

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

vides us with a suitably simple starting point. The fly brain should not be underestimated,

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 d v a n t i n e

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

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.

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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 old.

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 D t in iti A ti tin A i tin

My own research group discovered how a protein called DDK, an essential activator of DNA replication, actually triggers DNA replication in cells. DDK (for *Ddf4-dependent protein kinase*) 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, 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.

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

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

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

Assistant Professor Adam KepecsorfukdAmlfr5-9fo5-d1fl51fy5odtadAepAeprrd1fl51fy5fg51fh51fl5

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.

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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.

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 post-doctoral 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 Uni-

Education Programs

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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

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

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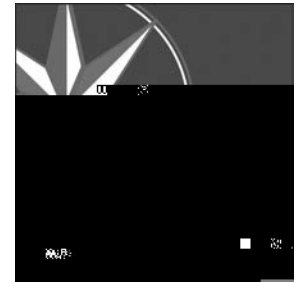
In its second year of operation, the Harlem DNA Lab made significant strides in reaching underserved students and teachers in New York City schools. The statistics speak for themselves: 75% of the 6400 precollege students that attended field trips to the Harlem DNA Lab were African American or Latino; 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.

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Since 1933, the CSHL Press has continuously evolved and adapted its publications to best serve the contemporary audience.

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.



Charity Navigator logo

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 precious 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 Syzalski, 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.

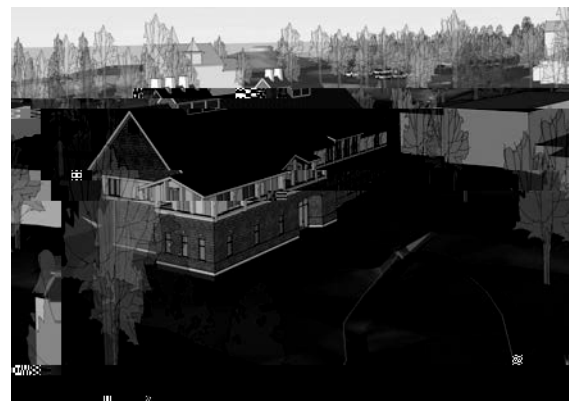
CSHL's Sammis Hall, designed by the noted postmodernist architect Charles Moore, was featured in the Heckscher Museum's exhibit, "ARCADIA/SUBURBIA: Architecture on Long Island, 1930-2010." This dormitory residence on the grounds of the Banbury Conference Center was a stop on the house tour associated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



Hershey Laboratory site rendering

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 cancer-related 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.

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 sto-

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



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

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|---------------------|----------------------------------------------------------|----------------------|----------------------|
| 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