Highlights of the Year

Research

Research at Cold Spring Harbor Laboratory (CSHL) has a major impact in the areas on which our principal investigators focus: cancer, neuroscience, plant biology, and quantitative biology. It has often been noted that our influence is especially remarkable for an institution of CSHL's comparatively small size. A recent survey by the respected science publisher Thompson Reuters in fact placed CSHL first in a group of 20 "heavy hitters" in molecular biology and genetics, selected from among 42,000 research institutions worldwide. During the first decade of the 21st century, research papers based on work conducted in CSHL laboratories had more impact—as measured by their frequency of citation by peers—than papers originating in any other institution, including the Massachusetts Institute of Technology, the Salk Institute for Biological Studies, Memorial Sloan-Kettering Cancer Center, The Rockefeller University, and Harvard University.

This survey is not the only measure of our worth or that of any institution, but it does suggest the power of the work being performed at CSHL and its relevance, as measured by those who use it—our colleagues at laboratories throughout the nation and across the globe. Together, we are engaged in a vital enterprise, in which we bring all of our intellectual skills and technical ingenuity to bear on fundamental questions of biology and generate knowledge that forms the basis for biomedicine to move forward in its mission to relieve the major causes of human suffering. Below, we summarize just a few of the many fascinating and important findings made by CSHL's dedicated team of investigators during 2010.

Antisense Therapy Reverses Spinal Muscular Atrophy in Mice

Professor Adrian Krainer achieved a milestone this past year in his continuing effort to understand spinal muscular atrophy (SMA), the leading genetic cause of death in infants. SMA is the result of mutations in the survival of motor neuron 1 (*SMN1*) gene. These lead to abnormally low levels of SMN protein in motor nerve cells of the spinal cord and to the degeneration of those cells. Last year, Adrian and colleagues identified a compound that stimulates SMN production by altering RNA splicing. This year, they carried the work an important step further: By introducing chemically modified pieces of RNA called antisense oligonucleotides (ASOs) into the spinal cords of mice, they succeeded in reversing symptoms of Type III SMA. This result exemplifies how superb basic science—in this case, work in the Krainer lab on the cell's splicing ma-



A. Krainer

chinery—can be fertile ground for value-added science, the kind of research activity that adds commercial value to fundamental discoveries. Krainer's team has collaborated with scientists at Isis Pharmaceuticals in designing and synthesizing ASOs, which can be designed to bind to any piece of RNA. The team zeroed in on an ASO that optimally enhanced the inclusion of an exon that in people with SMA is "skipped" by cellular machinery that cuts and pastes bits of RNA "message" together to form a template for protein manufacture. A particularly encouraging aspect of the team's progress this year was learning how to overcome barriers to delivering ASOs directly into the fluid that surrounds the brain and spinal cord. The treatment's therapeutic effect in mice persisted for half a year after it was discontinued, indicating that the ASO is very stable. In addition, the team reported no inflammation or toxicity.

Reversing Alzheimer's-like Memory Loss in Drosophila

Work published this year by Professor Yi Zhong's team demonstrated a means of reversing memory loss in fruit flies caused by brain plaques similar to those implicated in Alzheimer's disease. Modeling a complex human illness such as Alzheimer's is an important goal of basic science, and the fly provides us with a suitably simple starting point. The fly brain should not be underestimated, for in it we see significant conservation of DNA sequence found in human genes known to affect the structure and function of neural networks. Protein fragments of the β -amyloid molecule associated with Alzheimer's are known to alter many cell-signaling proteins such as phosphoinositol-3 kinase (PI3K), causing a wide range of neuronal dysfunctions. In flies engineered to produce the human β -amyloid protein in their brains, Yi's team set out to better comprehend the molecular basis of memory loss. This yielded a finding that went against received wisdom that attributed a protective role to the kinase. Yi's team instead found that the increased PI3K activity caused a type of neurotransmission that is pathologically enhanced when β amyloid is present in the fly brain. Injection of chemicals that block the kinase's action and separate efforts to turn off the gene that encodes it both had the effect of restoring normal signals in the fly brain. This research also intriguingly suggests that brains affected by Alzheimer's might become insulin resistant because of elevated PI3K activity.

Y. Zhong

A Possible Inflammatory Component in Resistance to a Targeted Lung Cancer Drug

Thus, the kinase becomes a potential target for novel therapeutics.

A critical question about cancer concerns the molecular mechanisms involved in resistance to chemotherapy. Particularly vexing is the phenomenon of resistance to the best drugs developed to date, so-called targeted therapies. Assistant Professor Raffaella Sordella's lab this year shed new light on resistance to Tarceva (erlotinib), a targeted therapy approved in 2004 for a subset of patients

with non-small-cell lung cancer (NSCLC) and for some patients with pancreatic cancer. Tarceva's molecular target is known—the cell membrane receptor called epidermal growth factor receptor (EGFR)—as are processes that lead to about half of observed cases of resistance. But what about the other 50%? Raffaella and colleagues from Weill Cornell Medical College and the Boltzmann Institute in Vienna discovered a subpopulation of NSCLC cells that are intrinsically resistant to Tarceva. These tumor cells were observed to secrete elevated amounts of a growth factor called transforming growth factor- β (TGF- β), which in turn increases secretion of interleukin-6 (IL-6), an immune signaling molecule. Significantly, these effects were independent of the EGFR pathway. The team therefore hypothesizes that inflammation is one of the factors that can render a tumor cell resistant to treatment with Tarceva.



R. Sordella

A Protein Linked to Leukemia "Bookmarks" Highly Active Genes in Dividing Cells

When CSHL Fellow Christopher Vakoc and colleagues demonstrated this year how so-called epigenetic instructions are stably transferred from one generation of cells to the next, they provided a

compelling explanation of how a protein called MLL (mixed lineage leukemia) may be involved in triggering leukemia. During cell division, gene activity is normally shut down temporarily. The dividing cell's chromosomes condense and expel most of the proteins that cling to them, which are called epigenetic marks. These marks at other times in the cell cycle help to determine which genes are accessible to the cellular machinery and can be expressed and which genes are inaccessible and cannot be expressed. Unlike most other chromosome-bound epigenetic marks, Chris' team found that the MLL protein stays tethered to the genetic material during cell division. It acts as a "bookmark," preserving a bit of vital gene expression information. But as the cell divides, sometimes the MLL proteins shift to new locations on the chromosome. Interestingly, they seem to attach to genes that are the most active before cell division shuts down all gene activity. This, in turn, can draw



other proteins to the same area, with the net effect of jump-starting gene expression. Chris is now studying how MLL mutations might promote the abnormal proliferation of cells in leukemia.

A Potential Way to Reverse Cancer Cell Metabolism and Tumor Growth

Eighty years ago, Nobel laureate Otto Warburg observed the altered metabolic state of cancer cells and tried to connect it, biochemically, with processes that give rise to the rapid proliferation that characterizes cancer. In particular, cancer cells are distinct in the way in which they metabolize glucose. They also produce large quantities of a by-product called lactate. A protein called PK-M2 is a key mediator of glucose metabolism in cancer cells, and this year, Professor Adrian Krainer led a group including researchers at Harvard Medical School and The Broad Institute that discovered three molecular factors contributing to high levels of PK-M2 in cancer cells. PK-M2 is one of two isoforms, or slightly varying versions, of an enzyme called pyruvate kinase. A single gene called *PK-M* gives rise to both, via alternative splicing. Adrian's expertise in splicing helped the team to understand how the benign isoform of the enzyme, PK-M1, is switched off and the dangerous M2 isoform is switched on in cancer cells. By manipulating three known splicing factors, the team was able to halt M2 production and separately to restore production of the benign M1 isoform. This sheds light on the so-called Warburg Effect and points to possible new targets for drugs that might reverse the pathological metabolism of cancer cells.

How Blood Stem Cells Are Maintained in the Bone Marrow Niche



G. Enikolopov

Hematopoietic stem cells (HSCs) have unique abilities that are prized by medical researchers. They can self-renew and develop, or differentiate, into any kind of blood cell, which enables them to replenish the body's entire blood and immune system. Researchers have understood that these qualities are traceable to a distinct locale or niche within the bone marrow that HSCs target, but the identity and function of the niche-forming constituents had not been clearly defined until this past year, when Associate Professor Grigori Enikolopov and colleagues from the medical schools at Harvard, Albert Einstein, and Mount Sinai published a report in the journal *Nature*. HSCs retain their unique features, they observed, in response to signals from another stem cell population, called mesenchymal stem cells (MSCs), that create a supportive bone marrow niche for the HSCs. It was the first demonstration that one type of stem cell could regulate another type of stem cell.

In a series of experiments, Grisha and the team discovered that genetic factors essential for HSC maintenance are highly concentrated within neighboring MSCs. They speculate that if we can control the niche, we can also manipulate the HSC population within it. This raises the prospect of developing a drug to target the niche in order to enhance stem cell production. This would be useful in regeneration therapies or could help to prevent the development of certain leukemias and other illnesses related to unregulated stem cell proliferation.

Next-Generation Sequencing Enables Team to Find Cause of Devastating Rare Illness



G. Hannon

Professor Gregory Hannon and his talented graduate student Yaniv Erlich—who in 2010 received his Watson School doctorate as well as a prestigious appointment as a Fellow at the Whitehead Institute—were part of an international team that discovered a genetic mutation that causes Joubert syndrome, a rare inherited neurological disease found most often among Ashkenazi Jews. Children whose parents both carry a copy of the mutated gene, and who inherit a copy from each, develop devastating pathologies including malformation of the brain, developmental delay, and muscular and visual impairment. The CSHL contribution to the discovery of the mutation's precise location involved a technological insight. Rather than sequence the entire genome of patients in search of the genetic culprit, which would be time-consuming and very costly, the team could use a

powerful genome fractionation method devised by Greg's team to sequence only those portions of the genome that encode proteins. This is called the exome, and it consists of less than 2% of the entire human genetic sequence. This was one of the very first instances in which next-generation sequencing was used to find the genetic cause of a rare disease and demonstrates that similar methods can be used to find the causes of other uncommon illnesses that otherwise might not get the attention that their sufferers so desperately need.

Identifying the (Few) Protein Differences between Neanderthals and Modern Humans

A closely related sequencing technology enabled Professor Hannon, postdoctoral researcher Emily Hodges, and others in Greg's lab to play an important part in a story that *Science* called one of 2010's most important. After years of effort, a team led by Svante Pääbo at the Max-Planck Institute in Germany succeeded in piecing together a draft of the full genome of our Neanderthal predecessors. This was notable in part because the bone fragments from which the DNA was sampled were so old—approaching 40,000 years. But it was also remarkable because the fragments were highly corrupted, some containing as little as two tenths of 1% of Neanderthal DNA. One challenge was how to sift such a tiny portion from the corrupted remainder. This was where the Hannon lab's technique called array-capture resequencing proved to be especially useful. They used it to sequence 14,000 genes known to be different in humans and our closest relatives on the tree of life—chimpanzees. Although about three-fourths of the proteins encoded by those genes are different in humans and chimps, Greg's team showed that stunningly few of them differed in humans and Neanderthals. In fact, they found only 88 amino acid differences, correlating with 83 proteins. In that register, at least, we are scarcely different from the "cave men."

A Gene Variant Is Found to Dramatically Boost Tomato Yields and Sweetness

Superb basic science gives rise to perspective-altering discoveries such as the one just described, but it also leads to insights that have immense practical value. An example can be found in the work of Assistant Professor Zachary Lippman, who in collaboration with scientists at Hebrew University in Israel identified a gene that pushes hybrid tomato plants to increase their yield by as much as 60%. Not only is the yield-boosting power of the gene—which works when plants make flowers—active in different species of tomatoes and under a range of environmental conditions, it also can help to boost the yields of many other flowering crops. The team made the discovery while hunting for genes that boost hybrid vigor, a property first noted by Charles Darwin and then rediscovered at CSHL by George Shull a century ago. Hybrid vigor, or heterosis, can be seen when the breeding of two plant varieties gives rise to a new generation with higher yield than either

Z. Lippman

of the parental lines. The key to the spectacularly high yields in Zach's plants was a mutation that leaves only one active copy (instead of the normal two) of the florigen gene, whose function is to instruct plants to cease making leaves and begin making flowers, which in turn produce fruit. Zach tells us, incidentally, that the super-high-yield tomatoes are surprisingly sweet because the florigen mutation also boost plants' sugar production.

An Asexual Path to Limitless Food Plant Yield?

A very different approach to boosting yield in food crops is to bypass sexual reproduction altogether. Indeed, this has been a fantasy of plant breeders for many years. When male and female gametes sperm and egg—combine randomly to generate a unique seed during sexual reproduction, valuable parental traits that have been selected by breeders are erased. A subset of plants does reproduce asexually, however, through a process called apomixis. The offspring of the common dandelion, for instance, are clones of the parent. In 2010, Professor Rob Martienssen collaborated with scientists in



R. Martiensson

Mexico to try to coax a flowering plant, the mustard plant *Arabidopsis thaliana*, to reproduce via apomixis. Key to the experiment was shutting down the activity of a protein called Argonaute 9. By doing this, the team tricked an *Arabidopsis* ovule into manufacturing multiple gametes, rather than one. These gametes carried the full complement of genetic material for the next generation, then, and not half, as is the case when the plant reproduces sexually. The offspring were, in this sense, clones. Intrigued by the observation that mobile genetic elements, or transposons, seemed to promote sexual reproduction, it seemed logical to Rob and colleagues to find a molecule that could silence transposons—Argonaute 9 is one—and determine whether it inhibited sexual reproduction. They succeeded. The trick now will be to detect whether this approach works in other plants that reproduce sexually and then specifically in the subset on which we rely for food.

A Protein Critical for Activating DNA Replication

My own research group discovered how a protein called DDK, an essential activator of DNA replication, actually triggers DNA replication in cells. DDK (for *D*df4-*de*pendent protein *k*inase) is an enzyme that attaches phosphate molecules to other proteins to modify their activity. We found that it performs this operation, called phosphorylation, on a protein called Mcm4, specifically within a domain that acts as a built-in brake to prevent the DNA double helix from being unwound. The phosphorylation by DDK releases this brake, thus initiating the replication of unwound DNA strands. Because DDK is often deregulated in human cancers, this new understanding of its role in DNA replication may help to shape the development of new cancer therapies. Indeed, anti-DDK drugs have recently been introduced into the clinic. The discovery of this self-inhibitory activity within Mcm4 and the finding that DDK is required to overcome it were a surprise. It leads us to ask, why such complexity? We suspect that it might have evolved in response to the importance of precision and accuracy in DNA replication. This fits with the broad picture that we have assembled over the years of how replication is coordinated and controlled by kinase proteins.

Cold Spring Harbor Laboratory Board of Trustees

The Board of Trustees, which includes up to 35 members, meets in full, executive, and other committee sessions numerous times throughout each year to perform its duties as the governing body of the institution. Many significant developments related to board leadership occurred this year and deserve mention.

On behalf of the board, I would like to thank Eduardo G. Mestre, who served on the board since 2001 and was Chairman from 2004 to 2010. With Eduardo's leadership during the first decade of the 21st century, CSHL achieved unprecedented growth and expansion in infrastructure and programs. Serving on committees ranging from Capital Campaign, Executive, Nominating, Research,



E.G. Mestre, D. Ayres

and Robertson Research Fund, he challenged fellow trustees and the leadership of the Laboratory to think strategically. As a result, we were able to prevail in the face of significant external challenges that threatened support for basic research across the country. I am pleased that he will remain associated with CSHL as an honorary trustee.

On November 6, 2010, the board elected a new Chairman, Jamie C. Nicholls, and new slate of officers: Vice Chairs Robert D. Lindsay, comanaging partner Lindsay Goldberg, and Marilyn Simons, President of The Simons Foundation; Treasurer Leo Guthart, CEO of Topspin Partners; and Secretary Ed Travaglianti, President of TD Bank, Long Island. I look forward to working closely with Jamie, who, as CSHL Treasurer since 2009, has demonstrated her unique ability to translate her business expertise to the nonprofit, academic world.



E. Travaglianti, L. Guthart, M.H. Simons, J.C. Nicholls, R.D. Lindsay, B. Stillman

Four new trustees were elected to the CSHL Board of Trustees this year: Tania Baker, Howard Hughes Medical Institute Investigator, E.C. Whitehead Professor, and Codirector of the biology graduate program at Massachusetts Institute of Technology; David Boies, Chairman of the law firm Boies, Schiller and Flexner LLP; Howard Morgan, President of Arca Group Inc. and Director of Idealab; and Dinakar Singh, founding partner of TPG-Axon Capital.

Thank you Lola N. Grace, Vice Chairman from 2004 to 2010, for your enduring commitment to CSHL. Lola retired from the Board this year and was elected an honorary trustee. Lola served on the Board of Trustees since 1995, playing an active part as a member of many committees and providing leadership as an officer since 1998.

We also extend our affection and gratitude for devoted service to retiring trustees Kristina Perkin Davison (2002 to 2010) and Laurence F. Abbott (2004 to 2010).

Two dear friends and former trustees passed away this year. We fondly remember George W. Cutting, Jr. and Charles E. Harris III, who both contributed in unique and generous ways to the growth of CSHL's research and education programs. "Butch" Cutting was instrumental in the formation of the Long Island Biological Association, which was later named the CSHL Association. Butch served on the CSHL Board of Trustees from 1986 to 1993. Charlie served on the Board from 1998 to 2004 and was a founder of the President's Council, created to support the CSHL Fellows program.

CSHL Association

Thank you to the Cold Spring Harbor Laboratory Association (CSHLA) active leadership team of President Tim Broadbent and 25 elected directors, who organized events and letter-writing campaigns to raise \$5.6 million of unrestricted funds in support of early-career scientists at CSHL.

This year, more than 140 women gathered at Peacock Point, an exclusive enclave of Long Island's Gold Coast, for the Women's Partnership for Science lecture and luncheon: "Autism: Breaking the Code." The speaker, Alea Mills, Ph.D., has received numerous awards for her work in the field of cancer research and has recently turned her expertise in molecular biology toward understanding the genetic basis of autism. Alea spoke about her recent success in generating a novel mouse model with a chromosomal abnormality that is frequently found in children with autism. These mice, which demonstrate the unique behavioral features of humans with autism, are the subjects of intense



A. Abbott, L. Trafelet, B. Stillman, E. Ainslie, M. Snow, K. Davidson

research in her lab as well as with a team of neurobiologists at CSHL. In its 9th year, the event started by Kristina Perkin Davison has raised more than \$500,000 to benefit the research of CSHL's female investigators.

Other friend-raising and fund-raising events initiated by the CSHLA directors included hosting a Regional Junior Chess Tournament and a Major Donor Reception in Old Westbury at the home of Cornelia Guest.

Research Faculty

Awards

Professor and Neuroscience Program Chair Tony Zador was awarded a prestigious \$2.17 million Transformative Research grant by the National Institutes of Health. He will use the 5-year research



T. Zador



A. Kepecs

leads to diseases such as autism.

Tony also received one of seven Distinguished Investigator grants from the Paul G. Allen Family Foundation. These—the first of their kind—are part of a program launched by the Foundation to advance important neuroscience and cellular engineering research. Tony, whose grant totals \$1.6 million, proposes to develop a highly efficient method for determining the neural wiring diagram for any genetically accessible organism, a crucial requirement for understanding how the brain functions.

grant to analyze the connectome-the brain's wiring-and determine how its disruption

Assistant Professor Adam Kepecs was named a John Merck Scholar and received a \$300,000 research grant to develop new technologies that would help to reveal the role of the cholinergic nervous system in cognitive tasks involved in learning and attention.

Adam also won recognition in the fall as a finalist for the Eppendorf and Science Prize in Neurobiology. The award recognizes outstanding international neurobiological research by a young, early-career scientist, as described in a 1000-word essay based on research performed within the last 3 years. Dr. Kepecs's essay, entitled "Are you certain? The neural basis for decision confidence," is available online at www.sciencemag.org.

Assistant Professor Raffaella Sordella received the 2010 Damon Runyon–Rachleff Innovation Award to carry out bold, high-risk research to determine the molecular basis of cancer drug resistance and strategies to overcome it, a result that could provide life-changing benefits for a large number of cancer patients.

In November, *Genome Technology* asked researchers in the field of systems biology to identify its rising stars. Three of the 24 rising stars on the list were from CSHL. Two are



T. Kelly, L. Goldman, B. Stillman

recent WSBS graduates: Yaniv Erlich, for work in "Fast-Paced Bioinformatics," and Nicholas Navin, for work in "The Evolution of Cancer Tumors." Assistant Professor Michael Schatz was recognized for his work on "Genome Assembly and the Cloud."

I was honored to receive the 2010 Louisa Gross Horwitz Prize from Columbia University with Thomas J. Kelly, M.D., Ph.D., of Memorial Sloan-Kettering Cancer Center, for our work in elucidating mechanisms involved in the process by which DNA—the genetic material contained within the nucleus of nearly all our cells—replicates itself. Tom and I are proud to have contributed to understanding the way cells work in humans and to have shed light not only on the duplication of normal cells, but also on how the process goes awry in cancer.



N. Navin

New Staff

Fritz Henn, Professor, joined CSHL from neighboring research institution Brookhaven National Laboratory (BNL), where he oversaw the biology and medical departments and performed research, often using sophisticated imaging techniques, that has contributed to our knowledge of how the brain functions, particularly in the field of depression. Fritz earned a Ph.D. in physiological chemistry from The Johns Hopkins University in 1967 and an M.D. from the University of Virginia in 1971. He performed his residency in the Department of Psychiatry at Washington University School of Medicine from 1971 to 1974. He began his career at the University of Iowa College of Medicine, and, in 1982, he joined Stony Brook University (SBU), where he became Professor and Chair of the department of psychiatry and behavioral medicine. Following an extensive period in Heidelberg, Germany, Fritz returned to the United States as Deputy Director of BNL before accepting a professorship at CSHL. He has collaborated with Assistant Professor Bo Li.

Anne Churchland, Assistant Professor, joined CSHL after completing her doctorate at University of California, San Francisco, and postdoctoral research in a primate lab at the University of Washington, Seattle. Shifting from primate research to rodent research, she will be studying the circuitry underlying multimodal decision-making, in which animals rodents—gather evidence from multiple sources, for instance, aural and visual, before making a decision.

Molly Hammell, Assistant Research Professor, comes to CSHL after 5 years as a research associate in genetics and genomics under Victor Ambros at the University of Massachu-



F. Henn



A. Churchland



M. Hammell

C. Hammell

J. Kinney

M. Schatz

setts. At CSHL, she is applying prediction algorithms to problems in cancer research. She is also Manager of the CSHL Cancer Center's Bioinformatics Shared Resource.

Chris Hammell, Assistant Professor, did his doctoral work at Dartmouth College and his postdoctoral work in the lab of Victor Ambros at the University of Massachusetts. There, he became interested in the machinery that prepares microRNAs to target specific genes, which they in turn regulate. Using *Caenorhabditis elegans* and forward genetics, he continues to focus on how mutations in this machinery could perturb a given microRNA's gene-regulatory activity so as to give rise to a developmental timing defect and set in motion a chain of events culminating in human illness.

Justin Kinney was named our second Quantitative Biology Fellow. He earned his doctorate in physics from Princeton University and spent the last 2 years in postdoctoral fellowships at Princeton and at CSHL, applying his quantitative skills to biological problems. As a Fellow, he will focus on the question of how sequences of very specific regions in the genome interact with proteins to execute gene expression. He seeks to characterize the sequence–function relationship quantitatively.

Michael Schatz, Assistant Professor, developed methods for large-scale computational analysis of DNA sequencing data at the University of Maryland. He is known for his pioneering use of cloud

computing for genomics and for the last several years has helped to run a large National Science Foundation cloud computing project. His research at CSHL will focus on metagenomics—trying to understand individual genomes within a larger genomic context and on genome assembly and validation projects.

Hongwu Zheng, Assistant Professor, earned his Ph.D. in biochemistry at Boston University and completed postdoctoral studies at Harvard Medical School. He focuses on glioblastoma, a brain cancer with a poor prognosis. He uses mice to recapitulate genetic and epigenetic aspects of the cancer and approaches the problem from a developmental perspective. Hongwu is exploring ways to resolve differentiation in cells as a method of halting tumor progression.

H. Zheng

Promotions

Congratulations to Dinu Albeanu, who was appointed Assistant Professor. Nicholas Navin was promoted to the position of Research Investigator in the laboratory of Michael Wigler. Dan Levy was promoted to the position of Senior Computer Scientist.

Departures

CSHL is proud of our long history as an incubator for early-career researchers who go on to successful careers all over the world. In 2010, Matthew Vaughn became a Research Associate at Texas Advanced Computing Center in Austin. Sheldon McKay took on the job of Scientific Lead, Engagement Team, iPlant Collaborative at the University of Arizona, Tucson. Professor Michael Zhang moved to Dallas to become Director of the Center for Systems Biology, department of molecular and cell biology, University of Texas, Dallas.



Education Programs

Watson School of Biological Sciences

In the National Research Council (NRC)'s latest assessment of 5000 doctoral programs across 62 fields at 212 universities nationwide, the Watson School of Biological Sciences (WSBS) was ranked between third and 17th across 20 cumulative categories. In the category of citations per publication, CSHL ranked first. The NRC assessment is performed over the period of 10 years, and so this is the first opportunity that the WSBS program has had to be included in this national evaluation.

Ten WSBS students, all of whom matriculated between 2004 and 2006, received their Ph.D.s at the 2010 WSBS Commencement Convocation in April. 2010 graduate Yaniv Erlich won the Fred Hutchinson Cancer Research Center's Harold M. Weintraub Graduate Student Award for outstanding achievement during graduate studies.

Honorary degrees were conferred upon Carla Jo Shatz, Ph.D. and Thomas R. Cech, Ph.D. Dr. Cech is a Nobel laureate and pioneer in the study of RNA enzymes and telomerase and was recently President of the Howard Hughes Medical Institute. Dr. Shatz, whose research has helped to establish some of the basic principles of early brain development, is Professor of biology and neurobiology and Director of the Bio-X program at Stanford University School of Medicine. She was also an instructor in our neuroscience advanced courses program.

The 2010 Gavin Borden Visiting Fellow Lecture was presented on March 15 by Dr. Gerald F. Joyce, Dean of the Faculty, Professor, Departments of Chemistry and Molecular Biology, and Investigator, The Skaggs Institute for Chemical Biology, The Scripps Research Institute. The title of the 16th annual CSHL Gavin Borden lecture was "The Origin of Life in the Laboratory."

Meetings and Courses

On April 6, CSHL celebrated the opening of Cold Spring Harbor Asia Conferences in Suzhou, China, a meetings program that aims to be the premier hub for scientists throughout Asia who are exploring the frontiers of molecular biology, biomedicine, and biotechnology. The program kicked off with the first James Watson Cancer Symposium, organized by leading scientists representing important current areas of research: Dr. Xiaodong Wang, a Howard Hughes Medical Institute Investigator affiliated with the University of Texas Southwestern Medical Center and the National Institute of Biological Sciences, Beijing; Dr. Scott W. Lowe of HHMI and CSHL; Dr. Yusuke Nakamura of the University of Tokyo; Dr. Tak Mak of the University of Toronto; and Dr. Karen Vousden









National Research Council assessment publication

B. Stillman, T.R. Cech



CSH Asia logo

of the Beatson Institute for Cancer Research in the United Kingdom. This 6-day meeting was followed by the first Francis Crick Neuroscience Symposium, which was similarly organized by leaders in the field: Dr. Z. Josh Huang of CSHL; Dr. Mu-ming Poo of the CAS Institute of Neuroscience, Shanghai and the University of California, Berkeley; Dr. Linda Richards of the University of Queensland, Australia; Dr. Joshua Sanes of Harvard University; and Dr. Keiji Tanaka of the Laboratory for Cognitive Brain Mapping, Riken, Japan. In all, the new CSHL Asia program, which operates from a 600,000-square-foot facility—the Suzhou Dushu Lake Conference Center hosted 10 meetings and more than 2000 scientists from around the world, but primarily from Pacific Rim countries.

Suzhou is only 60 miles west of a "megacity" even larger than New York—the economic powerhouse of Shanghai, population 20 million. Importantly, the new conference center is less than an hour by high-speed rail from Shanghai and, served by two regional airports, is only a 2- to 3-hour plane ride from Japan, South Korea, Taiwan, and Hong Kong. Singapore and Sydney, Australia, are, respectively, 5 and 10 hours distant by air.

This year marked the 75th anniversary of the Cold Spring Harbor Laboratory Symposia on Quantitative Biology. The 2010 Symposium, with close to 70 talks and attendance of more than 400 scientists, was organized by Terri Grodzicker, David Spector, David Stewart, and me. It focused on the topic of Nuclear Organization and Function. To celebrate the history of the symposia, Jan Witkowski, Jim Watson, and I organized a special 1-day event chaired by Robert Tjian, CSHL alumnus and President, Howard Hughes Medical Institute, called "Biology, Society, and the Future." More than 225 guests attended the lectures presented by world experts including Charles Sawyers, Memorial Sloan-Kettering Cancer Center; Spencer Wells, National Geographic Society; Henry Louis Gates, Harvard University; Mark Bear, Massachusetts Institute of Technology; Story Landis, National Institute of Neurological Disorders & Stroke; Peter Neufeld, The Innocence Project; Craig Venter, J. Craig Venter Institute; and Richard Roberts, New England BioLabs, Inc.

The Symposium on Quantitative Biology has become the cornerstone for our annual program of Meetings and Courses, which in 2010 posted record attendance. A total of 7500 researchers from around the globe attended meetings, and more than 1300 attended training courses on our Long Island campuses. A new experimental laboratory teaching suite funded by the Howard Hughes Medical Institute was opened in our Hillside Laboratories complex.



Opening ceremony, CSH Asia Conferences

CSH Asia poster session



Symposium attendees

Dolan DNA Learning Center

In its second year of operation, the Harlem DNA Lab made significant strides in reaching underserved students and teachers in New York City schools. The statistics speak for themselves: 75% of the 6400 precollege students that attended field trips to the Harlem DNA Lab were African American or Latino; 75% of students attending the Harlem DNA Lab came from Title 1 schools, where 40% or more of students are considered low income.

CSHL's DNA Learning Center led by David Micklos also won acclaim for the success of its iPhone app, "The 3D Brain." With 50,000 downloads, it reached no. 7 among education apps for the iPhone and no. 1 of educational iPad apps.

Cold Spring Harbor Laboratory Press

Since 1933, the CSHL Press has continuously evolved and adapted its publications to best serve the contemporary needs of the scientific community. This year, John Inglis' team launched a new initiative, *CSH Perspectives in Biology*, a monthly online publication comprising reviews spanning the complete spectrum of the molecular life sciences. This new venture is intended to provide the life sciences community with authoritative analyses of progress in emerging areas of molecular, cell, and developmental biology, genetics, evolutionary biology, neuroscience, cancer biology, and molecular pathology. The contributions are written by leading researchers in each field and commissioned by a board of eminent academic editors. Subject Collections gradually accumulate articles as new issues of the journal are published and, when complete, each represents a comprehensive survey of the field that it covers.



CSH Perspectives in Biology

Development

More than 60 CSHL supporters participated in the Fall President's Council retreat, the 16th year of this event. Participants donated more than \$25,000 to support early-career scientists in pursuit of the most promising and innovative research projects. The 2-day retreat immerses these generous philanthropists in the hottest topics in science. This year's event, organized by Diane Fagiola, tackled "The Science of Nanomedicine," with a keynote on the applications of nanotechnology in medicine by Bob Langer, David H. Koch Professor at the Massachusetts Institute of Technology. Other experts included Harvard Professor George Whitesides, University of North Carolina chemistry department



President's Council retreat

head Joseph DiSimone, and Dr. William Sherman of Brookhaven National Laboratory's Center for Functional Nanomaterials.

For the fifth year, 400 guests gathered in early November at the Mandarin Oriental Hotel in Manhattan to honor recipients of the Double Helix Medal—extraordinary individuals who have benefited human health through game-changing biomedical research or by raising awareness and funds for such endeavors. Geneticist Mary-Claire King was honored for outstanding contributions toward understanding the genetics of breast cancer and mental illness. Evelyn H. Lauder received the Medal for her leadership as the Founder and Chairman of The Breast Cancer Research Foundation, which has raised more than \$300,000 million to support breast cancer research worldwide. Nobel laureate in Economic Sciences John F. Nash was awarded the Medal for having brought worldwide awareness to and appreciation for people suffering with schizophrenia. The gala event, produced by Charlie Prizzi's team in the development department, raised more than \$3 million. A special feature of this event was a musical performance by composer Carter Burwell, whose biography includes a 2-year stint as Chief Computer Scientist at CSHL.



CSHL received Charity Navigator's coveted four-star rating for sound fiscal practices, placing CSHL among the most fiscally responsible of more than 1.5 million philanthropic organizations that currently exist in America. This is the ninth consecutive year that CSHL has achieved this top ranking.

Infrastructure Projects

In June, members of the CSHL community celebrated the completion of an expansion and renovation of the Carnegie building, which dates to the institution's infancy in 1905. In addition to a new state-of-the-art climate-controlled vault for storage of pre-

cious archival collections that trace the history of molecular biology and genetics, the updated building now also boasts an annex, named for CSHL alumnus and benefactor Waclaw Syzbalski, Ph.D. Joining us at the opening ceremony was Nobelist Sydney Brenner, who generously donated his archives to CSHL this year.

In November, Art Brings and the facilities department began a project to replace a structure that was originally constructed in 1906 as a green house and potting complex. This structure, which was ultimately named the Hershey Laboratory, after Nobel Prize–winning CSHL scientist Alfred Hershey, was renovated in 1979 to provide offices and to support research activities. The new building currently under construction will be ~18,000 square feet and will house a teaching lab, a seminar room, and a computer classroom for the Laboratory's Meetings and Courses program. It will also be home to the CSHL Cancer Center Shared Resources Flow Cytometry and Microscopy facilities, which have been temporarily moved to the Hillside Laboratories. The Howard Hughes Medical Institute provided \$9 million for this project.

CSHL's Sammis Hall, designed by the noted postmodernist architect Charles Moore, was featured in the Heckscher Museum's exhibit, "ARCADIA/SUBURBIA: Architecture on Long Island, 1930–2010." This dormitory residence on the grounds of the Banbury Conference Center was a stop on the house tour associated with the exhibit.

Community Outreach

In celebration of National Lab Day, Professor Gregory Hannon opened the doors of his three-story laboratory building named for Nobelist Barbara McClintock to more than 150 fifth and ninth graders from Long Island and Manhattan schools. With help from his graduate students and postdocs, the visiting children learned to use microscopes to identify lung cancer cells and fruit fly neurons, among other lessons. Greg also spoke about his research endeavors at the February meeting of



Renovated Carnegie building



Charity Navigator logo

Hershey Laboratory site rendering



CSHL Partners for the Future

the Secret Science Club in Brooklyn, a monthly gathering of ~400 science enthusiasts primarily from New York City.

CSHL's Partners for the Future program continues to recruit the brightest of Long Island's budding scientists. This year, seven seniors from high schools across Long Island were accepted into the program, giving them daily access to a CSHL mentor and a laboratory in which to conduct a research project of their own. The students devote a large part of their year to working in a laboratory and learning what it is like to be a researcher. At the end of the school year, the students present their findings in a scientific seminar in Grace Auditorium. This year, three students working on cancerrelated research projects took an additional step, taking the time to translate their scientific presentations for the public and the media. We offer thanks to the American Cancer Society for partnering with us to publicize this as part of its local Relay For Life events.



DNA Day Scavenger Hunt poster

Spearheaded by Amanda McBrien, Assistant Director of Instruction at the DNALC, CSHL cohosted a National DNA Day scavenger hunt with local museums and merchants in Cold Spring Harbor village. More than 200 area residents participated in the weekend event celebrating the storied history of the village. April 25 is congressionally designated as National DNA Day, commemorating the completion of the Human Genome Project in April 2003 and the discovery of the double helix structure of DNA in 1953. Each year, the National Human Genome Research Institute encourages national participation in the creation of opportunities

for students, teachers, and families to explore the latest developments in genomic research.

The Harlem DNA Lab Instructor Ileana Rios and a banana DNA extraction experiment have become a regular attraction at the World Science Festival Street Fair in Manhattan. CSHL is pleased to have been able to participate once again in this event, which engages many thousands of New York City residents in the celebration of science for a week each June.

Thanks to our students and postdocs who make our CSHL tour program such a success. This year, our tour guides hosted 500-plus visitors. The 2hour walking tours showcase the history of our science, research, and edu-



Community tours logo



cation programs. Participants also experience the beauty of the campus' architecture and landscapes.

The CSHL DNA Learning Center's public programs continue to be a hit in the community. During the school year, the DNALC opened its doors on Saturdays for "Saturday DNA," geared to middle and high school students and their parents. During the summer months, more than 900 students in grades 5 through 12 attended

week-long camp sessions, on topics ranging from "Fun with DNA" and "World of Enzymes" to "Forensic Detectives" and "Silencing Genomes."

We are thankful for the partnerships that we have with local organizations with whom we interact in many different ways throughout the year. This year, Assistant Professor Hiro Furukawa lectured at a meeting of the Alzheimer's Association of the Long Island Board. We hosted a lecture and tour for the Leukemia & Lymphoma Society board of directors, at which Chris Vakoc spoke. Diane Esposito, Research Investigator in Mike Wigler's laboratory, was an invited speaker on breast cancer research for three different occasions, which were sponsored by the Suffolk County Women's Bar Association, the Women's Center of St. Francis Hospital, and the Adelphi N.Y. Statewide Breast Cancer Program. CSHL representatives cheered on participants in the LI2Day Walk and judged the organization's annual scholarship program. We were also well represented at a local Swim Across America event. We thank these and many other partners who support CSHL through grants and donations.

For details on grants and philanthropic donations received this year, please refer to separate sections of this report. In addition, please visit our newly designed public website, www.cshl.edu for all of the latest news and information about the institution, including electronic access to annual reports, the *Harbor Transcript* magazine, links to stories about us in the media, and postings about research results and education program achievements.

Public Lectures at Cold Spring Harbor Laboratory

March 21—Roger Reeves, Ph.D.: "Theory to Therapeutics in Mice and Men with Down Syndrome," cosponsored by CSHL, the Association for Children with Down Syndrome, the Down Syndrome Connection of Long Island, and the National Down Syndrome Society.

April 26—Thomas R. Cech, Ph.D., Distinguished Professor, University of Colorado-Boulder; Investigator, Howard Hughes Medical Institute; winner, Nobel Prize in Chemistry, 1989: "Learning to Teach, Teaching to Learn."

June 8—Alea A. Mills, Ph.D., CSHL Associate Professor, with Nikita Anand, Cold Spring Harbor High School, Norah Liang, Patchogue-Medford High School, Joshua Weiss, Smithtown High School East: "Next-Generation Cancer Research: Long Island Teens on the Front Line of Discovery."

June 29—Sydney C. Gary, Ph.D., CSHL Director, research operations; Adam Kepecs, Ph.D., CSHL Assistant Professor; Stephen Dewey, Ph.D., The Feinstein Institute of Medical Research; Edward Nunes, M.D., Professor of clinical psychiatry, Columbia University: "Addiction: How the Brain Measures Reward and Response," cosponsored by CSHL, the North Shore– Long Island Jewish Health System, and St. Johnland Nursing Center.



A. Mills

September 26-Steven Allen, M.D., Associate Chief of Hematology,

North Shore-LIJ; Johannes Zuber, M.D., CSHL Clinical Research Fellow; Christopher Vakoc, M.D., Ph.D., CSHL Fellow: "Hitting Leukemia Where It Hurts: Researchers and Physicians Unite to Knock Out Cancer," cosponsored by CSHL, The Don Monti Memorial Research Foundation, and the North Shore–Long Island Jewish Health System.



S. Allen, C. Vakoc, J. Zuber

November 14—Nancy Berlinger, Deputy Director and Research Scholar at The Hastings Center: "Ethics of Hope in End-of-Life Care," The Lorraine Grace Lectureship on Societal Issues of Biomedical Research (cancelled due to a sudden unavoidable conflict).

As the Internet continues to evolve, it offers more opportunities for our researchers to speak to the public online. A web magazine, BigThink.com, this year featured interviews of four of CSHL's finest. Interviews are accessible on demand if you visit www.bigthink.com and search for our "experts": James D. Watson, Michael Wigler, Tony Zador, and Adam Kepecs.

Public Concerts at Cold Spring Harbor Laboratory

February 16:	Peter Orth, pianist	September 3:	Di Wu, pianist
March 19:	Ran Dank, pianist	September 24:	Hahn-Bin, violinist
April 24:	Carducci String Quartet	October 8:	Diane Walsh, pianist
May 7:	Soo Bae, cellist	October 29:	Aaron Goldberg Trio
May 21:	Einav Yarden and Sergey		
	Ostrovsky, pianist and violinist		

Looking Forward

As we began 2010, our efforts in strategic planning prepared us for a challenging year. We accomplished so much in the face of many external challenges, and this was possible because of the dedication of our more than 1000 employees to excellence in research, education programs, and operations. No doubt, we will continue to face direct challenges related to the recovering economy and leadership changes in federal and state governments, but I am convinced that our continued commitment to excellence will help us to navigate and ultimately prevail. Thanks to all of you who work for and with CSHL.

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