Highlights of the Year

Research

Good scientists know how to judge the relative contributions of their colleagues, peers, and institutions, mostly via a subjective assessment of research. Indeed, it is part of the process of recruiting new faculty; early-career scientists are judged on their potential for an outstanding research career, and Cold Spring Harbor Laboratory (CSHL) is known as a place in which such young people excel. There are, however, some objective criteria, such as the number of times research papers are cited by colleagues, indicating on average a relatively high impact.

This year, Thompson Reuters, a science publisher well known for its Essential Science Indicators, again placed CSHL atop a list of 20 "heavy hitters" in molecular biology and genetics selected from a database comprising more than 42,000 research institutions worldwide. This particular measure of impact, covering the last 10 years, was based on the number of times, on average, papers written by a given institution's faculty were cited by their peers. Other institutions in the top 20 were Massachusetts Institute of Technology, Salk Institute for Biological Studies, Memorial Sloan-Kettering Cancer Center, The Rockefeller University, and Harvard University. Other rating organizations also place CSHL at the very top of research institutions worldwide, and CSHL has consistently been placed as number one in these ratings for the past three decades. These ratings are not the only measure of research impact, of course, and we do not use such information when assessing the progress and promotion of our individual scientists. But in general, the rating does reflect the view I have long held of our institution, based on intimate first-hand knowledge. An exciting research agenda is part of what makes CSHL a great place to work. In 2009, our scientists were as productive as ever, a fact reflected in the highlights of some of the research that appear below.


ScienceWATCH.com
TRACKING TRENDS & PERFORMANCE IN BASIC RESEARCH
Interviews | Analyses | Data & Rankings
Sci-Bytes : 2008 : 05.25.2008 : Institution Rankings in Molecular Biology & Genetics 1997-2007
SCI-BYTES - WHAT'S NEW IN RESEARCH : 2008
Week of May 25, 2008
Institution Rankings In Molecular Biology & Genetics 1997 - 2007
Based on citations per paper among institutions with 50,000 or more citations. Data from Thomson Reuters's Essential Science Indicators SM, January 1997 to December 2007

Rank	Institution	Citations per paper
1	Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, USA	91.06
2	Salk Institute for Biological Studies, La Jolla, CA, USA	76.48
3	MIT, Cambridge, MA, USA	74.15
4	Memorial Sloan-Kettering Cancer Center, New York, NY, USA	67.92
5	European Molecular Biology Lab, Heidelberg, Germany	63.93
6	Cancer Research UK, various locations, United Kingdom	60.56
7	University of Texas Southwestern Medical Center, Dallas, TX, USA	58.80
8	Rockefeller University, New York, NY, USA	58.19
9	Massachusetts General Hospital, Boston, MA, USA	58.02
10	Harvard University, Cambridge, MA, USA	53.88

Essential Science Indicators lists institutions ranked in the top 1% for a field over a given period, based on total citations. For the current version, 373 institutions are listed in the field of molecular biology and genetics, meaning that a total of 37,300 institutions were reviewed to obtain these results. Of the 373, 56 institutions collected 50,000 or more citations. Cancer Research UK supports research at many institutions throughout the United Kingdom, and is similar in its organization to the Howard Hughes Medical Institute in the United States.

Visit Essential Science Indicators from Thomson Reuters.
This item also appeared in the Times Higher Education magazine, reprinted with their permission.

CSHL ranked number one for worldwide impact in molecular biology and genetics

Mouse Models of Leukemia That Predict Human Response to Chemotherapy

This past year, Scott Lowe and colleagues developed new mouse models for human acute myeloid leukemia (AML), a devastating cancer of white blood cells. Most patients with AML receive intense chemotherapy followed by additional chemotherapy cycles or bone marrow transplantation; only a quarter of patients are cured and most die within a few months. The range in treatment response is due to AML's genetic heterogeneity, meaning that the 100 or so mutations associated with this form of cancer occur in different combinations in each patient and influence therapeutic outcomes in different ways. Scott's group identified the most commonly occurring mutations in a sample of 111 children with AML and then engineered these mutations into mice, which soon developed leukemia. Of the two most common mutations they observed, one, in an oncogene called *AML1/ETO*, previously had been associated with a favorable therapeutic outcome in people; the other, in an oncogene called *MLL,* was associated with an adverse outcome. To design an animal model that predicts these outcomes, the team introduced each mutation individually into stem and progenitor cells along with another oncogene, called Nras, which also appears frequently in human AML and is commonly found in concert with *AML1/ETO* and *MLL* oncogenes. These altered stem cells were transplanted into mice pretreated with radiation to destroy existing bone marrow cells. The altered stem cells then took over the "host" bone marrow and promoted the development of leukemia, which, within weeks, showed the same genetic and pathological features as human AML. Just as in humans, leukemias in mice that received the *AML1/ETO* oncogene were also sensitive to chemotherapy and soon regressed, whereas *MLL*-triggered


S. Lowe

leukemias remained resistant and eventually killed their hosts. These findings suggest that such models can predict how human cancers will respond to therapy and help to identify genes promoting resistance or sensitivity to any cancer drug. The mouse models also serve as an effective test system for new drugs and treatment strategies. Indeed, CSHL Fellow Chris Vakoc, in collaboration with Scott's laboratory, is now searching for new therapeutic targets for the *MLL* form of leukemia.

A Protein That Blocks Progression of Malignant p53-deficient Tumors

More than half of all human cancers have mutations that disable a protein called p53. The product of a master tumor-suppressor gene by the same name, p53 is central in several cancer-fighting operations within cells. When cells lose p53, tumors grow aggressively and often cannot be treated. But this past year Alea Mills and colleagues demonstrated that there is a chink in the armor of p53-deficient tumors—a protein called TAp63, the product of a gene called *p63*, which Alea discovered as a postdoctoral student a decade ago. The *p63* gene is usually intact and not mutated in most cancers. Mills and her team succeeded in shutting off growth in tumors in which p53 is missing by turning up the production of TAp63 proteins; it completely blocked tumor initiation by inducing senescence, a state of growth arrest in which tumor cells are still metabolically alive but fail to divide. More importantly, turning up the levels of TAp63 in p53-deficient cells blocked the progression of established tumors in mice. As Alea suggests, this means that we now have a model of how to attack refractory human cancers that have damaged p53.

A. Mills

A Drug Candidate for Treating Spinal Muscular Atrophy

Spinal muscular atrophy, or SMA, is a devastating illness, and although quite rare, it is nevertheless the leading genetic cause of death in infants. It is caused by mutations in a gene called Survival of Motor Neuron 1 (*SMN1*), which cause levels of SMN protein in the motor nerve cells of the spinal cord to diminish. These nerve cells, or neurons, are the cells that control muscle activity, and without the protein, they degenerate. Infants born with *SNM1* mutations progressively lose the ability to move, swallow, and breathe. There are no approved therapies for SMA. This year, we were excited to learn that Adrian Krainer's lab, in collaboration with colleagues at Paratek Pharmaceuticals and Rosalind Franklin University of Medicine and Science, has identified a tetracycline-like compound that stimulates SMN production by altering RNA splicing. Called PTK-SMA1, it is the only small molecule known to specifically alter RNA splicing by directly and solely targeting the splicing reaction. The team confirmed that the effect of PTK-SMA1 on RNA splicing and exon inclusion ultimately results in increased levels of full-length and functional SMN protein. The compound boosted protein levels in cells isolated from SMA patients and cultured in lab dishes. The team also proved its ability to work in vivo by injecting it into mice carrying a human *SMN2* gene. The mice showed a more than fivefold increase in human SMN protein levels within a week of treatment. Adrian and colleagues will next tackle the questions of how PTK-SMA1 redirects RNA splicing and will seek a way of getting it across the blood-brain barrier and into affected neurons in the spinal cord. His laboratory is also working on other therapeutic strategies for SMA that look very promising

A. Krainer

Small RNAs That Protect the Germline

CSHL is at the forefront of research on small RNAs. Two fascinating studies published by our faculty this past year reveal the vital role played by these tiny bits of nucleic acid in the defense of the germline, in very different species. Rob Martienssen led a team that looked at sperm cells in plant pollen grains. In this setting, sperm are cocooned within larger "companion" cells, called pollen vegetative cells. It has long been known that the companion cells provide sperm with energy and help move them to their targets during fertilization. Rob's team determined that they also provide sperm with instructions that protect their DNA from damage and thus help pass on a stable genome

R. Martienssen

to the next generation. The instructions offered to sperm specifically come in the form of small RNA molecules that companion cells pass on to sperm. These small RNAs can inactivate, or "silence," specific DNA sequences. In this way, they help set up gene expression patterns in sperm, providing the next generation with instructions that specify which regions of the genome should be turned on and which should be switched off and protect the sperm from expressing genes that might be detrimental when the pollen fertilizes cells for the next generation.

A separate study by Greg Hannon and colleagues examined how the germline in fruit flies is protected from genetic parasites called transposons. These bits of DNA sequence have infiltrated host genomes over the eons and can cause damage by copying and inserting themselves in random fashion across genomes, disrupting genes and regulatory sequences. To protect themselves from transposons, animal germline cells have developed a molecular immune system, operated by an army of small RNA molecules called Piwi-interacting RNAs (piRNAs) and a set of proteins belonging to the Piwi family. Greg's team discovered that in the ovaries of fruit flies, nongermline, or "somatic cells," that surround germline cells have also developed an antitransposon defense system. Over the years, fruit fly researchers have uncovered genomic mutations that lead to sterility and abnormal development. Because these defects could have been caused by unchecked transposon activity, mutant flies are a good experimental resource to uncover exactly how piRNA pathways work and how they might get disrupted. Hannon's team analyzed eight such mutants, showing how the genes disrupted in each mutant impact the piRNA pathway and how it alters the type and number of piRNAs that cells are able to generate. These studies help us understand the broad picture of how the piRNA pathway has been genetically stitched together to perform its vital role in protecting the germline and genetic information that will be passed from parents to the next generation.

G. Hannon

Mobile Small RNAs That Set Up Leaf Patterning in Plants

Anyone who has taken the time to carefully inspect a plant leaf knows that the top and bottom surfaces are not quite the same. In fact, this difference is the product of a developmental program that establishes an asymmetry crucial for the leaf's function: It ensures that the leaf develops a flattened blade optimized for energy production by photosynthesis, with a top surface specialized for light harvesting and a bottom surface containing tiny pores that serve as locales for gas exchange. Plant scientists have known that the top/bottom axis is established by a signal derived from the meristem, the stem cell-rich growing tip of the plant from which all new leaves arise. Other signals that traffic between the upper and lower sides of the leaf are thought to stably maintain this polar axis. In 2009, Marja Timmermans and her team were the first group to uncover the identity of one such positional signal—a family of mobile small RNAs generated on the upper surface of young leaves but which traffic to form a concentration gradient across each leaf. This graded distribution pattern of small RNA molecules creates discrete regions of gene activity so that cells in each half of a leaf develop a distinct "top" or "bottom" identity. Besides providing a remarkable example of a morphogen-like small RNA signal, Marja and her team have also shown that the location of the various biochemical ingredients required for small RNA activity can impact pattern formation. Together, their discoveries explain how mobile small RNAs can generate leaf patterns during development.

M. Timmermans

Identification of a Protein That Enhances Long-term Memory by Controlling Rest Periods

Students everywhere—those who study, at any rate—know from experience that studying improves memory, but only under certain conditions. Facts are preserved longer in memory if a student spaces out learning sessions between rest intervals. This past year, Yi Zhong and his team discovered how


Y. Zhong

this so-called "spacing effect" is controlled in the brain at the level of individual molecules. Yi has long been interested in genes that when mutated trigger learning and memory disorders such as Noonan's syndrome, a rare genetically inherited disease. More than half of Noonan's patients have mutations in a gene called *PTP11*, which encodes the SHP-2 phosphatase protein. In contrast to many disease-related mutations that shut off protein production or impair protein activity, these *PTP11* mutations do the opposite—they boost the activity levels of SHP-2 phosphatase. To understand how this change impedes long-term memory, Zhong's team engineered these mutations into a gene in fruit flies called *corkscrew* that is the functional equivalent of *PTP11* in humans. The team found that normally, as each learning period ends, SHP-2 phosphatase activity inside stimulated neurons triggers a wave of biochemical signals, which have to peak and decay before the next learning session can begin. They discovered that the repeated formation and decay of the biochemical signal during each rest interval induces long-term memory. In normal flies, these signal waves took 15 minutes to peak and decay. In the mutants that had excess protein activity, however, the signaling wave took 40 minutes to decay. This research shows it is crucial that the period of rest should last as long as it takes for a signal wave to form and reset. Yi's team succeeded in reversing memory deficits in mutant flies, by reducing the activity of mutated SHP-2 phosphatase to normal levels with drugs or simply altering training regimens to include 40-minute rest intervals instead of the normal 15 minutes. These results suggest a potential means with which to address memory impairments in an illness such as Noonan's syndrome.

Structure of the NMDA Subunit Reveals Target for Drugs Against Neurological Diseases

Hiro Furukawa and colleagues obtained crystal structures this year for one of several subunits of the NMDA (*N*-methyl-D-aspartate) receptor. This receptor type is one of a family that mediates excitatory transmission in nerve cells in the brain. One theory of causation in Alzheimer's, Parkinson's, and multiple sclerosis posits that excessive amounts of the excitatory neurotransmitter glutamate can cause an overstimulation of glutamate receptors, including the NMDA receptor. Such excitotoxicity, the theory holds, can cause nerve cell death and subsequent neurological dysfunction. The search is well under way for molecules that can shut down the NMDA receptor. To do so in a highly specific manner—one that would potentially carry lower risk of unwanted side effects—we need a precise map of the receptor and its active sites at the level of individual atoms. Hiro's team focused on a portion of the extracellular domain of the receptor, a subunit called NR2B. It includes a domain of particular interest called the ATD (the amino terminal domain), whose structural distinctiveness makes it a potentially attractive target for future drugs. Hence, the importance of the team's achievement: A crystal structure revealed by the powerful light source at nearby Brookhaven National Laboratory that shows the ATD to have a clamshell-like appearance that proves to be important for its function. Work can now proceed on rational design of a drug that can precisely bind the ATD within what Hiro and colleagues call its "clamshell cleft," based on the crystal structure they have obtained.


H. Furukawa

Roles of a Key Protein, Associated with Mental Retardation, on Both Sides of the Synapse

This past year, Linda Van Aelst and colleagues demonstrated the mechanism by which a signaling protein found throughout the brain controls the maturation and strength of excitatory synapses, the tiny gaps across which the majority of neurons communicate. The discovery is important, in part, because deficits of the signaling protein in question, called oligophrenin-1 (OPHN1), have previously

L. Van Aelst

been associated with X-linked mental retardation. Indeed, problems at the synapse—in their formation and in the mechanisms through which the strength, or plasticity, of their connections are regulated—are thought to contribute to numerous mental and neurological disorders. Linda points out that at least 280 genes have already been implicated in metal retardation. But what we have not done, to date, is connect the genetic abnormalities to biological processes that establish and modify the function of neuronal circuits. Previously, Linda had shown that dendritic spines—knoblike structures that protrude from a neuron's branch-like dendrites and receive signals across synapses from the axons of other neurons—are short and misshapen when expression of the *OPHN1* gene is acutely reduced. Her team's new experiments showed that the OPHN protein is not essential for the formation of dendritic spines, but it is needed for the proper maintenance of their structure. Importantly, in this maintenance function, the OPHN1 protein was found to have a key role both in the maturation of excitatory synapses and in their plasticity, or ability to vary in strength. In related experiments, focusing on the presynaptic side of the gap between nerve cells, they found that OPHN1 also helps neurons to transmit messages, by controlling the recycling of synaptic vesicles in presynaptic terminals. This suggests that symptoms of X-linked mental retardation could stem not only from having both immature and deformed dendritic spines, but also from inefficient neuronal vesicle retrieval and recycling.

A Reference Genome for Maize

In late 2009, a 4-year, multi-institutional effort co-led by three CSHL scientists culminated in publication of a landmark series of papers in the journal *Science* revealing in unprecedented detail the DNA sequence of the maize plant. Maize, or corn, as it is commonly called in North America, is one of the world's most important plants and the most valuable agricultural crop grown in the United States, representing $47 billion in annual value. The sequence spans 2.3 billion DNA base-pairs and contains ~32,500 genes, or about one-third more than the human genome. This version of the maize genome—taken from a variant called B73—is regarded by the scientific and agricultural communities as a reference version. Doreen Ware, one of the CSHL coprincipal investigators, contributed important annotation and evolutionary analysis. In a parallel effort, Doreen's CSHL team also helped generate a draft haplotype map of maize, in collaboration with the USDA. As in humans, the maize HapMap gauges genomic diversity by comparing distinct individuals—in this case, 27 maize lines—with the reference version. Dick McCombie and Rob Martienssen were the other CSHL coprincipal investigators on this important project. Having the sequence and a HapMap of this critical plant will enable scientists to find genes associated with quantitative traits—genes that affect traits of importance to agriculture, everything from the size of the seeds to when the plant flowers to whether it can tolerate drought or dampness. This may help plant scientists develop maize varieties that will thrive as the planet warms in the period ahead.

D. Ware

R. McCombie

Likely Origin of Facial Cancer Decimating the Tasmanian Devil Population

An international team led by Greg Hannon and his former student, Elizabeth Murchison, of CSHL and the Australian National University, succeeded in identifying the likely point of origin for the deadly facial tumors decimating Australia's Tasmanian devil population: Schwann cells, cells of the nervous system which form a tissue type that cushions and protects nerve fibers. The discovery stems from the team's effort to carry out a genetic analysis of tumor cells in devil tumor facial disease. DFTD is a unique type of cancer transmitted from animal to animal via biting or other physical contact. Tumors in the canine-sized devils are mostly found on the face and mouth, but they often spread to internal organs. With no diagnostic tests, treatments, or vaccines currently available, the aggressive disease could wipe out the Tasmanian devil species, which is found only on that island-state of Australia, in 25 to 35 years. The largest surviving marsupial carnivores, the devils have become a cause célèbre for conservationists worldwide. Greg and his team determined the identity of the originating cell by using advanced sequencing technology to uncover the tumors' transcriptome—the complete set of genes that are turned on in tumor cells. Comparing this readout to that from other tissues, they found that the tumors' genetic signature best matched that of Schwann cells. Armed with the tumors' genetic profile, researchers now can start hunting for genes and pathways involved in tumor formation. A catalog of devil genes compiled by the Hannon–Murchison team should be useful in designing vaccines and other therapeutic strategies.

Cold Spring Harbor Laboratory Board of Trustees

The Board of Trustees elected three new members this year: Michael R. Botchan, Ph.D., Goldman Professor and Chair of the Department of Molecular and Cell Biology, University of California, Berkeley, and a former faculty member at CSHL; Thomas Quick, President of First Palm Beach Properties, Inc., who begins a second period as Trustee; and Samuel L. Stanley, Jr., M.D., the fifth president of Stony Brook University.

In addition, the Board named Nancy Marks as an Honorary Trustee. Nancy served on the board as a Trustee from 2004 to 2009 and participated in the Development Committee (2004–2006), the Capital Campaign Committee (2006–2008), and the Building Committee (2000–2009).

Congratulations to CSHL Scientific Trustee Charles L. Sawyers, M.D., chair of the Human Oncology and Pathogenesis Program at Memorial Sloan-Kettering Cancer Center, who in September received the 2009 Lasker-DeBakey Clinical Medical Research Award for groundbreaking work on the treatment of chronic myeloid leukemia.

CSHL mourned the passing of Honorary Trustee John P. Cleary, Honorary Trustee, early in the year. John and his wife Rita made significant philanthropic contributions toward the research and education mission of the Laboratory, recently supporting the expansion of CSHL's research infrastructure and the creation of the Broad Hollow Bioscience Park to promote biotechnology research on Long Island.

The CSHL community also grieved for Trustee Donald Everett Axinn who died in November 2009. The Donald Everett Axinn Laboratory opened this year as part of the largest construction project ever undertaken by CSHL. The successful completion of this building project was in large part due to Don's support and guidance.

I thank the CSHL Board of Trustees for its leadership and generosity in the successful completion of the Capital Campaign, which began in 2005 with a goal to raise $200 million to realize a 40% expansion of the Laboratory's research capacity. With significant contributions from our Trustees, we surpassed the original goal and raised $340 million over the period of the Capital Campaign. In June 2009, we celebrated the dedication of the six new buildings that make up the new Hillside Laboratories.

The Cold Spring Harbor Laboratory Association, under the leadership of president Tim Broadbent, had a successful year, raising $4.8 million of critical unrestricted funds to support early-career scientists at CSHL. Events that contributed to this achievement included the Double Helix Medals

Dinner, which alone raised more than $3 million; the President's Council, which raised over $375,000; and the Women's Partnership for Science luncheon, which raised close to $50,000. The balance was contributed by CSHL Association members.

On behalf of CSHL, our Board of Trustees, and our Development Department, I thank all those who helped us achieve our goals. Private philanthropy is the engine of innovative research, and your contributions are pushing the boundaries of science forward. Please refer to the back of this Annual Report for a complete list of our generous supporters.

Research and Education Management

Our research and education management teams performed exceedingly well in the face of the challenges that the world financial crisis presented. CSHL's investigators and administrators worked closely to effectively manage existing programs under conditions where we had to cut our budget mid year. In an unprecedented team effort, CSHL secured more than $22 million in federal stimulus grants issued under the American Recovery and Reinvestment Act (ARRA). These 2-year funds will support research in cancer, neuroscience, epigenetics, and plant biology, as well as research training and laboratory enhancements.

In applying for research grants, applicants were encouraged to develop innovative and bold ideas in relatively short grant proposals. CSHL scientists had a 30% success rate in securing ARRA grants, much higher than the national average. I suspect that this is because much of our innovative science is supported by philanthropy or by internal endowment funds, and our scientists are used to proposing bold ideas. If such proposals were submitted in normal individual research grant proposals (the so-called RO1 mechanism), such ideas would invariably be shot down and not funded. Perhaps this is a lesson of how the National Institutes of Health (NIH) should consider funding some science in the future.

True to CSHL's legacy as a breeding ground for the latest technologies and approaches to solving biological questions, CSHL secured special 5-year grants for "transformative" research projects. Our researchers Josh Dubnau, Ph.D., and Partha Mitra, Ph.D., received these grants for neuroscience projects that the NIH deemed "exceptionally innovative, high-risk, original, and/or unconventional… [with] the potential to create new or challenge existing scientific paradigms."

We were also encouraged by a pledge of continued support to stem cell research from New York Governor David A. Paterson, who visited CSHL in October with State Health Commissioner Richard F. Daines, M.D., in order to be briefed on stem cell research projects by CSHL investigators Drs. Linda Van Aelst, Grigori Enikolopov, Marja Timmermans, and CSHL Clinical Fellow Dr. Johannes Zuber.

The CSHL Scientific Advisory Council (SAC) met for the first time this year in March, lending third-party scientific expertise to help CSHL continue to maintain its global leadership position in

Govenor Patterson visits with stem cell researchers

Scientific Advisory Committee members and CSHL leadership. (*Left to right*) David Spector, Tony Pawson, Cornelia Bargmann, David Botstein, Carol Greider, Markus Meister, Joanne Chory, Bruce Stillman, Max Wicha, Frederick Alt, Leonid Kruglyak, and Sydney Gary

research and education. To provide the SAC with requisite background, the CSHL leadership devoted a number of sessions to a broad overview of the research, environment, and philosophy of CSHL. Several other sessions were devoted to discussions of specific questions and topics that CSHL senior administration had provided in advance of the meeting. In addition, SAC members met with both postdoctoral fellows and graduate students and held a session open to all CSHL faculty. The meeting ended with the SAC members providing helpful recommendations and feedback on specific issues related to research at CSHL. I thank the SAC Chair Fred Alt and all the members of the committee who provided very valuable advice.

CSHL Education Programs

CSHL's Watson School of Biological Sciences (WSBS) marked its first decade on April 26, graduating five new Ph.D.s: Allison Blum, Daniel Chitwood, Shu-Ling Chiu, Keisha John, and Jeremy Wilusz. SarahJane Locke received the Master of Science degree. This year brings the total number of WSBS graduates thriving in the outside world to 35. I am particularly pleased that even in its short history, six graduates of the school already have faculty positions at major universities or research institutes, supporting our thesis that the path to scientific independence need not be long.

WSBS honorary degree recipient Winship Herr, Ph.D., commemorates the 10-year anniversary of the establishment of the Watson School

The 2009 Commencement Convocation ceremony also conferred honorary degrees upon individuals who have made remarkable contributions to CSHL's wide-ranging and innovative education programs, including the Dolan DNA Learning Center, the Undergraduate Research Program, the CSHL Press and our advanced courses, and the Watson School of Biological Sciences: David Micklos, Alfred Goldberg, Jeffrey Miller, and Winship Herr, each of whom has made remarkable contributions to educational programs at CSHL.

CSHL's advanced scientific course offerings expanded into new facilities that were supported by the Howard Hughes Medical Institute. This new laboratory enables our advanced courses to expand teaching on brain anatomy and neural networks, cognition and behavior.

The 74th CSHL Symposium, "Evolution: The Molecular Landscape," celebrated Charles Darwin's 200th birthday and the 150th anniversary of his revolutionary work, *On the Origin of Species*. Approximately 400 scientists gathered at this 6-day-long conference to discuss a wide range of evolution-

74th CSHL Symposium

Suzhou Dushu Lake Conference Center auditorium

A courtyard within the Dushu Lake campus

themed topics, ranging from the origins of life on a molecular scale to the emergence of species both simple and complex over the last three billion years.

The reputation of CSHL's Meetings and Courses Program continues to grow, as evidenced not only by attendance, which reached a record of 6500 this year, but also by external, independent ratings. The September 2009 edition of the magazine *Genome Technology* ranked CSHL's "Biology of Genomes" meeting as "the most recommended" among general genomics meetings. Another CSHL meeting called "Genome Informatics" was the "most recommended" in the Bioinformatics/ Information Technology category.

Cold Spring Harbor Laboratory Conferences Asia convened its first meeting in Suzhou, China in November. This invitation-only Banbury-style meeting was held in temporary facilities while our purpose-built conference center was being completed. The meeting focused on transgenic crops and served as a prelude to the opening of a complete program of large-scale meetings on a wide range of topics in the biological sciences in 2010. The $70-million 600,000-square-foot conference center can accommodate up to 500 participants.

The Dolan DNA Learning continues to blaze new trails in web-based educational experiences. This year, DNALC's BioMedia Group launched "Genes to Cognition Online" (www.g2conline.org), which is distinguished by both its content and its presentation on the web. The site uses a unique approach to depict the complex and interlocking relationships between different aspects of brain anatomy and function. Just as the brain itself is composed of interconnected networks of cells, the site graphically represents information about these components as members of a vast network, whose nodes are interconnected.

DNALC three-dimensional brain iPhone app

The BioMedia Group also produced an exciting *iPhone* application that can be download for quick and easy access to a three-dimensional model of the brain and its functions. Rapidly, this application became one of the top educational tools downloaded to *iPhones.*

The CSHL Press published *Cold Spring Harbor Perspectives in Biology*, a new online publication spanning the complete spectrum of the molecular life sciences. Each issue includes reviews covering a wide variety of topics in molecular, cell, and developmental biology, genetics, neuroscience, immunology, cancer biology, and molecular pathology. Contributions are written by leading researchers in each field and commissioned by a board of eminent academic editors.

Awards and Honors

Many of CSHL's younger researchers received prestigious awards this year, recognizing their early-career accomplishments. Adam Kepecs was made a Klingenstein Fellow in Neurosciences and was also named an Alfred P. Sloan Research Fellow. Adam's laboratory is combining its behavioral expertise with molecular and optical techniques to monitor and manipulate genetically identified circuit elements in behaving mice. Bo Li received a Dana Foundation Award to investigate how hyperactive brain synapses may be key to understanding depression and formulating a treatment.

A. Kepecs

B. Li

Z. Lippman

P. Osten

Zach Lippman won a Human Frontier Science Program Career Development Award to continue his work in understanding the molecular dynamics that underlie altered developmental fates of certain plant meristems. Pavel Osten received the McKnight Technological Innovations in Neuroscience Award for his use of novel imaging technology to map changes in neural circuits in mice that carry genetic mutations linked to autism and schizophrenia. Grisha Enikopolov was the recipient of the Ellison Foundation Senior Scholar Award.

Lin He, a former CSHL postdoctoral fellow was named a MacArthur Fellow by the John D. and Catherine T. MacArthur Foundation. She was honored for advancing our understanding of the role of microRNAs in the development of cancer and laying the groundwork for future cancer treatments.

Former CSHL Fellow and Faculty member Carol Greider, along with her colleagues Elizabeth Blackburn and Jack Szostak, won the 2009 Nobel Prize for Physiology or Medicine for discovering how chromosomes are protected during cell division by telomeres and the enzyme telomerase. During her fellowship from 1988 to 1990, Dr. Greider identified the RNA component of the enzyme telomerase that adds DNA to the ends of chromosomes. She continued her research career as a member of the CSHL faculty from 1990 to 1997 and is currently Daniel Nathans Professor and Director of Molecular Biology and Genetics at the Institute for Basic Biomedical Sciences at Johns Hopkins School of Medicine.

C. Greider, winner of the 2009 Nobel Prize for Physiology or Medicine

Development

For the eighth consecutive year, CSHL earned a four-star rating for sound financial practices from the philanthropic evaluator Charity Navigator. Only 1% of the approximately 5000 nonprofit organizations analyzed by Charity Navigator have achieved this milestone.

Building Projects

Congratulations to the entire team of CSHL Facilities Department staff and the many Long Island craftsmen and women who were part of the Hillside Laboratories complex project. The construction of the largest building project in CSHL history was completed this year—on schedule and within

CSHL received Charity Navigator's highest rank for the eighth consecutive year

budget. Commissioning of the Hillside Laboratory buildings was accomplished, with the new Simons Center for Quantitative Biology and the relocated operations of the CSHL Cancer Center occupying finished space. The Hillside Laboratories complex also contains an additional animal facility that was brought on line in 2009. The CSHL Information Technology Department and an updated and expanded datacenter were relocated to the Hillside complex. This is the new home of the High Performance Computing Center (HPCC)—CSHL's very own supercomputer.

For 120 years, CSHL has been a proud steward of the Long Island shoreline and local ecosystem. The design and construction of the Hillside Laboratories demonstrates our continued commitment to the environment. The new facilities were designed to be 30% more efficient than standards set by the American Society of Heating, Refrigeration, and Air-Conditioning Engineers (ASHRAE). With help from the Long Island Power Authority (LIPA), CSHL successfully reduced the environmental footprint of the new facilities and reduced energy costs associated with facility operations. The total cost of electrical energy efficient measures incorporated into the project was $1,057,022, which was offset by a $224,940 Commercial Construction rebate from LIPA.

The Hillside Laboratory complex also breaks ground architecturally. The project won the Platinum Award from the American Council of Engineering Companies of New York for Excellence in Engineering for outstanding design. The awards ceremonies were held in March 2010 at the Waldorf Astoria Hotel in New York City.

Hillside Laboratories

Campus view from Cold Spring Harbor Village

In addition to the new construction on the upper campus, we completed scheduled improvements to the ca. 1927 Delbruck Laboratory building's historic teaching lab space. The project, which was made possible by funds from the Howard Hughes Medical Institute, included reconstruction of the top floor and roof of the building and the renovation and expansion of an existing conference room.

Across the harbor at the Banbury Conference Center in Lloyd Harbor, we also completed the interior renovations to the ca. 1937 Robertson House, which provides lodging for visiting scientists who attend Banbury meetings and participate in CSHL's advanced courses on the latest scientific technologies and techniques. Installation of modern HVAC, electrical, and data systems now make the manor house comfortable for guests throughout the entire year.

The reconstruction and addition to the Carnegie Building, which is home to the CSHL Library and Archives and The Genentech Center for the History of Molecular Biology, was largely complete by the end of the year. We look forward to the official reopening of the building in the spring of 2010.

At the Genome Center in nearby Woodbury we constructed a new, state-of-the-art greenhouse to allow for an expansion of our plant biology program that is being led by a new faculty member, Zachary Lippman, Ph.D., who studies varieties of tomato plants to understand the mechanisms that control flower, fruit, and seed production.

To increase operational efficiency across the expanding Laboratory, we are leasing a facility in Syosset that allows us to centralize receiving, storage, and fulfillment operations. This facility also provides needed office and administrative space.

Special Events

- **Gavin Borden Visiting Fellows.** The 15th Annual Gavin Borden Visiting Fellow Lecture, in memory of the publisher of *Molecular Biology of the Cell*, was held on March 24. The lecture was presented by Ralph J. Greenspan, Senior Fellow in Experimental Neurobiology, Lewis B. and Dorothy Cullman Senior Fellow, The Neurosciences Institute, San Diego, California.
- **Symposium.** During the 74th Symposium, "Evolution: The Molecular Landscape," the traditional Dorcas Cummings Memorial Lecture for scientists and guests from the community was delivered by Kevin Padian, Professor of Evolutionary Biology and Paleontology, University of California, Berkeley. The title of the lecture was "Darwin, Dover, and Intelligent Design."
- **Women's Partnership for Science.** On June 14 at Peacock Point, at the Lattingtown home of Mr. and Mrs. Daniel P. Davison, nearly 140 women lunched and learned about the link between viruses and cancer, specifically human papillomavirus (HPV), a prime cause of cervical cancer. The speakers included the Dean of the Watson School of Biological Sciences and Howard Hughes

Greenhouse at the Woodbury Genome Center

Medical Institute Investigator, Leemor Joshua-Tor, Ph.D., and Felicia Callan, M.D., obstetrician/gynecologist at the Mount Sinai School of Medicine/North Shore Medical Group. Money raised at this event supports women who pursue careers in biomedical research at CSHL.

L. Joshua-Tor

- **Hillside Laboratories Opening.** On June 12, CSHL dedicated the Hillside Laboratories, with remarks from Chairman of the CSHL Board of Trustees Eduardo Mestre; Chancellor Emeritus Jim Watson, Ph.D.; Bill Grover, FAIA, founding partner of Centerbrook Architects and Planners; and myself. The keynote address, "Thoughts on the Future of Biological Sciences," was delivered by Philip A. Sharp, Ph.D., Nobel laureate, University Professor, Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology.
- **The President's Council.** CSHL Board Chairman Eduardo Mestre and his wife Dr. Gillian Shepherd hosted an April 16 reception to announce the theme of the members-only 2009 President's Council program: "Personal Genomes." Special guests at this Manhattan event were Linda Avey and Anne Wojcicki, co-founders of the genome sequencing company 23andMe. The annual fall President's Council retreat was held on October 16-17 and featured Peter Neufeld, co-founder and -director of The Innocence Project. Other speakers that weekend included: David Botstein, a geneticist and CSHL Scientific Trustee; Esther Dyson, whose own genome was among the first sequenced in the Personal Genome Project; Elaine Mardis, Co-Director of The Genome Center, Washington University School of Medicine; Dr. Philip Marshal of WebMD Health Services; and CSHL Assistant Professor Gurinder "Mickey" Atwal.
- **The Double Helix Medals Dinner.** The 4th Double Helix Medals Dinner was held at the Mandarin Oriental Hotel in Manhattan on November 10. Medals for Scientific Research were presented to Herbert W. Boyer, Ph.D. and Stanley N. Cohen, M.D., who co-discovered recombinant DNA. Life-long philanthropist and advocate for research Kathryn W. Davis, Ph.D., was honored for Humanitarianism. In recognition for his unprecedented support of biomedical research, Maurice "Hank" Greenberg was presented with the medal for Corporate Philanthropy. Violin virtuoso Joshua Bell performed with accompaniment by pianist Frederic Chiu. The event was cochaired by Mr. and Mrs. Eli Broad, Mr. and Mrs. Christopher Davis, Ms. Florence A. Davis, Mr. and Mrs. Edward E. Matthews, and Dr. Richard H. Scheller.

Double Helix Medal

President's Council members Thomas Lehrman, Kristina Perkin Davison, Judy Carmany, and George Carmany (*front row, left to right*) discuss personal genomes

Double Helix Medals Dinner at the Mandarin Hotel, Manhattan

- **The Lorraine Grace Lectureship on Societal Issues of Biomedical Research.** On November 29, science journalist Nicholas Wade, Ph.D., presented the first annual lecture, introducing his newly published book, *The Faith Instinct—How Religion Evolved and Why It Endures.*

CSHL Public Lectures

March 23—William C. Mobley, M.D., Ph.D.: *The Future of Down Syndrome: Improving Memory and Cognition*, sponsored by the National Down Syndrome Society and the Down Syndrome Connection of Long Island.

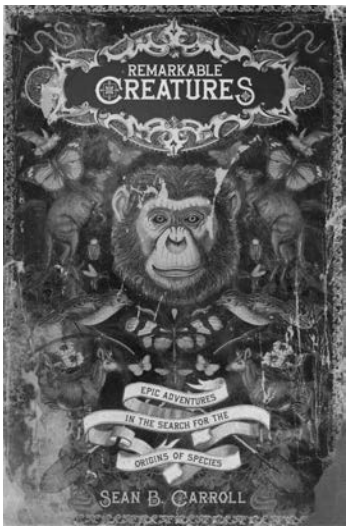
April 27—Josh Dubnau, Ph.D., CSHL Assistant Professor: *Memories of a Fly: What a Fly's Brain Can Teach Us About Our Own.*

May 26—Darwin Commemorative Lecture: Sean Carroll, Ph.D., Professor of Molecular Biology, Genetics and Medical Genetics, University of Wisconsin, Madison: *Remarkable Creatures: Epic Adventures in the Search for the Origin of Species.*

September 17—Rob Martienssen, Ph.D., CSHL Professor: *Designing Bioenergy Crops: Developmental Problems and Genetic Solutions.*

October 13—Scott Lowe, Ph.D., CSHL Professor and HHMI Investigator: *Cancer Research at Cold Spring Harbor Laboratory: Our Latest Successes and the Road Ahead.*

October 22—Senthil Muthuswamy, Ph.D., CSHL Assistant Professor: *Breast Cancer Research in 3-D: A New Way of Looking at How Tumors Develop.*



Sean Carroll, author of *Remarkable Creatures,* presented the Darwin Commemorative Lecture at CSHL

CSHL Public Concerts

April 17—Irina Muresanu and Dana Ciocarlie, violinist and pianist

May 1—Michelle Cann, pianist

May 15—Frederic Chiu, pianist

September 4—Margarita Shevchencko, pianist

September 11—Steven Beck, pianist

September 25—Ken Noda and Tamara Mumford, pianist and mezzo soprano

October 2—Inbal Segev, Dmitri Berlinsky, and Elena Baksht, cellist, violinist, and pianist

October 9—Daria Rabotkina, pianist

Laboratory Employees

New Staff

S. Shea

This year, we welcomed two new Assistant Professors: Stephen Shea and Mikala Egeblad. Stephen Shea received his Ph.D. from University of Chicago in 2004 and completed his postdoctoral fellowship at Duke University. Stephen studies the neural circuitry of social communication and decisions. His laboratory's efforts are directed at answering a number of related questions such as: What are the neural mechanisms for interpreting social information and selecting appropriate behaviors? How do we discriminate and remember familiar individuals? How do emotion and social context shape our attention and memories? And how are social cues from our various senses integrated to shape behavioral decisions? Stephen directly addresses these questions using natural social communication behavior in mice.

M. Egeblad

Mikala Egeblad joins us from University of California, San Francisco, where she was an Assistant Researcher. Mikala received her Ph.D. from the University of Copenhagen and the Danish Cancer Society in 2000. Her work addresses the challenge of separating functions and behaviors of the different stromal components of the tumor. In her lab, she uses mouse models of breast cancer and powerful real-time imaging of cells in tumors in live mice. This enables her to follow the behaviors of and the interactions between cancer and stromal cells in tumors during progression or treatment.

Promotions

A. Krasnitz

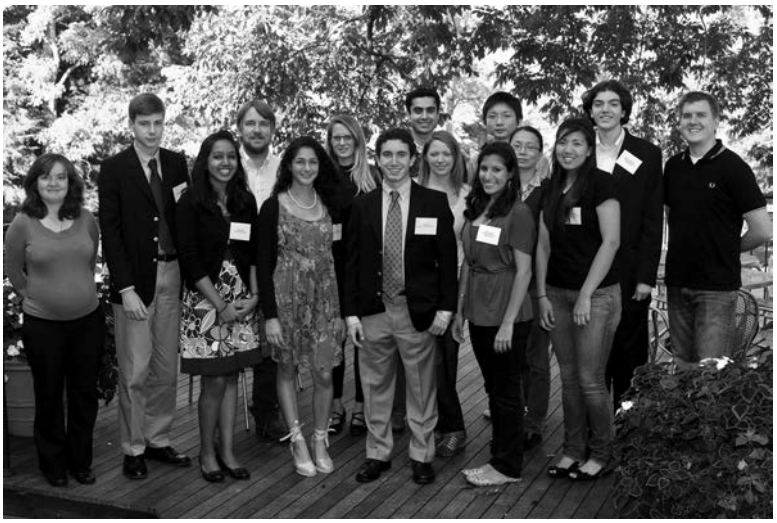
Congratulations to Marja Timmermans, Ph.D., who was promoted this year to full professor, and to Alexander Krasnitz, Ph.D., who was promoted to assistant professor.

Departures

In 2009, several faculty members left CSHL for appointments in other parts of the country. Jacek Skowronski is now a professor at Case Western Reserve University, School of Medicine. William Tansey is a professor at Vanderbilt University. Tim Tully is Chief Science Officer at Dart Neuroscience.

Community Outreach

In addition to the Cultural Series of concerts and lectures for the public that we organize each year in cooperation with local organizations, CSHL continues to be an active participant in the community here on Long Island. We are also becoming an increasingly visible part of science-related action in New York City.



2009–2020 Partners for the Future with CSHL faculty

Last year, our campus welcomed 30 community-based groups as part of a program that is staffed by a very energetic team of CSHL students and postdocs. Thanks to them, attendance in our regularly scheduled Saturday morning walking tours for the public had a waiting list! The Dolan DNA Learning Center's hands-on Saturday programs and summer camp sessions continue to sell out.

Seven Long Island high school seniors recommended by their school's science chairs were selected for this year's Partners for the Future program at CSHL. These promising young people worked hand-in-hand throughout the school year on real experiments with some of CSHL's top scientists: Drs. Tony Zador, Josh Huang, Michael Zhang, Alea Mills, Doreen Ware, and David Jackson. In close collaboration with the Cold Spring Harbor School District, CSHL participated in this community's first American Cancer Society "Relay for Life" event, with remarks from CSHL Director of Research David Spector and Dr. Michael Wigler. CSHL students, postdocs, and researchers volunteered at several science fairs judging the projects of middle and high school students across Long Island. CSHL students and postdocs also hosted local elementary school students, teachers, and parents for a field trip.

Spearheaded by Harlem DNA Lab instructor Ileana Rios, CSHL participated in the second annual World Science Festival (WSF) in Manhattan, serving as a laboratory workshop for high school kids participating in the festival's "Pioneers in Science" Program. Highlights of the event included a demonstration of banana DNA extraction at a street fair in Washington Square that drew a total crowd of 100,000 New Yorkers! Jim Watson was also involved in the WSF this year, as part of the gala and as a central figure in a performance by artist Anna Deavere Smith in "Watching Watson and Wilson," a one-woman show composed of vignettes that portray Jim and E.O. Wilson.

CSHL employees volunteer at local science fairs

Community Support

Each year, our employees demonstrate their commitment to the local community in so many ways. We held three blood drives on campus this year in February, August, and October. This effort set a record, collecting 20% more blood in 2009 than in 2008.

We continue to participate in the Secure the Call Foundation's effort to convert used cell phones to 911 emergency-use phones for those in

DNALC instructor Ileana Rios at the World Science Festival Street Fair in Manhattan

need. CSHL volunteers prepared and served dinner at the Ronald McDonald house to 40 families of seriously ill children. We also collected 300 pounds of food in support of the Long Island Cares Harry Chapin Food Bank.

Looking Forward

The financial and economic setbacks in 2008–2009 will most likely cause a major change in the long-term prospects for both philanthropic and federal support of science. We can be secure that our science continues to be world leading and hence will attract support, but increasingly in tight times, we must be aware that both members of Congress and taxpayers are increasingly looking at the outcomes of basic research. The economic impact of research is obvious, but changing how we interact with industry is going to be necessary if we are to achieve these goals. More fundamentally, we must increase the applied value of our research internally. Finding a mechanism of funding to do this will create a major challenge in the future.

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