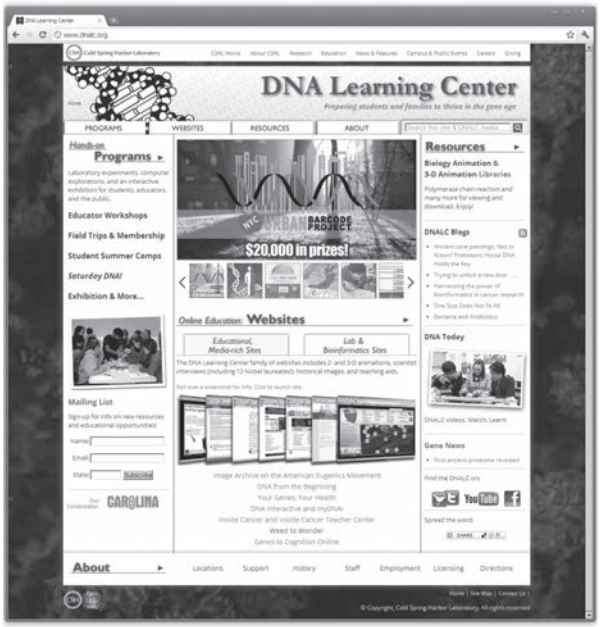
Outside groups use the Center for training young scientists, and we have developed close relationships in particular with the National Institute of Mental Health (NIMH) and the Boehringer Ingelheim Foundation. This year's NIMH "brain camp" was attended in full by the Institute's director, Dr. Thomas Insel. Banbury workshops in 2011 focused on areas of intense interest including autism spectrum disorders and pancreatic cancer.

DNA Learning Center

The DNA Learning Center (DNALC) continues to convey the wonders of molecular biology to young people, K–12 teachers, college faculty, and members of the general public. To date, the DNALC has introduced the concepts and technologies central to the field to more than 600,000 people. In 2011, 28,648 local students participated in labs, through field trips to DNALC facilities in Cold Spring Harbor, Lake Success, and Harlem, New York City, and via in-school instruction and the use of equipment footlockers.

More than 2800 of these students were from underserved Long Island and Queens school districts, and 60.2% of *Harlem DNA Lab* students in upper Manhattan were members of ethnic groups that are underrepresented in science. Enrollment in the DNALC summer camp programs set a new record, exceeding 1000, and collaborations with Cold Spring Harbor High School, the Watson School of Biological Sciences, and Stony Brook University continued.

Educator training was expanded in 2011: More than 1000 educators took part in training workshops across the United States, and more than 1600 people attended presentations or short workshops at professional meetings. In a continuing partnership with the New York City Department of Education, funded by the HHMI, the DNALC also provided training at the *Harlem DNA Lab* to 128 teachers in 44 1-day workshops, plus 2-week leadership training to 18 highly qualified teachers.



In late 2011, the DNALC portal (www.dnalc.org) was awarded the *Science* Prize for Online Resources in Education (SPORE). An essay in *Science* by DNALC founder and executive director David Micklos and two members of the team, Sue Lauter and Amy Nisselle, described the evolution and impact of the DNALC's suite of websites, apps, and YouTube resources that attract more than 7 million visitors annually. In 2011 alone, the DNALC added three more websites, a new "app," and an e-book to the portal.

In 2010–2011, studies were undertaken to measure the effects of DNALC programs on students. When compared with other educational methods and media, use of the two tested DNALC sites, *Inside Cancer* and *Genes to Cognition* (*G2C*) *Online*, helped increase student academic performance, on average, by one letter grade.

CSHL Press

The goal of the Press is to identify important research, technologies, and scientists; amplify their effectiveness by selecting, aggregating, and curating information research communities can use; and deliver that information when, where, and how the communities want it.

During 2011, research articles published by the Press' seven scientific journals continued to have a high impact in their respective fields; more than 2100 electronic journal subscriptions were fulfilled at academic institutions in 150 countries, including all leading American universities, and 39,600 copies of print books were shipped. This reach is complemented by interest from foreign publishers in translating certain books into languages such as Chinese, Japanese, Arabic, and most recently, Vietnamese.

As measured by impact factor, the best-known metric of worth, all CSHL journals advanced in 2011. *Genes & Development* and *Genome Research* continue to occupy the first tier of genetics, biotechnology, and developmental biology journals, and of the 8000 most important science journals published in the world, they are within the top 1.2%. All of the journals exceeded financial expectation, and *Cold Spring Harbor Protocols*, in its 5th year, had a remarkable increase in subscriptions. A new journal, *Cold Spring Harbor Perspectives in Medicine*, was launched on schedule in September, with papers on AIDS, Alzheimer's disease, and Parkinson's syndrome.

Seventeen new books were published during the year, bringing the number of available titles to more than 150. Former Trustee James Darnell's book, *RNA: Life's Indispensable Molecule*, published in July to critical acclaim, was named one of the 25 Outstanding Academic Titles for 2011 by *Choice* magazine. The best-selling titles of the year were the classic handbooks *At The Bench* and *At The Helm*, the iconic manual *Molecular Cloning*, and the magisterial history of molecular biology *The Eighth Day of Creation* by Horace Freeland Judson, whose passing at the age of 80 during the year we noted with great sadness.

The mission of the Press is being profoundly altered by changes in distribution channels. Laboratory protocols and topic-specific review articles are two types of content for which the Press has been renowned. Five years ago, that content was delivered only in printed books. Now, it comes also in the much more usable form of online-only, subscription-based review journals made possible by the reputation of those print books and the strategies used in creating them. Thus the same content types now have an additional means of delivery and a different, more robust business model, but the same exceptional quality. E-books and device apps are being explored. All Press journals online are now optimized for reading on mobile phones and tablet devices.

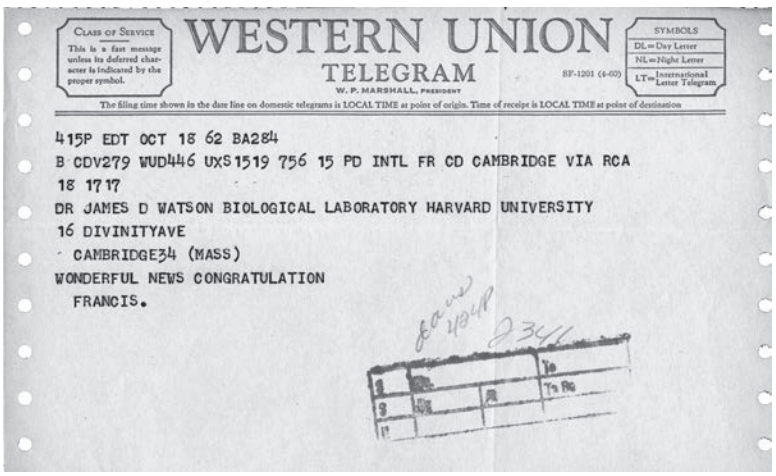
Library and Archives

Part of CSHL's broad education mission, the Library and Archives continued to promote open access to science history through grant-supported digitization projects.

Supported by wellcome trust

Backed with a generous $600,400 grant from the Wellcome Trust and with the assistance of photographer Ardon Bar-Hama, who has digitized the Dead Sea Scrolls at the Israel Museum and the archives of the New York Philharmonic, CSHL is now rendering nearly all of its comprehensive archives of Dr. Watson's papers, manuscripts, lectures, and many of his photographs in high-resolution digital format. Altogether, more than 250,000 Watson items will be digitized, as well as more than 100,000 items from the collection of Sydney Brenner. It is part of the Wellcome's 2-year pilot project on the theme of *Modern Genetics and its Foundations* that seeks to digitally "reunite" archival collections of the major players in the development of molecular biology (in addition to Watson and Brenner, these include Francis Crick, Maurice Wilkins, and Rosalind Franklin, among others). The collections will be made available through the Wellcome Digital Library website and our own CSHL Library's Archives Digital Collections Database.

Through a grant from the New York State Documentary Heritage Program Basic Processing Project, CSHL will arrange and describe three collections that represent CSHL's predecessor institutions, providing insights into the lives of scientists working at the Lab from 1890 to 1974. This will include



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W. P. MARSHALL, PRESIDENT
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DR JAMES D WATSON BIOLOGICAL LABORATORY HARVARD UNIVERSITY
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WONDERFUL NEWS CONGRATULATION
FRANCIS.

Item from the James D. Watson Archive

E. Watson, P.J. Kennedy, J.D. Watson, C. Moraetis, G. Echt, and S. Echt, at the President's Council meeting

material from the Eugenics Record Office, an organization that also existed in the Cold Spring Harbor neighborhood from 1910 to 1939.

Other notable initiatives undertaken by the Archives include a grant from the National Archives and Records Administration/National Historical Publications and Records Commission Basic Processing Project to process 630 linear feet of CSHL archival collections and a Preservation Assistance Grant for Smaller Institutions from the National Endowment for the Humanities that allowed for a general preservation assessment of our collections and a preservation workshop attended by institutional librarians and archivists across the New York metropolitan area.

Development

The Honorable Patrick J. Kennedy, cofounder of "One Mind for Research," opened the 27th annual President's Council on October 14, greeting donors whose $25,000 gifts support CSHL's most talented young scientists. The retreat focused on "The Science of Addiction" and featured Susan Foster, Columbia University; Joanna Fowler, Brookhaven National Laboratory; Philip Low, Chairman, Neuro Vigil; Eric Nestler, Friedman Brain Institute and Mount Sinai School of Medicine; and Howard Shaffer, Harvard Medical School. CSHL Assistant Professor Adam Kepecs discussed his work on neural circuit principles behind decision making, which he hopes will lead to better treatments for diseases such as addiction. We thank event chairpersons Howard Morgan, Cynthia R. Stebbins, and Steve Wiggins.

P.J. Kennedy, B. Stillman

Double Helix Medals Dinner

At our sixth Double Helix Medals dinner, $3.3 million was raised to strengthen and expand research and education programs.

The Double Helix Medal honors individuals who have positively impacted human health by raising awareness and funds for biomedical research. Each of this year's honorees—Temple Grandin, Harold Varmus, and Kareem Abdul-Jabbar—has made extraordinary contributions that have helped to transform the way in which doctors, patients, and society approach all types of cancer and neurological conditions such as autism.

Double Helix Medal Winners H. Varmus, K. Abdul-Jabbar, and T. Grandin

Infrastructure Projects

The Laboratory received a National Science Foundation Infrastructure Improvement Grant for greenhouse renovations at Uplands Farm. Growth facilities were renovated and improved, and all

Hooper House

three greenhouses received lighting, ventilation, and control system upgrades necessary to accommodate the evolving plant research program.

The circa 1830 Hooper House received a facelift in 2011. The entire exterior structure was renovated, with new cedar siding, windows, doors, and trim work. The existing wood and aluminum windows were replaced with modern equivalents that recall the 1830 originals. The renovation offered the Laboratory the opportunity to restore gable details and a central front porch that had been lost during earlier renovations.

Originally built as a single-family residence in the late 1960s, Osterhout was renovated to serve as the new home of the Laboratory's Public Affairs Department. The structure was gutted, reinforced, and modernized for current office needs, but its original exterior character was retained.

The Olney Barn, built in the late 19th century as a companion to the nearby Olney House, was in drastic need of renovation, but a survey of the structure and the site showed that it was impractical to renovate the existing structure. To provide a suitable workspace for the Laboratory's groundskeepers, we constructed a new barn at a more suitable location.

Concerned both with the health of its employees and with rising healthcare expenses, the Laboratory contracted North Shore–LIJ Health System (NSLIJ) to operate an on-site wellness center. The center was constructed in the space formerly occupied by two sleeping rooms in Dolan Hall. An NSLIJ Nurse Practitioner provides confidential health counseling and wellness services to CSHL employees and graduate students.

Osterhout Cottage

Olney Barn

Opening of the Center for Health and Wellness

Hershey Building

Great progress was made during the year on construction of the new, nearly 16,000-square-foot Alfred D. Hershey Building. Construction began in 2010 and is expected to be complete by the spring of 2012, just in time for summer courses. Funded by the HHMI, the building will also be home to the Laboratory's microscopy facilities, the Flow Cytometry shared resource, one course laboratory, and two spacious seminar rooms.

Our Hillside Laboratories, opened in 2009, continue to be recognized for their innovative architecture. In 2011, the project (designed by Centerbrook Architects) was recognized by the American Institute of Architects Connecticut Design Award and was a finalist in the *World Architecture News* Colour in Architecture competition.

Information Technology

CSHL is committed to staying ahead of the information technology curve and accordingly has made considerable investments during the last several years. Our plan has been to provide for strong IT disaster recovery/business continuity preparedness; a unified, redundant high-speed data network; and highly available, large-scale storage for scientific data.

In 2011, we successfully commissioned our Business Continuity/Disaster Recovery environment, which maximizes availability of core IT resources through mirroring of data and services and providing instant, nondisruptive restoration of mission-critical resources. The CSHL campus high-speed fiber-optic data network was upgraded to provide access to high-bandwidth applications at additional CSHL facility locations, including the Banbury Conference Center, Uplands Farm, and the Knight House.

The entire campus now also enjoys fully redundant, dual-path connection to our Internet service provider (ISP) and a 10-fold increase in bandwidth product, from 100 Mbp to 1 Gbp. Our research is better protected as a result of an improved data backup system and the expansion of data storage systems for scientific computing (high-speed sequencing and data analysis). CSHL's IT department currently manages more than 3 PBs of research data!

Community Outreach

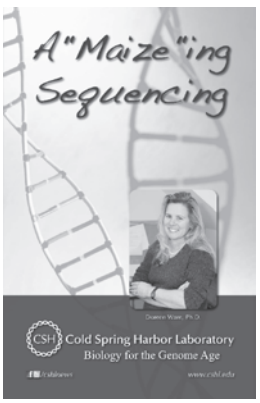
CSHL's guided Walking Tour Program was enjoyed by more than 600 visitors in 2011, who came from nearby communities as well as faraway lands including Singapore, Japan, Korea, Brazil, and Germany. We thank our team of a dozen graduate students and postdocs who are the docents.

Local families battled the inclement April weather to explore the history of Cold Spring Harbor Village's Main Street and DNA on April 16–17 as part of the Lab-sponsored DNA Day Scavenger

DNA Day Scavenger Hunt map

Hunt. Neighboring educational organizations such as the Cold Spring Harbor Public Library and Environmental Center, the Cold Spring Harbor Whaling Museum, the Firehouse Museum, and our own DNA Learning Center all took part.

DNA Day is celebrated across the country, with educational events sponsored by the National Human Genome Research Institute (NHGRI), a part of the National Institutes of Health.



Orlando Science Center poster announcing Doreen Ware's talk

In Orlando, Florida, visitors to the Orlando Science Center's DNA Day celebration engaged in Skype video conference sessions with CSHL faculty members Dick McCombie and Doreen Ware and Research Investigator Emily Hodges. Among the three scientists, they covered DNA-relevant topics ranging from genome sequencing and plant biology to Neanderthal bones.

Seventy-five winners from the 2011 Brentwood District Science Fair celebrated DNA Day by genetically engineering bacteria that glow. Funded by the National Grid Foundation, the hands-on scientific experiences delivered by the DNALC are just one example of the ways in which the DNALC partners with school districts to enhance biology curricula.

At the fourth annual World Science Festival in Manhattan, the DNALC showcased the Urban Barcode Project as part of the festival's lively Street Fair event. The city-wide barcode project competition, funded by a grant from the Alfred P. Sloan Foundation, has attracted 103 high school teams and will culminate in June 2012 with the award of scholarship prizes to students on winning teams.

NYC URBAN BARCODE PROJECT

CSHL continued its partnership with the Long Island 2-Day Walk to Fight Breast Cancer, judging the annual scholarship essay contest and cheering on walkers during the event. Our faculty, staff, and students participated in many other fundraising events that benefit our research; they are organized by disease-based organizations in our local community including Swim Across America, the Don Monti Memorial Research Foundation, the Joni Gladowsky Breast Cancer Research Foundation, and the Manhasset Women's Coalition.

The year 2011 became the year that CSHL broke into the social-media world, launching an institutional Facebook page, blogging on our own LabDish page, and amassing a significant Twitter following. Our monthly electronic *NetLetter* won national acclaim from PR News for its highly interactive and visually appealing platform, which delivers news and information about CSHL that is both useful and relevant to a diverse and growing audience.

Public Lectures at Cold Spring Harbor Laboratory


P. Glimcher

April 4—Paul W. Glimcher, Ph.D., Julius Silver Professor of Neural Science, Economics, and Psychology and Director for the Center for Neuroeconomics, New York University: *Neuroeconomics and the Biological Basis of Decision-Making*.

June 22—Fritz Henn, M.D., Ph.D., CSHL Professor; **Husseini Manji, M.D.**, Global Head of Neuroscience at Johnson & Johnson Pharmaceutical Research & Development, LLC; *New Approaches to Treatment of Depression and Bipolar Disorder*, cosponsored by CSHL, Brain & Behavior Research Foundation, Bank of America-Merrill Lynch, and St. Johnland Nursing Center.

July 6—Partha Mitra, Ph.D., CSHL Professor: *Mapping the Mouse Brain*, hosted by the Secret Science Club, Brooklyn, New York.

August 24—Rob Martienssen, Ph.D., CSHL Professor and HHMI Investigator: *Send in the Clones: Superseeds, Superweeds, and Green Energy*, hosted by the Secret Science Club, Brooklyn, New York.

October 23—Anne Churchland, Ph.D., CSHL Assistant Professor; **Concetta M. Tomaino, D.A., M.T.-B.C., L.C.A.T.,** Executive Director/Cofounder, Institute for Music and Neurologic Function; Senior Vice President, Music Therapy Services, Beth Abraham Family of Health Services; **Irene Gubrud, D.F.A.**; Soprano, Voice, and Meditation Teacher; **Steven Finch, M.M.**; Conductor, Choral Clinician: *Music: How It Can Rewire Your Brain*, cosponsored by CSHL and St. Johnland Nursing Center.

CSHL Public Concerts

April 15:	Two Plus One, trio
April 29:	Jennifer Johnson, soprano
May 6:	Hiroko Sasaki, pianist
May 20:	Xun Wang, pianist
August 19:	Margarita Shevchenko and Lev Polyakin, pianist and violinist
September 9:	Bella Hristova, violinist
September 23:	Natalia Lavrova, pianist
October 14:	Yoonie Han, pianist

Looking Forward

As we look ahead, I remain confident that CSHL is well-positioned to fulfill its research and education mission, continuing to lead the field of molecular biology and genetics to its next major achievements. My confidence is based on this institution's faculty, staff, and students, who make my job as President such a source of pride. I thank you, our Board of Trustees, and generous donors for your support.

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